COURSE CODE: **VPM 403**

COURSE TITLE: **INTRODUCTORY VETERINARY IMMUNOLOGY**

NUMBER OF UNITS: **2 Units**

COURSE DURATION: **Two hours of lecture per week**

COURSE DETAILS:

COURSE DETAILS:

**Course Coordinator: Dr. Olufemi Ernest Ojo** *D.V.M****.,*** *M.Sc****.***

**Email: oeoefemi@yahoo.com**

**Office Location: COLVET**

**Other Lecturers: Dr. M. A. Oyekunle, Dr. M. Agbaje**

COURSE CONTENT:

Evolution of immunity, Types of immunity, Organs and cells involved in immune response,

Antigens, antibodies and their interactions, Complement system. Immune complexes, Autoimmunity

and Autoimmune Diseases, Cytokines, The major histocompatibility complex, Genetic

regulation of immune response, Hypersensitivity reactions, immunological tolerance, immunesuppresion

and antigenic variation, Immune response to bacteria, fungal, viral, and parasitic

infections and tumours, Vaccine and adjuvant types and functions, Application of biotechnology

to vaccine production.

COURSE REQUIREMENTS:

This is a compulsory course for all 400 level students in the College of Veterinary Medicine. In

view of this, students are expected to register for the course and participate in all the course

activities. A minimum of 75% attendance in lecture and practical periods is required to qualify

for continuous assessment tests and the final examination.

READING LIST:

1. Quinn P. J., Markey B. K., Carter M. E., Donnelly W. J. C. and Leonard F. C.: Veterinary Microbiology and Microbial Disease, 4th Edition. Blackwell Science, 2001
2. Gupte S.: Short Textbook of Medical Microbiology, 7th Edition. Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, India, 1999.
3. Salimonu L. S.: Basic Immunology for Students of Medicine and Biology, 2nd Edition. College Press and Publishers Ltd., Jericho GRA, Ibadan, Nigeria, 2004.
4. Stites D. P., Stobo J. D., Fundenberg H. H. and Wells J. V.: Basic and Clinical Immunology, 4th Edition. Lange Medical Publications, Los Altos, California, 1982.
5. Nester, EW, Anderson, D.Ce, Roberts (Jr), C. E Pearsal, N.N. Nester, M.T and Hurley. D:Microbiology, A Human perspective 4th ed., published by McGraw Hill Higher Education, 2004.
6. Brooks, G.F., Butel, J.S and Morse, S.A.: Jawetz, Meinicte and Adelberg’s Medical

Microbiology, 23rd ed. Published by McGrawHill Education, 2004.

1. Day M. J. and Schultz R. D.: Veterinary immunology principles and practice

Nester, EW, Anderson, D.Ce, Roberts (Jr), C. E Pearsal, N.N.

Nester, M.T and Hurley. D (2004).Microbiology, A Human perspective 4th ed., published by McGraw Hill Higher Education

1. Brooks, G.F., Butel, J.S and Morse, S.A. (2004), Jawetz, Meinicte and Adelberg’s Medical Microbiology, 23rd ed. Published by McGrawHill Education

E

LECTURE NOTES

**INTRODUCTION**

**(Dr. M. A. Oyekunle)**

Immunology is an area of science which helps in understanding the way by which animals

gained protection from disease causing agents. It also includes the use of antibody-antigen

reaction or other laboratory work i.e. serology and immunochemistry.

Immunology involves the study of immunity or protection against infectious or other agents and

conditions arising from the mechanisms involved in immunity.

**History of Immunology**

· The Nobel Prize in Physiology and Medicine (1908) was awarded to llya llytic Metchni-

Koff (1845-1916) with Paul Erlich in recognition of their work in immunity.

· Late 18th century, Jenner Edward introduces cowpox vaccine for protection against

smallpox (1798).

Late 19th century

· Pasteur: germ theory, attenuated & killed vaccines i.e. anthrax vaccine, also developed

rabies vaccine.

· Kock (1882) described tubercule bacillus and produced killed vaccine.

· Metchnikoff (1884) described phagocytosis.

· Pasteur (1885) developed rabies vaccine.

· VouBehring & Kitasato (1890) prepared killed vaccine.

· Bordet, Pfeiffer (1895) discovered complement activity.

· Ehrlich (1891) standardized diphtheria toxin so that its potency can be assessed and

antitoxin measured against it.

· Durhan- bacterial agglutination.

**Mid 20th Century to date**

1902 Landsteiner discovered blood group.

1903 Wright and others discovered antibody in the blood of immunized animals.

1903 Antigenic determinant – Landsteiner ,Heidegerger, Murrack

1903 Electrophoretic separation of gammaglobulin by Kabat & Tiselius

1903 Antiglobulin test – Coobs, Mourant and Race

1903 Recognition of immunity.

1955 Clononal selection theory of immunity – Burnet & Jerae

1953 Medabear – discovered immune tolerance

1962 Porter – propose basic structure for immunoglobulin G molecule

Transplant immunology, tumor immunology, Rhesus immunization, Deficiency states

and role of thymus

Relationship between structure and biological activities of immunoglobulin Molecules

and genetic control mechanism

- Determinant of immunogenicity of antigen molecule

- Immunogenetic and evolution of immune system

- Lymphocyte activation and cell cooperation.

- Role of macrophages – antibacterial and cytotoxic effects.

1975 Monoclonal antibody production technique by Kholer & Milstein

1983-1984 Mullis developed Polymerase Chain Reaction (PCR)

1986 First vaccine (Hepatitis B vaccine) produced by genetic Engineering approved for

human use.

1986 Chickenpox vaccine approved for use in the U.S.

**IMMUNOLOGY CONCEPT**

Immunology is the study of host immune system from the moment of birth and sometimes even

before that. |The body exists in an environment filled with potentially harmful organisms and

agents. Over the course of thousands of years of evolution, the protective mechanism that

developed in human–animal immune system reflects many aspect of this evolution ranging from

the innate immunity afforded by the skin and mucous membranes to the highly complex specific

response of T -cells and antibodies which recognizes invading pathogens if they are encountered

again.

**TERMINOLOGIES**

**Antibody (AB):** A protein produced as a result of interaction with an antigen. The protein has

the ability to combine with the antigen that stimulated its production.

**Antigen (Ag):** A substance that can react with an antibody. Not all antigens can induce antibody

production; those that can are also called immunogens.

**B cell (also B lymphocyte):** Strictly, a bursa–derived cell in avian species and, by analogy, a cell

derived from the equivalent of the bursa in non-avian species. B cells are the precursors of

plasma cells that produce antibody.

**Cell–mediated (cellular) immunity:** Immunity in which the participation of lymphocytes and

macrophages is predominant. Cell–mediated immunity is a term generally applied to the type IV

hypersensitivity reaction (see below).

**Chemokines:** low–molecular–weight protein that stimulate leukocyte movement.

**Chemotaxis:** A process whereby phagocytic cells are attracted to the vicinity of invading

pathogens.

**Complement:** A set of plasma proteins that is the primary mediator of antigen-antibody

reactions.

5

**Cytolysis:** The lysis of bacteria or of cells such as tumor or red blood cells by insertion of the

membrane attack complex derived from complement activation.

**Cytotoxic T cell:** T cells that can kill other cells infected with intracellular pathogens.

**Endotoxins:** Bacterial toxins released from damaged cells.

**Epitope:** Site on an antigen recognized by an antibody. Also known as an antigenic determinant

**Hapten:** A molecule that is not immunogenic by itself but can react with specific antibody.

**Histocompatible:** Sharing transplantation antigens.

**Humoral immunity:** Pertaining to immunity in a body fluid and used to denote immunity

mediated by antibody and complement.

**Immune response:** Development of resistance (immunity) to a foreign substance (e.g.,

infectious agent). It can be antibody-mediated (humoral), cell-mediated (cellular), or both.

**Innate immunity:** Nonspecific resistance not acquired through contact with an antigen. It

includes skin and mucous membrane barriers to infectious agent and a variety of non specific

immunologic factors, and it may vary with age and hormonal or metabolic activity.

**Adaptive immunity:** Protection acquired by deliberate introduction of an antigen into a

responsive host. Active immunity is specific and is mediated by either antibody or lymphoid

cells (or both)

**Immunoglobulin:** A glycoprotein, composed of H and L chain, that functions as antibody. All

antibodies are immunoglobulin, but not all immunoglobulin have antibody function.

**Inflammation:** Local accumulation of fluid and cells after injury or infection.

**Interferon:** One of a heterogeneous group of low-molecular-weight proteins elaborated by

infected host cells that protect non-infected cells from viral infection. Interferons, which are

cytokines, also have immunomodulating functions.

**Leukocyte:** General term for a white cell.

**Lymphocyte:** A cell 7-12μm in diameter containing a nucleus with densely packed chromatin

and a small rim of cytoplasm, lymphocytes include the T cells and B cells, which have primary

roles in immunity.

**Macrophage:** A phagocytic mononuclear cell derived from bone marrow monocyte and found in

tissues and at the site of inflammation. Macrophages serve accessory roles in immunity,

particularly as antigen presenting cells (APCs).

6

**Major histocompatibility complex (MHC):** A cluster of genes located in close proximity e.g.,

on human chromosomes, that encoded the histocompability antigens (MHC molecules).

**Membrane attack complex:** The end product of activation of the complement cascade, which

contains C5, C6, C7, and C8 (and C9). The membrane attack complex makes holes in the

membrane of gram-negative bacteria killing them and, in red blood or other cells, resulting in

lysis.

**Monoclonal antibodies:** Each B lymphocyte produces antibody of a single specificity.

However, normal B cells do not grow indefinitely. If B cells hybridization and fused cells that

secret the desired antibody-producing cell line, known as a hybridoma, is contained, and these

hybrid cells produce monoclonal antibodies.

**Monocyte:** A circulating phagocytic blood cell that develops into tissue macrophages.

**Natural killer (NK) cells:** Large lymphoid cells with no known antigen-specific receptors. They

are able to recognize and kill certain abnormal cells, e g tumor cells.

**Opsonin:** A substance capable of enhancing phagocytosis. Antibodies and complement are the

two main opsonins.

**Opsonization:** The coatings of an antigen or particle (e.g., infectious agent) by substances, such

as antibodies, complement components, fibronectin, and so forth, that facilitate uptake of the

foreign particle into a phagocytic cell.

There are two types of immunity,

1. Non-adaptive immune response or innate immunity. This is the immunity that is not

affected by prior contact with the infectious agent or other material involved and is not

mediated by lymphocytes.

7

2. Adaptive immune response/specific immune response/Acquired immunity. This is the

immune response that depends on the recognition and the elimination of antigens by

specific lymphocytes.

Adaptive/acquired Immunity can be natural or artificial, active or passive

Active Passive

Natural Exposure to antigen induces

an immune response s

immunity that follows

attacks of measles or canine

distemper

Transfer of antibodies or

cells produced by others as

temporary immunity from

antibodies of the mother

transferred to infant across

the placenta or in milk.

Artificial Deliberate exposure to

antigen induces an immune

response e.g. immunization

of children or young

animals.

Antibodies in immune

serum are introduced into

body e.g. injection of rabies

immune globulin after dog

bite.

**The Innate Defenses**

The innate defense system is composed o first-line defenses, sensor systems such as toll-like

receptors and complement, and phagocytes. Inflammation is a coordinated response that involves

many aspects of the innate defenses.

**First-Line Defenses**

Physical Barriers:

· The skin provides the most difficult barrier for microbes to penetrate; it is composed of

two main layers- the dermis and the epidermis.

· The cells of the mucous membrane are constantly bathed with mucous and other

secretion that help wash microbe from the surfaces. Some mucous membranes have

mechanisms that propel microbes, directing them towards areas where they can be

eliminated more easily.

**Antimicrobial Substances:**

Lysozyme, peroxidase, enzymes, lactoferrin, and defensins are antimicrobial substances that

inhibit or kill microorganisms

**Normal Flora:**

Members of the normal floral competitively exclude pathogens and stimulate the host defenses.

**The Cell of the Immune System**

1. **Granulocytes**

8

There are three types of granulocytes- neutrophils, basophils and eosinophilis.

2. **Mononuclear Phagocytes**:

Monocytes differentiate into either macrophages or dendritic cells.

3. **Lymphocytes**

Lymphocytes, which include B cells, T cells and Natural Killer (NK) cells, are involved in

adaptive immunity.

**Cell Communication**

Surface receptors bind ligands that are on the outside of the cell, enabling the cell to detect that

the ligand is present.

**Cytokines:**

Cytokines include interleukins (ILs), colony-stimulating factors (CSFs), tumor necrosis factors

(TNFs), chemokines, and interferons.

**Adhesion Molecules**

Adhesion molecules allow cells to adhere to other cells.

**Sensor Systems**

Toll-Like Receptors

Toll-like receptor enables cells to detect molecules that signify the presence of microbes.

**The Complement System**

· Complement proteins circulate in the blood and the fluids that bath tissues, in response to

certain stimuli that indicate the presence of foreign material, they become activated.

· The major protective outcomes of complement activation include opsonization, lysis of

foreign cells, and initiation of inflammation.

**Phagocytosis**

The Process of phagocytosis

· The step of phagocytosis includes chemotaxis, recognition and attachment, engulfment,

destruction and digestion, and exocytosis.

**Attributes of Macrophages:**

1. Macrophages are always present in tissues to some extent, but are able to call in

reinforcements when needed.

2. A macrophage can increase its killing power, becoming an activated macrophage.

3. Macrophages, giant cells, and T- helper cells form concentrated groups called

granulomas that wall off and retain organisms or other material that cannot be destroyed

by macrophages.

**Attributes of Neutrophils**

9

Neutrophils play a critical role during the early stages of inflammation, being the first cell type

recruited from the blood stream to the site of damage.

**Inflammation- A Coordinated Response to Invasion or Damage**

Swelling, redness, heat, and pain are the signs of inflammation, the attempt by the body to

contain a site of damage, localized the response, and restore tissue function.

Factors that Initiate the Inflammatory Response:

Inflammation is initiated when pro inflammatory cytokines or other inflammatory mediators are

released as a result of the engagement of tolls-like receptors or activation of complement by

invading microbes, or when tissue damage occurs.

The Inflammatory Process

· The inflammatory process leads to a cascade that result in dilation of small blood vessels,

leakage of fluids from those vessels, and the migration of leucocytes out of the

bloodstream and into the tissues.

· Acute inflammation is marked by a preponderance of neutrophils, chronic inflammation

is characterized by the prevalence of macrophages, giant cells, and granulomas.

**Outcomes of Inflammation**

Inflammation can contain an infection, but the process itself can case damage, a system response

can be life threatening.

**Apoptosis – Controlled Cell Death that Circumvent the Inflammatory Process.**

Apoptosis is a mechanism of eliminating self-cells without evoking an inflammatory response.

**Interferons**

· One of the roles of interferons is to induce cells in the vicinity of a virally infected cell to

prepare to cease protein synthesis in the event they become infected with a virus. Doublestranded

RNA signifies to the cell that it has been infected.

**Fever**

· Fever occurs as a result of certain pro-inflammatory cytokines released by macrophages

when their toll-like receptors bind microbial products.

· Fever inhibits the growth of many pathogens and increases the rate of various body

defenses.

10

**Strategy of the Adaptive Immune Response**

The Humoral Immunity:

Humoral immunity is mediateds by B-cells in response to extracellular antigens. These maybe

triggered to proliferate and then differentiate into plasma cells that function as antibody

producing factories.

**Cellular Immunity**

Effector T- cytotoxic cells are able to induce apoptosis in ‘self’ cells that present abnormal

protein that signify danger. Effector T-helper orchestrates the various response of cellular and

humoral immunity.

**Anatomy of the lymphoid system**

Lymphatic Vessels:

Lymph, which may contain antigens that have entered tissues, flows in the lymphatic vessels to

the lymph nodes.

**Primary lymphoid Organs**

Primary lymphoid organs are the sites where B-cells and T-cells mature.

**Secondary lymphoid organs**

Secondary lymphoid organs are the sites at which lymphocytes gather to contact antigens; they

facilitate the interactions and transfer of cytokines between the various cells of the immune

system.

**The Nature of Antigens**

· Antigens are molecules that react specifically with an antibody or lymphocyte.

Immunogen refers specifically to an antigen that elicits an immune response.

· The immune response is directed to antigenic determinant, or epitopes, on the antigens.

**The Nature of Antibodies**

Structures and Properties of Antibodies

· Antibodies monomers have a Y shape with an antigen-binding site at the end of each arm

of the Y. The tail of the Y is the Fc region.

· The antibody monomer is composed of two identical heavy chains and two identical light

chains; each chain forms several domains. The variable region contains the antigen

binding site; the constant region encompasses the entire Fc region as well as part of the

Fab regions.

**Protective Outcomes of Antibody-Antigens Binding**

Antibody-antigens binding result in neutralization, immobilization and prevention of adherence,

agglutination and precipitation, opsonization, complement activation, and antibody-dependent

cytotoxicity.

11

**Immunoglobulin Classes**

There are five major antibody classes, IgM, IgG, IgA, IgD, and IgE, and each has distinct

functions.

**Clonal Selection of Lymphocytes**

· When antigens enter a secondary lymphoid organ, only the lymphocytes that specifically

recognize the antigen will respond; the antigen receptor they carry on their surface

governs this recognition.

· Lymphocytes may be immature, naïve, activated, effector, or memory cells.

**B-lymphocytes and the antibody response**

The Response to T-Dependent Antigens:

· B-cells present antigen to effector T-helper cells for inspection. If an effector T-helper

cell recognizes the antigen, it will deliver cytokines to the cell, initiating the process of

clonal expansion, which ultimately forms plasma cells that produce antibody.

· Under the direction of effector T-helper cells, the expanding B-cell population will

undergo affinity maturation and class switching, and form memory cells.

· In the primary response, a lag period occurs before antibodies can be detected; memory

cells are responsible for the swift and effective secondary response, eliminating invaders

before they cause noticeable harm.

The response to T-independent antigens:

T-independent antigens include polysaccharides that have multiple identical evenly spaced

epitopes and LPS.

**T-lymphocytes: Antigen Recognition and Response**

· The T-cell receptor recognizes antigen presented by major histocompatibility (MHC)

molecules.

· T-cytotoxic cells are referred to as CD8 T cell; T-helper are referred to as CD4 T-cells.

**Functions of Effector T-Cytotoxic (CD8) Cells**

· T-cytotoxic cells induce apoptosis in cell that produce proteins associated with danger,

they also produce cytokines that allow neighboring cells to become more vigilant against

intracellular invaders.

· All nucleated cells present peptides from endogenous protein in the groove of MHC class

molecules.

**Functions of Effector T-helper (CD4) Cells**

· T-helper cells respond to exogenous antigen, which are presented to MHC class II

molecules.

· T-helper 1 (Th1) cells judge antigens presented by macrophages, a responding Th1 cell

activates that particular macrophage and secrete cytokines that help orchestrate the

immune response.

12

· Th2 cells judge antigen presented by B-cells; a responding Th2 cell activates that

particular B-cell and supports actions that enhance its effectiveness

**Activation of T Cells**

· Naïve T-cells require signals to become activated, upon activation the cell stimulates its

own proliferation and then gain its effector functions.

· Dendritic cell sample material in tissues and then travel to the secondary lymphoid

organs to present the antigen to naïve T-cells. Those that detect molecules associated with

danger produce co-stimulatory molecules and are able to activate both subsets of Thelper-

cells

**Natural Killer (NK) Cells**

· NK cells mediate antibody-dependent cellular-cytotoxicity (ADCC).

· NK cells kill host that are not bearing MHC class I molecules on their surface.

**Lymphocyte Development**

**Generation of diversity**

Mechanisms used to generate the diversity of antigen specificity in lymphocytes include

rearrangement of gene segments, imprecise joining of those segments, and combinatorial

associations of heavy and light chains.

Negative Selection of Self-Reactions B-cells

Negative selection occurs as B cells develop in the bone marrow, cells which material binds to

their B-cell receptor are induced to undergo apoptosis.

**ANTIGENS**

**(Dr O. E. Ojo)**

Antigens are substances which are able to induce detectable immune responses when introduced

into an animal host. Immune responses could be cellular or humoral

**Requirement for antigenicity**

· Molecular size: molecules with high molecular weight are capable of eliciting a better

immune response than those with low molecular weight. That is Proteins > carbohydrates

> lipids > nucleic acids. Molecules with molecular weight less than 10,000 dalton are

weakly antigenic or non-antigenic.

· Chemical complexity: molecules with high complexity are good antigens

Polymers are more antigenic than monomer

· Genetic make-up of the animal host

The response of an animal to an antigen is regulated by genes

The ability to mount an immune response to a antigen varies with genetic

composition of the animal

· Method of antigen administration

Immune response may differ according to the route of administration

Level of immune response is dose-dependent

Excessively high dose may induce a state of specific unresponsiveness

**EPITOPES**

**(Dr O. E. Ojo)**

· Most foreign particles are composed of complex mixture of proteins, polysaccharides,

lipopolysaccharides, lipids and nucleoproteins

· Such large molecules have specific regions responsible for antigenicity

· Epitopes are regions on the surface of molecules that specifically trigger immune

reactions

· Epitopes are also called antigenic determinants

· An antigen mau possess more than one antigenic determinant

· The antigenic determinants on an antigen vary in immunogenicity

· Animal host respond better to an immunodominant epitope on an antigen

14

· An antigen may possess similar epitopes to those present on the host’s self antigen

· However, the cell of the immune system only recognize and respond to foreign epitopes

· The number of epitopes on an antigen is related to its size

· Usually about one epitope is present for each five kDa of protein

· Immunopotency describes the capacity of a region of an antigen molecule to serve as an

antigenic determinant and induce the formation of specific antibody

· Immunopotency is determined by:

Accesibility: exposure to the aqueous environment

Charge: electrical charges are dominant factor in specificity

Genetic factor: ability to induce immune response is under genetic control

**HAPTENS**

**(Dr O. E. Ojo)**

· Small molecules (e.g. drugs, hormones), or chemical groups with molecular wight of less

than 1000Da which when bound to other larger molecules can function as epitopes

· Haptens are too small to be appropriately processed and presented to the immune system

and are therefore not antigenic

· When haptens are linked to a larger molecule, a new epitope is formed on the larger

molecule

· When this is injected into an animal host, immune response develops with antibody

formation

· The antibody can react with the hapten in the larger molecule

· Haptens are non-immunogenic substances but can react with antibody in a specific

manner

· Antigens are capable of inducing cellular immunity mediated by T-lymphocytes but

haptens are unable to do so.

· The reactions of drugs which serve as haptens with body proteins may lead to allergies

· Examples of haptens: dinitrophenols, penicillin.

·

**ADJUVANTS**

**(Dr O. E. Ojo)**

· Substances that enhance the immune response to an antigen when administered along

with that particular antigen

· Mechanism of action:

Depot adjuvants: serve to protect antigen from rapid degradation and thereby

prolong immune responses

Particulate adjuvants: effectively deliver antigens to antigen presenting cells,

enhance cytokine production by antigen presenting cells, enhance T-helper cell

responses and enhance cell mediated immunity

Immunostimulatory adjuvants: enhance cytokines production, T-helper cell

response and enhance cell mediated immunity

· Examples:

Depot adjuvants: Aluminium phosphate, Aluminium hydroxide, Treund’s

incomplete adjuvants (water-in-oil emulsion)

Particulate adjuvants: liposomes, microparticles, immunestimulatory complex

Immunostimulatory a djuvants: glucose, dextran sulphate, detergents, saponins,

lipopolysaccharides, anaerobic corynebacteria, bacillus calmette-Guerin (BCG m.

boris), Borditella pertussis etc.

Mixed adjuvant: treund’s complete adjuvant (water-in-oil emulsion plus

mycobacterium)

**Tutorial Questions**

Define the following terms

i. Antigen

ii. Autoimmunity

iii. Haptens

iv. Adjuvants

v. Epitopes (*4 marks each = 20marks)*

**Tutorial Questions2 (10 marks)**

i. Describe lupus erythematosus cells

ii. Give the examples of systemic autoimmune diseases

iii. Outline three features of lymphocytic thyroiditis

16

iv. In equine polyneuritis, what acts as autoantigen?

v. What is the distinct clinical feature of reproductive autoimmune diseases resulting

from the injection of testicular extract along with freund’s complex adjuvants in male

animals? *(10 marks)*

**ANTIGEN-ANTIBODY REACTION**

**(Dr O. E. Ojo)**

When an antibody comes in contact with its homologous antigen, it becomes attached to it by

one of its of its combining sites which reacts with a determinant area on the antigen. This

reaction leads into formation of an antigen-antibody complex

Ag + Ab ---------------àAg-Ab complex

The forces that hold these together are at their strongest under physiological conditions of ionic

strength and pH. If the pH is lowered, the antigen-antibody complex will dissociate.

Features of antigen-antibody reaction:

Close proximity: non-covalent binding forces are involved in antigen-antibody combination.

The shape of each of the combining site on an immunoglobulin molecule is an accurate

mould of the shape of the antigenic determinant and the two must be brought into very close

contact to fit into each other.

Specificity: the union of an antigen with its antibody is specific. The antigen react with its

corresponding antibody and with no other. Specificity is dictated by the presence of

determinant groups on the antigen and the type and pattern of amino acids present in the

antigen-binding region of immunoglobulins.

pH range: physiological range of pH (7.2-8.2) is required for a firm union. The optimal

temperature for an antigen-antibody reaction depends on the type of antibody. IgM reacts

best at 40C (cryoglobulin) while IgG reacts best at 370C.

Optimal proportion: there is an optimum concentration where antigen-antibody reaction

occurs. This optimum concentration is referred to as equivalence zone. The occurrence of an

antigen-antibody reaction can be detected by the presence of some secondary phenomenon

such as precipitation or agglutination complex. The presence of cisible agglutination of

precipitation reaction will be inhibited by an excess of antibody and this is termed ‘prozone

phenomenon’.

17

**Forces Responsible for the Union of Antigen and Antibody**

The forces of interaction responsible for antigen-antibody reaction are the same as those seen in

other proteins such as enzymes and transport proteins. The final strength of the bond is a

summation of the various binding or repelling forces present on both antigen and antibody

molecules. Covalent chemical bonding is not important and there is no obligatory requirement

for charged groups on antigens. However, there can be strong attraction or repulsion between

negatively charged ions and positively charged ions on these molecules at physiologic pH. The

forces invoved in antigen-antibody union include the followings:

1. Electrostatic forces

2. Hydrogen bonding

3. Hydrophobic attraction

4. Van der waal forces

Electrostatic forces: these are due to the attraction between oppositely charged ionic groups on

proteins side chains. An example is the interaction between an ionized amino group (-NH3

+) on a

lysine of one protein and an ionized carboxyl group (-coo--) on a glutamate of another protein.

Hydrogen bonding: if molecules carrying hydrophilic groups such as –OH, -NH2 and –COOH

approach closely, they form hydrogen bridges which are relatively weak and reversible. The

interaction between threonine and tyrosine is an example of hydrogen boding.

Hydrophobic attraction: non-polar hydrophobic groups such as those of the side chains of valine,

leucine and phenylalanine tend to associate in an aquepus environment, just like oil droplets in

water merge to form a single large drop. It has been estimated that hydrophobic forces may

contribute up to 50% of the total strength of the antigen-antibody bond.

Van der waals forces: these are very weak forces which depend on interaction between the

external “electron cloud” of molecules. Complimentary electron cloud shapes on the combining

site of an antibody and on the surface determinant of an antigen fit the two molecules strongly

together like a lock and key.

**Antibody Affinity and Avidity**

The antibodies that are first produced by the body after it has been stimulated with an antigen do

not mate with so large an area of the antigenic seterminant as do those which are synthesized

later and especially those which appear after repeated immunization have been carried out. Thus,

antibodies produced soon after a first stimulation are very specific and have high affinity for a

18

particular area of the antigenic determinant. They are termed non-avid (i.e. the complexes they

formed with the antigen are easily broken down). The strength of the interaction of an antibody

with a monovalent hapten or a single antigenic determinant is referred to as affinity. Antibodies

produced later or after repeated immunization are avid. The strength of the interaction of an

antiserum with a fall antigen with its multiple determinants is termed avidity. The force binding

two determinant groups by antibody is usually many fold greater that the arithmetic sum of the

forces binding each separate antigenic determinant. Avidity makes for stronger bonds with the

antigen and often able to cross-react with other related antigens.

a. Early non-avid antibody molecules only combine with a small area of the antigenic

determinant

b. Later antibody, and antibody produced after repeated restimulation is very avid. It

combines strongly with a larger portion of the antigenic determinant than does non-avid

antibody.

c. Avid antibody is also able to combine with related antigenic determinants. The fit

however is not very close and the binding is weak.

**Mechanism of Protection by Antigen-Antibody Reaction**

Antibody can protect the body from infection or its effect by neutralizing soluble toxins, coating

organisms and thus promote phagocytosis, by direct lysis of organisms in the presence of the

compliment proteins and by preventing the spread of intracellular organisms.

**Consequences of Antigen-Antibody Reactions in-vitro**

Following the primary union of antigen to antibody in the laboratory, a number of events occur

which produce visible effects. This primary interaction gives rise to a number of secondary

phenomena such as precipitation, agglutination, flocculation, phagocytosis, cytolysis and

neutralization. These secondary reactions are the basis of a number of standard immunological

techniques. The primary reaction can simply be viewed as the specific recognition and

combination of the antigenic determinant with the binding site of its corresponding antibody.

Generally, primary tests are more sensitive than secondary tests. The quantitative tests that

employ the primary reaction include immunoflourescence, radioimmunoassay and

immunoenzymatic assays.

**Harmful Effects of Antigen-Antibody Reaction in the Body**

19

Antibody-antigen reactions in the body are not only helpful but can equally be harmful. In some

situations the immune attack on the invading organisms also damage host tissues. Autoimmune

reactions and hypersensitivity reaction and graft rejection are examples of harmful reactions.

**AUTOIMMUNITY**

**(Dr O. E. Ojo)**

· The body produces self-antigens

· Lymphocytes capable of binding and responding to self antigens in the body are

suppressed

· Self-antigens to which the immune system is exposed during foetal life are recognized as

self and the body develop tolerance to them

· Autoimmunity is a state in which the natural unresponsiveness of the lymphocytes

(tolerance) to self antigens is lost

· In autoimmunity, autoantibodies are produced which react with self components. This

may lead to disease condition and tissue damage

· Not all autoimmune responses are harmful. Infact, some are beneficial and crucial to

survival. Some autoantibodies serve physiological functions e.g. destruction of senescent

red blood cells

· The exact cause and mechanisms of autoimmunity are not well understood

· Autoimmunity could be mediated by either B cells or T cells (auto antibodies or T cells)

· **Mechanism of autoimmune diseases**

Normal immune response to an unusual or abnormal antigen

Abnormal immune response to a normal antigen: a situation in which regulations

preventing development of self-responsive T-cells fails

Aberrant response to a single specific antigen

General defect in the regulation of B- or T- cells functions

· **Normal immune response**

Normal immune response to a previously hidden antigen

Cross reactivity between an infectious agent and a normal body component

Abnormal antigen processing

20

· **Abnormal immune response**

Sustained immune response to hidden epitopes

Lymphoid tumour cells producing autoantibody

Defective destruction of self-reactive lymphocytes

· **Virus-induced autoimmunity**

Vaccine-induced autoimmunity: vaccines with adjuvants, especially excessive use

Example:

§ Endocrine diseases like lymphocytic thyroiditis, hyperthyroidism,

§ Neurological diseases: equine polyneuritis, canine polyneuritis,

degenerative myelopathy

§ Eye diseases: equine recurrent ureitis

§ Muscle diseases: myasthenia gravis, canine cardiomyopathy, polymyositis

§ Skin diseases: perphigus complex, epidermolysis bullosa

**AUTOIMMUNE DISEASES**

**(Dr O. E. Ojo)**

**Systemic autoimmune diseases**

· Associated with the presence of circulating immune complexes and complement in

tissues

· The deposition of immune complexes lead to chronic inflammation

· The initiating antigens are unknown but may well be infectious agents

· There is genetic predisposition linked with MHC

· Examples:

Systemic Lupus Erythematosus

· There is impaired clearance of apoptotic cells by macrophage phagocytosis

· Apoptotic cells accumulate in the tissue

· Nuclear fragments of apoptotic cells are processed by dendritic cells (antigen-presenting

cells)

· There is formation of autoantibodies (antinuclear antibodies, ANA)

· This leads to formation and deposition of immune complex and tissue damage

21

· There is dermatitis (skin lesions), polyarthritis, heamolytic anaemia, thrombocytopaenia,

proteinuria, positive ANA test, and positive LE cell test

· LE cells: cells that have phagocytosed opsonised nuclei oftern present in the bone

marrow of SLE patients

· Seen in humans, other primates, dogs, rats, horses, mice

**Sjogrens Syndrome: (**Horses, dogs)

· Characterized by keratoconjuctivitis sicca (conjuctival dryness), xerostomia (mouth

dyness) and rheumatoid factors

· Autoimmunity against salivary and lacrimal glands

· There is gingivitis, dental caries, excessive thirst, corneal dyness and abrasion leading to

kretitis and conjunctivitis as well as other ocular lesions\there is also rheumatoid arthritis

and polimuositis

· Autoimmune polyarthritis

· Deposition of immunoglobulins and immune complex within joints leading to joint

diseases

· Could be erosive polyarthritis (e.g reumathoid arthritis) or non-erosive (e.g. equine and

canine polyarthritis)

**Organ-specific/Tissue-specific Autoimmune Diseases**

Endocrine:

§ Lymphocytic thyroditis

§ Lymphocytic parathyroditis

§ Insulin-dependent diabetes mellitus

§ Atropic lymphocityx pancreatitis

§ Sutoimmune immune adrenatitis

§ Hyperthyroidism

Neurological

§ Degenerative neuropathy

§ Cerebellar degeneration

§ Equine polyneuritis

22

§ Steroid meningitis-arteritis

§ Canine polyneuritis

Eye diseases

§ Equine recurrent ureitis

§ Ureodermatological syndrome

Reproductive

Skin diseases

§ The pemphigus complex

§ Skin basement membrane disease

§ Alopecia areata

§ Relapsing poluchondritis

Nephritis

§ Autoimmune immune nephritis

§ Autoimmune haemolytic anaemia

§ Autoimmune immune thrombocytopenia

Muscle

§ Myasthenia Gravis

§ Polymyositis

§ Autoimmune masticatoryy myopathy

§ Canine cardinmyopathy

**Organ-Specific Autoimmune Diseases**

· Autoimmune diseases that affect a single organ or tissue

· Arises as a result of abnormal reponse to a small number of self- or foreign antigen but

not necessarily a major loss of control of the entire immune system

· Examples:

A Autoimmune endocrine diseases

I. Lymphocytic thyroditis

- Described in human, dogs and chicken

23

- Production of autoantibody against throglobulin which may also react with

triialothyronine (T3) or thyroxine (T4)

- There is dull, dry, coarse coat, scaling, hypotrichosis, hyperpigmentation, pyoderma.

Affected animals are fat sluggish and have area of in the skin

II. Lymphocytic parathyroiditis

i. Affects dogs and cats

ii. History of neurological or neuromuscular disorder like seizures

iii. There is marked lymphocalcaemia and low level of serum parathormones

iv. At histology, the normal parathyroid tissue is replaced by infiltrating

lymphocutes and some plasma cells

III. Insulin-dependent diabetes mellitus

i. There is development of autoantibodies against islet cells enzyme called

glutamic acid carboxylase

ii. There is atrophy of pancreatic islet and loss of b cells. Lymphocytes

infiltrate the islets.

B. Autoimmune neurological diseases e.g. development of autoantibody to brain tissue

following administration of rabies vaccines prepared in brain tissue

I. Equine polyneuritis

II. Peripheral myelin protein P2 acts as autoantigen stimulating the formation of

autoantibodies: There is a chronic granulomatous inflammation in the region of the

extradural nerve roots. The nerves affected are thickened and discoloured. There is loss

of myelinated axon, macrophage, lymphocyte, giant cells and plasma cells and plasma

cells infiltration and deposition of fibrous material in the perineurium

C. Autoimmune reproductive diseases

- Damage to the testes may release hidden antigens and consequently autoimmunity

- Injection of testicular extract in Treund’s complete adjuvant may produce

autoimmune orchitis in male animals

- The presence of sperm antigens in the circulation stimulates the production of IgE

or IgA autoantibodies

24

- The autoantibodies can agglutinate and immobilize sperm cells leading to

infertility

- Autoimmune dermatitis may occur in intact female dogs as a result of

hypersensitivity to endogenous progesterone or oestrogen

- This autoimmune dermatitis may coincide with oestrus or pseudopregnancy and it

is characterized by bilateral erythema and popular eruption with intense pruritus

D. Autoimmune Muscle Diseases

a. Myasthenia Gravis

i. Seen in humans, dogs and cats

ii. Disease of skeletal muscle characterized by abnormal fatique and

weakness following mild exercise

iii. There is degradation of acetylcholine receptors by IgG autoantibodies

iv. Autoantibodies also block acetylcholine binding sites and trigger

compliment-mediated damage

v. The deficiency of acetylcholine receptor: this leads to failure of

transmission of nerve impulses across the motor end-plate of striated

muscle

E. Autoimmune Haemolytic Anaemia

i. Destruction of red blood cells mediated by autoantibodies to red blood

cells antigens

ii. Red blood cells destruction could be intravascular haemolysis mediated by

complement or phagocytosis of antibody coated RBC in spleen and liver

by macrophages (extravascular)

iii. Autoimmune haemolytic anaemia has been attributed to alteration in red

blood cell surface antigen induce by drugs or viruses

iv. The condition is characterized by anaemia, weakness, lethargy, fever,

uterus and hapto- splebomegaly. There could be tarchycardia, anorexia,

vomiting or diarrhea

v. It has been described in human, dogs, horses, cats, mice, cattle and rabbits

25

**CYTOKINES**

**(Dr O. E. Ojo)**

· Proteins secreted by the cells of the immune system that regulate the immune

response by communicating among cells

· **Characteristics:**

§ Cell rarely secrete only one cytokine at a time e.g. macrophages secrete at least

five: IL-1, IL-6, IL-12, IL-18, and TNF-a

§ They affect a wide variety of cells and organs

§ Many different cytokines may have similar effect (redundancy) e.g. IL-1, TNF-a,

TNF-b, IL-6, all have pyrogenic effect

· Types and Groups:

1. Interleukins: cytokines that regulate the interaction between lymphocytes and

other leukocytes. They are numbered sequentially in order of their discovery, IL-1

– IL-30

2. Interferons

- Antiviral cytokines produced in response to immune stimulation and virus

infection

- Interferes with viral RNA and protein synthesis

- There are 2types: type I and type II

- Type I: interferon alpha (IFN-a) and interferon beta (IFN-b) (antiviral)

- Type II: interferon gamma (IFN-g) (immune activation)

- Some interferon are important in maintenance of pregnancy (e.g. type I

IFN-d)

3. Tumor Necrotic Factors (TNFs)

- Derived from macrophages and T-cells

- They destroy tumor cells

- They are important in acute inflammatory reactions especially TNF-a

- They play dominant role in immune regulation and inflammation

4. Growth Factors

- Colony stimulating factors

26

- Control leukocyte production by regulating stem cell growth

- Make immune cells available for body defence

5. Chemokines

- Regulates leukocyte circulation and migration (chemotaxis) during

inflammation

- They also activate leukocytes

- Example: Interleukin-8 (CXCL-8)

**Functions of Cytokines**

i. Cytokines are produced by antigenic stimuli acting through the T-cell and B-cell

receptors

ii. Antigen-antibody complex acting through Fc receptors

iii. Super antigens acting through the T-cell receptors

iv. Pathogen-associated molecules such as lipopolysaccharides acting through toll-like

receptors

**Pattern of Cytokine activities**

Autocrine: they bind to receptors on the cell that produced them.

Paracrine: they bind only to receptors on cells in close proximity to the cell of origin

Endocrine: they spread throughout the body thereby affecting cells in distant location from the

source of production

**Functions**

· when bound to target cells, cytokines may induce the target cell to divide or

differentiate

· They may stimulate the production of new proteins by the target cell

· They may inhibit cell division and differentiation

· They may inhibit the process of protein synthesis in the target cell

· Most cytokines act on different target cell types and initiate different responses in

each. This phenomenon in termed PLEIOTROPY

· Many different cytokines may act on a single target cell. This is termed

REDUNDANCY e.g. IL-3, IL-4, IL-5, IL-6, all affect B-cell function

27

· Some cytokines work optimally only when in association with other cytokines. This

is called SYNERGY e.g.IL-4 combines with IL-5 to stimulate B-cell switching to IgE

synthesis

· Some cytokines may prevent/inhibit the action of others. This is called

ANTAGONISM e.g. IL-4 and IFN-g are mutual antagonists.

**IMMUNE RESPONSE TO TUMOUR**

**(Dr O. E. Ojo)**

· Events leading to the development of tumour are pooly understood

· Tumour arises as a result of:

1. Infection with a tumourgenic virus e.g. herpes virus, papilloma virus

2. Mutation in gene controlling cell growth

3. Expression of pre-existing oncogenes (tumour genes)

4. Disturbance in normal growth control mechanisms so that a genetically

normal cell no longer displays normal differentiation

**Tumour antigens**

1. Antigens expressed on chemically or physically induced tumours

2. Antigens expressed on virally induced tumours

3. Antigens associated with oncodevelopmental products

4. Antigens of spontaneous tumour

**Types of Tumour Antigens**

i. Antigens of chemically induced tumours

ii. Antigens of virally induced tumours

iii. Onco-developmental tumour antigens

iv. Antigen of spontaneous tumours

· The major difference between a normal cell and a tumour cell is a loss of regulated

cell growth as a result of multiple mutation

· Mutation may make the tumour cells express abnormal proteins on their surfaces

28

· The abnormal proteins may be recognized by the body’s defence mechanism as being

foreign

· This recognition will induce immunological attack

**Antigenic Features of Tumour Cells**

Changes on the cell surface of tumour cells that make them different from the normal cells

- loss or gain of histocompatibility antigen

- loss of blood group carbohydrates

- appearance of virus-associated antigen (tumour associated viral antigen TAVA)

- tumour-associated transplantation antigens common for the tumour of the same

hytologic type (TATA)

- Tumour-specific transplantation antigen present on only one tumour type (TSTA)

- Antigen detected only by serologic reaction unique for a given tumour (Tumourassociated

serologic defined antigens TASA)

- Tumour-associated developmental antigens (TADA): markers shared by embryonic

or developing tumours and established tumours

Tumour-associated antigens

- Tumour cells may produce new proteins

- Tumour cells may produce excessive amounts of normal proteins

1. Some tumour cells may express the products of developmental genes that are turned off

in adult cells and are normally only expressed early in an individual’s development.

These proteins are called onco foetal antigens e.g. carcinoembryonic antigen (CEA,

CD66e) is a glycoprotein produced by tumour cells of the gastrointestinal tract which

should normally be found only in fetal intestine; a-fetoprotein produced by lepatoma

cells is an onco-foetal antigen normally found only in the foetal liver

- Onco-fetal antigens are poor immunogens and do not provoke protective

immunology

- Measurement of their level in blood may be useful in diagnosis and in monitoring

the progress of tumour

2. Antigens to spontaneous tumour

- Rarely demonstrate tumour-specific antigens/new antigens

- Normal antigens are expressed in unusual quantities

29

- There may be abnormal proteins associated with cell division e.g. glycosylation of

proteins

3. Antigens due to oncogenic viruses

- Tumour cells gained new antigenic character of inducing virus

- Antigens are coded in viral genome but not part of the virion

4. chemically induce tumour

- chemical may induce mutation

- tumour cells therefore expressed mutated surface antigens

- carcinogenic chemicals may produce different mutation

- Tumour induced by a particular chemical may be antigenically different

- Resistant to one chemically induced tumour does not prevent the growth of

another tumour induced by same chemical

· The ability of tumour cells to elicit immune reaction depends on their ability to

cause/induce inflammation

· A tumour cell that does not invade the lymphoid organs may not elicit immune

reaction

· Tumour cells that invade the lymphoid organs may elicit either a strong or a weak

immune reaction

· Tumour cells that are processed by dendritic cells elicit a strong T-cell response

· Tumour cells that are walled off may not be processed enough and thus only a weak

immune response

· Tumour cells that produce inflammation in tissue also trigger dendritic cell activation

and processing

**Effector Mechanism in Tumour Immunity**

§ Tumour cells express different antigens from normal cells

§ However, tumour cells are not always recognized as foreign

§ The normal molecules on tumour cells are not appropriately presented to the immune

cells especially cytotoxic T-cells

§ However, tumour cells may be attacked by natural killer cells, cytotoxic T-cells, activated

macrophages and antibodies

30

§ Natural killer cells are the most important in immunity to tumour

Humoral response

§ Antibodies can be demonstrated in the body against tumour

§ The presence of antibodies does not induce resistance to tumour

§ Antibody detection are important in serological characterization and isolation of tumourassociated

antigen

§ Therefore, antibodies can mediate anti-tumour activities

o Compliment-mediated lysis

o Opsonization and phagocytosis

o Loss of cell adhesion

Cell-mediated responses

§ Direct lysis by T-lymohocytes

o Immune T-lymphocytes can specifically recognize and kill target cells that share

the same antigens as the immunizing tumour cells

o Able to destroy solid tissue as well as dispersed tumours

§ Antibody-dependent cell-mediated cytotoxicity (ADCC)

o Tumour target cells coated with IgG can be destroyed by effector celss such as

granulocytes, macrophages and killer cells

§ Killing by activated macrophages

o Activated macrophages have tumouricidal capabilities

§ Lysis by natural killer cells

o They can discriminate between normal and abnormal cells

**Evasion of Immune Mechanism by Tumour Cells**

§ Tumour in privilege sites

o Tumour in the central nervous system and eyes

o Effector cells can not reach them

§ Antigenic modulation

o Loss of antigenicity or change in antigenic marker

o Tumour cells avoid immunologic destruction

§ Enhancement and blocking factors

31

o Humoral factors enhance tumour survival by interfering with the cellular assault

against tumour

o Early production of antibodies may result in absorption to tumour surface and

most tumour antigen

o This prevent induction of T-killer cell-mediated immunity

§ Immune capacity versus tumour mass

o If tumour challenge is sufficiently larger, the animal may succumb to the growth

of lethal cancer

§ Suppressor of T-lymphocytes

o Tumour-specific suppressor T-cels have been demonstrated in tumour-bearing

mice and may play a role in the apparent ineffectiveness of the response in

tumour-bearing mice

§ Suppression mediated by the tumour

o Some tumour synthesize various materials such as prostagladins which affect the

activity of immune response

**Immunodiagnosis**

Based on:

1. Detection of tumour markers e.g. alpha fetoproteins, carcinoembryonic antigen (CEA),

prostate-specific antigens (PSA)

2. detection of tumour-specific immunity using the presence of humoral or cellular

antibodies autoimmune immunity for diagnosis

**Immunotherapy**

· Active immunotherapy

- Stimulate the immune system non-specifically e.g. use of attenuated strain of

*glycobaterium bovis* BCG which activate macrophages and stimulates cytokines

release thereby promoting T-cells activity

- Use of tumour cells/antigens to stimulate immune response X-irradiated,

neuraminidase or glutaraldehyde-treated cells can be used in tumour vaccines

· Passive immunotherapy

- Cytokine therapy: IFN-a, TFN-a, IL-2

32

- Activated cytotoxic cell therapy: NK and NK-like cells activated

- Antibody therapy: use of monoclonal antibodies

**VACCINES AND VACCINATION**

**(Dr O. E. Ojo)**

· The term vaccine was coined from vacca (cow)

· Edward Jenner was the first to discover the use of vaccine to prevent infectious disease

· Jenner used vaccinia virus of cow to protect against smallpox in human in 1798

· Vaccines can be directed against infectious agents or its toxin

**History of vaccination**

Ancient time practices of vaccination fir disease protection:

- King Mithridates of Pontus protected himself from poison by drinking the blood of duck

given the poison

- Pliny the Elder in Rome ate liver of ‘mad dogs’ to protect against rabies

- Edward Jenner inoculated James Philip on the arm with material from a typical cowpox

on the hand of a milk maid

- Pasteur produced different vaccines against livestock diseases: *Fowl cholera* (using dead

bacteria to protect chicken in 1880). *Anthrax vaccine* for cattle and sheep in 1881 by

growing *B. anthracis* at 420C. *Rabbis vaccine* in 1885

**Types of vaccines**

· Homologous vaccines

Developed from the pathogen or from its virulent mutant e.g. *Salmonella typhi*

vaccine for the protection of typhoid in human, *E. Dublin* vaccine to protect

animals from virulent strains.

· Heterologous vaccines

Developed from different organisms to protect against another sharing close

antigenic properties e.g. rinderpest vaccine (TCRV) used for the protection of

goats from PPR

· Autogenous vaccine

33

Vaccine developed from organism recovered/isolated form an infected animal and

the vaccine administered to the same animal for protection. Used in case of

chronic diarrhea of animals

**VACCINATION**

**(Dr O. E. Ojo)**

· Active immunization

· Artificially acquired

· Long lasting protection against infectious agents

Advantages:

Better and cheaper than chemotherapy

No specific treatment for diseases (especially viral diseases) but they can only be

prevented

Prevention is better than cure; prevention of zoonotic disease

Decreases morbidity

Decreases mortality

· Duration of protection is influenced by:

Age

Immune complexes

Nutritional status

Nature of the antigen

Presence of adjuvants

Presence of maternal antibodies

Modified Live vaccine confers more prolonged immunity than killed, inactivated

vaccines

**Routes of administration**

· Aphthization

A crude method produced by Fulani herdsmen

In an outbreak of foot-and-mouth disease, cattle rearer obtained saliva from

clinically-ill cattle and rub it on the tongue of healthy cattle in the flock.

34

Infection is in the head and recovery is synchronized

· Mucus membranes

Newcastle disease vaccines given intravenously to day-old chicks

Infectious laryngotracheotis (ILT) vaccines rubbed into the mucus membranes of

cloaca

· Subcutaneous

*B. pertusis* vaccine, *Brucella S19, T1 vaccine* of CBPP, typhoid vaccine (TAB)

· Intramuscular

Yellow fever vaccine, tetanus toxoid

· Intradermal

Pox vaccines, tuberculosis (BCG) vaccine

· Oral

*E. coli* vaccine

Poliomyelitis vaccine

**Time of vaccination**

· Depends on the disease to be prevented

· Influence by government policies

· Age susceptibility of host

· Examples: BCG, polio, PPR, cumboro, rabies

· Pregnant animals may be vaccinated for passive protection of offspring

*C. perfrigens* type B and type D infection in lamb prevented by vaccinating

pregnant ewes 4 weeks and 2 weeks before lambing

*Brucella* vaccine given to calves 4-8 months old. *M. paratuberculosis* given to 30-

day old calves

**Advantage of vaccination over chemotherapy**

· Some diseases cannot be treated but can only be prevented e.g. viral diseases

· Vaccination is cheaper than chemotherapy

· Production of organic meat

**Danger of vaccination**

35

· Accidental self-innoculation

· Precipitation of the disease to be prevented

· Vaccine failure

· Hypersensitivity

· Contamination of vaccine by extraneous organism

**Vaccine production**

· Capital intensive

· Require skill personnels

**Process of vaccine preparation**

Killed viral or bacterial vaccine

Inactivated toxin or toxoids

Line attenuated vaccines

Recombinant vaccines

· Killed vaccines

Chemical killing e.g. formalin, beta-propiolactone

Heat killing, high temperature

Radiation killing e.g. UV light, ultrasonic wave, x-rays

Viability may be destroyed i.e. decreased immunogenicity

Beta-propiolactone destroys nucleic acid and preserve antigenicity

· Toxoids

Detoxified toxin

Use formalin or glutenaldehyde for detoxification

Antigenicity increased by adsorption on mineral carrier

· Live attenuated vaccines

Passages/several subculturing in monolayer tissue culture e.g. viral vaccine

Cultivation at abnormal temperature e.g. *B. anthracis* at 420C for anthrax vaccine

Culture on unusual media e.g. *B. abortus* S19 on potato medium or ox bile

medium for BCG

Use of avirulent strain of poor growth e.g. streptomycin-dependent mutants of

blingis spp

36

Biochemically-deficient *S. typhimurium*

· Recombinant vaccine

Mutant hybrids

Safe and effective

Genetic modification

Live attenuated:

a number of route of administration because they have relevant antigens for

protective immunity

high level of cell-mediated and humoral and mucosal surface protection

no need for adjuvants; they can replicate in the recipients

booster dose can be spaced widely. Spaced interval if needed because of good

immunological memory

Live attenuated vaccines can produce adverse reactions such as

immunosupression

Inactivated:

· Can induce high level of antibodies but less cell-mediated and mucosal immunity.

· Inactivated vaccines often contain many irrelevant antigenic substances some with

undesirable biological activity

Advantages of Live vaccines

Good antigen with good antibody production

Excretion of vaccine strains may protect those infected with the strain

Back mutation extremely rare. When present, it is due to deletion rather than

spontaneous mutation

Early non-specific protection is initiated within 1-2 days of administration in

cases of viral

Disadvantages of Live vaccine

Residual virulence may produce clinical signs e.g. S19 in bulls may produce

orchitis

Cannot withstand rough handling; storage condition is very strigent

37

Limited shelf-life or danger of contamination with other organism found on tissue

culture

Mutation of vaccine organism

Immunosuppression especially in young

Advantages of Killed Vaccine

Can withstand rough handling and ambient temperature

No overt diseases produced

Long shelf-life

Disadvantages of Killed Vaccine

Killing destroys essential antigens

Poor immunogens, therefore requires several inoculation

Adjuvants may be required with possible adverse reaction

Repeated vaccination may lead to hypersensitivity

Note: many disease agents still don’t have vaccines for their prevention

**Recombinant Vaccine/Biotechnology:** subunit or genetically engineered live vaccines

Increased efficacy

Increases safety

**RECOMBINANT VACCINES**

There are three categories:

1. Type 1 recombinant vaccine: composed of antigens produced by genetic engineering

2. Type II recombinant vaccine: genetically attenuated microorganism

3. Type III recombinant vaccine: composed of modified live viruses or bacteria into which

DNA encoding a particular antigen is introduced

Type I: subunit proteins produced by recombinant bacteria or other microorganisms. DNA

encoding the required antigen is isolated and introduced into a suitable bacterium or yeast in

which the recombinant gene/antigen is expressed. There is need for adjuvants to enhance their

immunogenicity. Have been used for FMD, feline leukemia and Lyne diseases (*Borrlia*

*burgdoferi)*

38

Type II: virulent microorganisms are rendered less virulent by gene deletion or site directed

mutagenesis. The genome of large DNA viruses (e.g. ) contains many genes not required for in

vitro replication. With DNA technology, a pseudorabies vaccine lacking the gene for thymidine

kinase has been produced. Thymidine kinase is required by this herpes virus to replicate in nondividing

cells such as neurons. The vaccine virus with deleted gene can infect neurons but unable

to replicate in their cells. The deleted mutants induce a protective immune response in pigs.

Deletion of the gene encoding for the glycoprotein gI on the pseudorabies virus prevent

differentiation of infected pigs which permit differentiation of infected pigs which produce

antibodies against gI from vaccinated pigs which lack the antibodies. Thus vaccination can be

done in countries where the disease is being eradicated without interfering with serological

recognition and removal of the infected pigs.

Type III: Necessitated because vaccine failure often result from delivery system.

Type III: modified live organism called vectors into which a gene is inserted and this organism

also serves as a delivery system in the recipient. Vector must not pose any threat to the host.

A vaccinia virus vector carrying the rabine G glycoprotein gene has been successfully used as an

oral vaccine administered to wild carnivores in baits.

39

**THE COMPLEMENT SYSTEM**

**(Dr. Michael Agbaje)**

**Components and functions of the complement system**

· complements (C) are heat labile proteins found in mammalian blood and make up the

complement system.

· This complex, multi-component system is composed of about 26 proteins.

· "Complement cascade" is non-specific but it must be activated in order to function.

The functions of complements include:

· making bacteria more susceptible to phagocytosis

· directly lysing some bacteria and foreign cells

· producing chemotactic substances

· increasing vascular permeability

· causing smooth muscle contraction promoting mast cell degranulation

Activation of the complement system

· Two distinct pathways; the *classical pathway* and the *alternate pathway*.

· Once initiated, a cascade of events (the "complement cascade") ensues, providing the

functions listed above.

· Some complement components are numbered (e.g. C1, C2, C3, etc.) while others are

referred to as "Factors".

· Some complement components must be enzymatically cleaved to activate their function;

others simply combine to form complexes that are active.

**ACTIVATION OF THE COMPLEMENT CASCADE**

**Classical Pathway**

· Starts with C1; C1 binds to immunoglobulin Fc (primarily IgM and IgG);

· C1 is composed 3 subunits; C1q, C1r, C1s.

· C1q (glycoprotein) is the actual recognition portion.

· C1q is made up of hydroxyproline and hydroxylysine that looks like a tulip flower.

40

· Upon binding via C1q, C1r is activated to become a protease that cleaves C1s to a form

that activates (cleaves) both C2 and C4 to C2a/b and C4a/b.

· C2b and C4b combine to produce C3 convertase (C3 activating enzyme). C4a has

anaphylactic activity (inflammatory response) and flows away.

· C3 is central to both the classical and alternative pathways.

· In classical, C4b2b (C3convertase) cleaves C3 into C3a/b. C3a is a potent anaphylatoxin.

· C3b combines with C4b2b to form C4b2b3b complex that is a C5 convertase. C3b can

also bind directly to cells making them susceptible to phagocytosis.

· C5 is converted by C5 convertase (i.e. C4b2b3b) to C5a/b. C5a has potent anaphylatoxic

and chemotaxic activities. C5b functions as an anchor on the target cell surface to which

the lytic membrane-attack complex (MAC) forms.

· MAC is formed by C5b, C6, C7, C8 and C9. Once C9 polymerizes to form a hole in the

cell wall, lysis ensues.

***Classical Pathway***

Component cleavage

Enzymatic activity

Component assembly

41

**Components of the Classical Pathway**

**Native**

**component**

**Active**

**component(s)**

**Function(s)**

**C1(q,r,s)**

**C1q Binds to antibody that has bound antigen, activates C1r.**

**C1r Cleaves C1s to activate protease function.**

**C1s Cleaves C2 and C4.**

**C2**

**C2a Unknown.**

**C2b Active enzyme of classical pathway; cleaves C3 and C5.**

**C3**

**C3a Mediates inflammation; anaphylatoxin.**

**C3b**

**Binds C5 for cleavage by C2b. Binds cell surfaces for**

**opsonization and activation of alternate pathway.**

**C4**

**C4a Mediates inflammation.**

**C4b**

**Binds C2 for cleavage by C1s. Binds cell surfaces for**

**opsonization.**

**Components of the Alternate Pathway**

**Native**

**component**

**Active**

**component(s)**

**Function(s)**

**C3**

**C3a Mediates inflammation; anaphylatoxin.**

**C3b**

**Binds cell surfaces for opsonization and activation of**

**alternate pathway.**

**Factor B**

**B Binds membrane bound C3b. Cleaved by Factor D.**

**Ba Unknown.**

**Bb Cleaved form stabilized by P produces C3 convertase.**

**Factor D D Cleaves Factor B when bound to C3b.**

**Properdin P Binds and stabilizes membrane bound C3bBb.**

42

**Components of the Membrane-Attack Complex**

**Native**

**component**

**Active**

**component(s)**

**Function(s)**

**C5**

**C5a Mediates inflammation; anaphylatoxin, chemotaxin.**

**C5b**

**Initiates assembly of the membrane-attack complex**

**(MAC).**

**C6 C6 Binds C5b, forms acceptor for C7.**

**C7 C7**

**Binds C5b6, inserts into membrane, forms acceptor for**

**C8.**

**C8 C8 Binds C5b67, initiates C9 polymerization.**

**C9 C9n**

**Polymerizes around C5b678 to form channel that causes**

**cell lysis.**

**Alternate Pathway**

· Initiated by immunologic (e.g. IgA or IgE) or non-immunologic (e.g. LPS) means.

· Cascade begins with C3.

· As a result of spontaneous cleavage of C3, small amount of C3b is always found in

circulating in the blood but concentration is always in check by some disintegrating

factors in the blood.

· When C3b binds covalently to sugars on a cell surface (Microbes), it can become

protected.

· Factor B binds to C3b on the cell surface.

· In the presence of Factor D, bound Factor B is cleaved to Ba and Bb; Bb contains the

active site for a C3 convertase.

· Next, properdin binds to C3bBb to stabilize the C3bBb convertase on cell surface leading

to cleavage of C3. Finally, a C3bBb3b complex forms and this is a C5 convertase,

43

cleaving C5 to C5a/b. Once formed, C5b initiates formation of the membrane attack

complex as described above.

· Only Gram-negative cells can be directly lysed by combination of antibody and

complement;

· Gram-positive cells are mostly resistant to the above combination. However,

phagocytosis is greatly enhanced by C3b binding (phagocytes have C3b receptors on

their surface) and antibody is not always required. In addition, complement can neutralize

virus particles either by direct lysis or by preventing viral penetration of host cells.

***Alternate Pathway***

Component cleavage

Enzymatic activity

Component assembly

**REGULATION OF THE COMPLEMENT CASCADE**

· Complement activation is mediated via 3 proteins and affects the complement component

C3b due to it central role in both pathways of complement activation.

44

1. **C1 Inhibitor** inhibits the production of C3b by combining with and inactivating C1r and

C1s. This prevents formation of the C3 convertase, C4b2b.

2. **Protein H** inhibits the production of C3b by inhibiting the binding of Factor B to membranebound

C3b, thereby preventing cleavage of B to Bb and production of the C3 convertase,

C3bBb.

3. **Factor I** inhibits the production of C3b by cleaving C3b into C3c and C3d, which are

inactive. Factor I only works on cell membrane bound C3b, mostly on red blood cells (i.e.

non-activator surfaces).

**HYPERSENSITIVITY**

**(Dr. Michael Agbaje)**

· This occurs due to inappropriate response of the immune system to antigen.

· There are four different types of hypersensitivities that result from different alterations of

the immune system. These types are classified as:

· Type I: Immediate Hypersensitivity

· Type II: Cytotoxic Hypersensitivity

· Type III: Immune Complex Hypersensitivity

· Type IV: Delayed Hypersensitivity

**TYPE I HYPERSENSITIVITY**

Type I or Immediate Hypersensitivity can be illustrated by considering the following experiment:

1. First, a guinea pig is injected intravenously with an antigen. For this example, bovine serum

albumin (BSA, a protein) will be used. After two weeks, the same antigen will be re-injected

into the same animal. Within a few minutes, the animal begins to suffocate and dies by a

process called *anaphylactic shock*.

2. Instead of reinjecting the immunized guinea pig, serum is transferred from this pig to a

"naive" (unimmunized) pig. When this second guinea pig is now injected with BSA, it also

45

dies of anaphylactic shock. However, if the second pig is injected with a different antigen

(e.g. egg white albumin), the pig shows no reaction.

3. If immune cells (T-cells and macrophages instead of serum) are transfered from the

immunized pig to a second pig, the result is very different; injection of the second pig with

BSA has no effect.

These results tell us that:

· The reaction elicited by antigen occurs very rapidly (hence the name "immediate

hypersensitivity").

· The hypersensitivity is mediated via serum-derived components (i.e. antibody).

· The hypersensitivity is antigen-specific (as one might expect for an antibody-mediated

reaction).

The details of this reaction can be summarized as follows:

1. Initial introduction of antigen produces an antibody response. More specifically, the type of

antigen and the way in which it is administered induce the synthesis of IgE antibody in

particular.

2. Immunoglobulin IgE binds very specifically to receptors on the surface of mast cells, which

remain circulating.

3. Reintroduced antigen interacts with IgE on mast cells causing the cells to degranulate and

release large amounts of histamine, lipid mediators and chemotactic factors that cause

smooth muscle contraction, vasodilation, increased vascular permeability, broncoconstriction

and oedema. These reactions occur very suddenly, causing death.

Examples of Type I hypersensitivities include allergies to penicillin, insect bites, molds, etc.

A person's sensitivity to these allergens can be tested by a cutaneous reaction. If the specific

antigen in question is injected intradermally and the patient is sensitive, a specific reaction

known as *wheal and flare* can be observed within 15 minutes. Individuals who are

46

hypersensitive to such allergens must avoid contact with large inocula to prevent

anaphylactic shock.

**TYPE II HYPERSENSITIVITY**

· Type II or Cytotoxic Hypersensitivity also involves antibody-mediated reactions.

However, the immunoglobulin class (isotype) is generally IgG.

· In addition, this process involves K-cells rather than mast cells. K-cells are, of course,

involved in antibody-dependent cell-mediated cytotoxicity (ADCC).

· Type II hypersensitivity may also involve complement that binds to cell-bound antibody.

The difference here is that the antibodies are specific for (or able to cross-react with)

"self" antigens. When these circulating antibodies react with a host cell surface, tissue

damage may result.

Examples of Type II hypersensitivity include:

· **Pemphigus:** IgG antibodies that react with the intracellular substance found between

epidermal cells.

· **Autoimmune hemolytic anemia (AHA):** This disease is generally inspired by a drug such

as penicillin that becomes attached to the surface of red blood cells (RBC) and acts as hapten

for the production of antibody which then binds the RBC surface leading to lysis of RBCs.

· **Goodpasture's syndrome:** Generally manifested as a glomerulonephritis, IgG antibodies

that react against glomerular basement membrane surfaces can lead to kidney destruction.

**TYPE III HYPERSENSITIVITY**

· Type III or Immune Complex hypersensitivity involves circulating antibody that reacts

with free antigen. These circulating complexes can then become deposited on tissues.

Tissue deposition may lead to reaction with complement, causing tissue damage. this type

of hypersensitivity develops as a result of systematic exposure to an antigen and is

dependent on i) the type of antigen and antibody and ii) the size of the resulting complex.

More specifically, complexes that are too small remain in circulation; complexes too

large are removed by the glomerulus;

· intermediate complexes may become lodged in the glomerulus leading to kidney

damage.

47

Example of a Type III hypersensitivity is **serum sickness**, a condition that may develop when a

patient is injected with a large amount of e.g. antitoxin that was produced in an animal. After

about 10 days, anti-antitoxin antibodies react with the antitoxin forming immune complexes that

deposit in tissues. Type III hypersensitivities can be ascertained by intradermal injection of the

antigen, followed by the observance of an "Arthus" reaction (swelling and redness at site of

injection) after a few hours.

**TYPE IV HYPERSENSITIVITY**

Type IV or Delayed Hypersensitivity can be illustrated by considering the following experiment:

1. First, a guinea pig is injected with a sub-lethal dose of *Mycobacterium tuberculosis* (MT).

Following recovery of the animal, injection of a lethal dose of MT under the skin produces

only erythema (redness) and induration (hard spot) at the site of injection 1-2 days later.

2. Instead of reinjecting the immunized guinea pig, serum is transfered from this pig to a

"naive" (unimmunized) pig. When this second guinea pig is now injected with MT, it dies of

the infection.

3. If immune cells (T-cells and macrophages instead of serum) are transfered from the

immunized pig to a second pig, the result is very different; injection of the second pig with

MT causes only erythema and induration at the site of injection 1-2 days later.

4. In a separate experiment, if the immunized guinea pig is injected with a lethal dose of

*Listeria monocytogenes* (LM) instead of MT, it dies of the infection. However, if the pig is

simultaenously injected with both LM and MT, it survives.

These results tell us that:

· The reaction elicited by antigen occurs relatively slowly (hence the name "delayed

hypersensitivity").

· The hypersensitivity is mediated via T-cells and macrophages.

· The hypersensitivity illustrates both antigen-specific (T-cell) and antigen non-specific

(macrophage) characteristics.

48

1. Initial introduction of antigen produces a cell-mediated response. *Mycobacterium*

*tuberculosis* is an intracellular pathogen and recovery requires induction of specific T-cell

clones with subsequent activation of macrophages.

2. Memory T-cells respond upon secondary injection of the specific (i.e. MT) antigen, but not

the non-specific (i.e. LM) antigen.

3. Induction of the memory T-cells causes activation of macrophages and destruction of both

specific (MT) and non-specific (LM) microorganisms.

**Immune responses to infectious agents**

**(Dr. Michael Agbaje)**

**The immune Response to Viral Infection**

Viruses constitute some of the most successful pathogens responsible for significant morbidity

and mortality in animal and human populations. This is possible because these organisms have

the potentials to evolve a range of strategies to circumvent or inhibit the host immune response.

Some these viruses (e.g retroviruses such as feline leukaemia virus, Fel V) have the ability to

integrate their genetic material into the host genome, others are able to alter their antigenic

appearance to produce repeated epidemics or pandemics of disease (e.g human and animal

influenza viruses) and yet other viruses are able to capture host genes and express host-related

proteins that interfere with development of the protective immune response (e.g the capture of

the human IL-10 gene by Epstein-Barr virus).

In an attempt to discuss immune response to virus infection, we shall focus on how the

immune system might handle a viral infection of the enterocyte lining of the intestinal tract, as

might be seen, for example, an intestinal rotavirus of domestic livestock. Upon arrival of

infectious virus particles at their target surface, they are often confronted by a myriad of innate

immune defences relevant to that surface as the first line of defence. In the intestinal mucosa

these will include the enterocyte barrier, luminal secretions coating surface of that barrier

(including mucus, antimicrobial enzymes and defensins and poly-reactive immunoglobulins) and

other innate immune cells that normally populate the epithelial compartment (e.g the TCR T

cells) and the underlying lamina propria (e.g macrophages, dendritic cells and NK cells).

Infection of host cells by virus particles generally begins by binding to a receptor

molecule expressed on the surface of the target cell. This receptor molecule is a normal host cell

49

surface protein that the virus employs as a receptor or co-receptor to access target cell. In our

model example, the virus interacts with receptor on the enterocyte surface to gain access to the

host cell. Once inside the cell, the virus is to replicates itself by producing new virions that might

eventually exit the infected cell (after which it will have been destroyed) to infect new targets. In

a bid for host cells to defend themselves and ultimately the host, most virus-infected cells begin

to secrete the antiviral cytokines IFN-α and IFN-β. These antiviral interferon transmits messages

to uninfected adjacent cells by binding to their receptors and stimulating the uninfected cell to

produce a legion of other proteins that aid in resisting the invading viral particle. The antiviral

cytokines (interferons) may also positively induce local NK cells to act. Alternatively, the

infected cell may process and present virus antigen in the context to MHC class I and II

molecules for other immune cells like macrophages to act.

Following viral infection, antigen presenting cells (APC) like dendritic cells may sample

virus antigen or even become infected by virus particles, allowing classic processing and

presentation by these APCs. The interaction between virus and APCs involves viral Pathogen

Associated Molecular Patterns PAMPs (often of nucleic acid origin) and dendritic cell PRRs

(pattern recognition receptor) that occur in the cytoplasm. These interactions lead to selective

gene activation in the APC.

Once the antigen-bound APC has entered the lymph node, it will locate and activate recirculating

antigen-specific naïve peptides. The interaction between Th0 cell and APC will be influenced by

the range of co-stimulatory surface molecules and cytokines that have been activated within the

APC following PRR-PAMP interaction. Since the most ‘relevant’ type of adaptive immune

response for viral infection is the Thl-regulated cytotoxic effector response, it is often expected

that APC will activate clones of ThI CD4- T cells and CD8 cytotoxic T cells. Recalling that Thl

cells also provide stimulatory help for those B cells committed to producing the subclass of IgG

antibody able to opsonize and destroy viruses.

Thl, Tc and B cells generated must then leave the mesenteric lymph node in efferent

lymph to enter the bloodstream and invade the anatomical site to viral infection (the intestinal

mucosa). Involved in this interaction is homing receptors such as the α4-β7 integrin and vascular

addressin MAdCAM (Mucosaladdressin cell adhesion molecule). Once adaptive immune cells

arrival the mucosa is achieved, the effector phase of adaptive immunity commences. Thl-derived

IFN-y will amplify the effects of NK cells and Tc cells. The Thl cell also stimulates B-Cell

50

transformation to plasma cells which secretes IgG subclass that contributes to the cytotoxic

process. Antibody bound to infected cells may also mediate the activation of the classical

pathway of complement which results in cell lysis. Although in a protective anti-viral immune

response the Thl arm of adaptive immunity is more prominent, Th2 effectors also plays a

passive role of stimulating the local production of anti-viral IgA that could be secreted across the

mucosal barrier to bind virus particles and block their interaction with receptors. Locally secreted

IgG may act in a similar fashion. Success of the adaptive immune response could lead to a late

stage immunosuppression (induced T-Cell receptors TCRs) and the development of T-and B-cell

memories.

**The Immune Response to Bacterial Infection**

We shall remain with the intestinal model by considering immune response that might be

generated in response to an enteric bacterial pathogen such a *Escherichia coli* or *Salmonella spp*.

in the intestinal tract. On arrival, these pathogenic organisms are confronted by a range of innate

immune defences. However, of note in this context is the presence of the endogenous intestinal

bacterial microflora, which will compete with the pathogen for necessities of life such as space

and nutrient thereby, making colonization much more tedious. Another interaction of innate

immunity we will be discussing in this class of infection is the ᵧᵟT cell occurring inside the

enterocyte layer. These cells are anatomically well cited for early interaction with bacterial

pathogens and are thought to be primarily activated in response to this type of organism.

Just like for viruses, bacteria most often require an initial receptor-mediated interaction with

target host cells. For example, the K88 and K99 pili of *E.coli* permit attachment to receptors at

the enterocyte interface between these bacteria and host tissue. Enteric pathogens, such as *E.coli*

or *Salmonella* spp., utilize a variety of mechanisms to induce disease, dependent on the genetic

strain of the bacterium. While some may secrete locally active enterotoxin to help bind toxin

receptors and result in osmotic imbalance and metabolic diarrhea, others attach to and disrupt

the epithelial surface or invade the intestinal mucosa and regional lymph nodes, resulting in local

pyogranulomatous inflammatory response. Such gram-negative rods, are also characterized by

the ability to produce severe generalized disease (endotoxaemia).

Once the innate immune response is breached and mucosal surface is colonized, the

adaptive immune will be called on to resolve the infection. Also, mucosal APCs like dendritic

51

cells carry out bacterial antigen screening and the process involves the interaction of PRRs with

a range of bacterial PAMPs. The activated dendritic cells migrate to the regional mesenteric

lymph nodes in orders in order to enlist and activate paracortical T cells and, in turn, follicular B

cells for response. The effector immune response phase here is one dominated by the production

of antigen-specific immunoglobulin. Hence, APC signalling of the Th0 cell leads to production

of Th2 effector which combine with antigen-specific B cells and then leave the mesenteric lymph

node to home back to the mucosal surface.

The most beneficial effector immune activity is the synthesis of specific IgA and IgG antibodies.

For those organisms mediating pathology via toxin production, IgG neutralization of toxin will

be important, IgG antibodies may also opsonize invasive organisms for phagocytosis or permit

the complement-mediated lysis of the bacteria. Bacterium-specific IgA antibodies will be

secreted to the luminal surface, where they may interfere with the interaction of organism with

receptor molecules. Again, in a successful immune response, final down-regulation of the

effector populations will be required together with the generation of immunological memory.

**The Immune response to fungal infection**

Fungal pathogens often provide challenges to immune system because of the relative size of the

colonies of organisms. In this discourse, we shall consider an example of the immune response

of the dog to colonization of the nasal sinuses and nasal cavity by the organism *Aspergilus*

*fumigatus*. This fungus produces large colonies over the mucosa of the nasal tissues with the

colonies comprising tangled mass of fungal hyphae.

To get fungal colonies established, the organism must overcome the normal innate

immune barriers of the upper respiratory tract, including the antimicrobial substances found

within nasal secretions. Although innate phagocytic cells such as neutrophils and macrophages

are capable of phagocytosing fungal spores, they fail to do so, simply because fungal hyphae are

large and massive.

APCs carrying fungal antigen induce response in regional lymphoid tissue such as the

nasopharyngeal tonsil or retropharygeal lymph nodes. The effector mechanism involves

infiltration by CD4+ Thl and probably Thl7 cells, as determined by up-regulation of gene

expression for IFN-y and IL-23 in inflamed tissue. Thl-derived IFN-y likely stimulate

macrophages to induce their destruction of any phagocytosed fungal spores. Antibody and

52

complement molecules also coat hyphal elements and form a bridge to FcR-bearing granulocytes

thereby subjecting them to destruction. Similar to helminth infection, these cells may degranulate

locally and induce focal damage to the hyphae. Infected dogs generally mount a strong serum

IgG antibody response to the organism. The inflammatory response itself it likely responsible for

the extensive tissue and bone destruction that may occur in this disease. Similar to observations

in leishmaniosis, there is an additional regulatory element to the response, as there is concurrent

up-regulation of lL-10 gene expression. Again, this is interpreted as an attempt by the adaptive

immune of systemic sequelae, but at the same time allows persistence of the infection and the

development of chronic sinonasal disease.

**IMMUNOLOGICAL TOLERANCE**

**(Dr. Michael Agbaje)**

I. Neonatal tolerance

This a phenomenon whereby exposure of the developing immune system to foreign antigen

either *in utero* or during early neonatal life leads to the induction of tolerance to that antigen such

that antigenic challenge in life fails to induce an immune response. This effect has been widely

carried out experimentally by immunizing neonatal laboratory rodents with antigen and

demonstrating tolerance in later life.

A good veterinary example of neonatal tolerance is that which develops to infection with bovine

viral diarrhoea virus (BVDV), the aetiology of ‘mucosal disease’ in cattle. If a foetal calf is

infected between days 42 and 125 of gestation (i.e before commencement of immunocompetence

in the last trimester), that animal will become persistently infected (PI) as it develops immune

tolerance to that particular strain of the virus. These PI animals are viraemic and continually shed

the virus, thereby acting as reservoir of infection within the heard. The PI animals remain seronegative

because of the tolerant state, but other animals in the heard will develop high-titre virus

neutralizing antibodies. The PI animals remain tolerant to the specific strain of virus that it

carries, but may it may be superinfected with a cytopathic biotype of BVDV to which it is not

tolerant and this may result in fatal mucosal disease.

II. Adult tolerance

53

Induction of tolerance has be shown experimentally in adult laboratory animals (**adult**

**tolerance**). This effect is very much dependent on the experimental protocol employed and the

dose of antigen given. Two fundamental protocols for tolerance induction are;

a. ‘High-zone’ tolerance which involves injecting the animal with a single very high dose of

antigen that induces paralysis of both T and B cells. In contrast,

b. ‘Low –zone’ tolerance, involves repeated injections of a low dose of antigen which induce Tcell

tolerance. As most antigens are T dependent, induction of T-cell tolerance generally leads to

concomitant B-cell tolerance.

III. Oral tolerance

The mechanism underlying oral tolerance is well elucidated. At one level the phenomenon may

relate to the route by which the tolerizing antigen is absorbed across the intestinal mucosa.

**Particulate antigens** to which an active immune response is induced are more likely to be

absorbed by **M cells** overlying the Peyer’s patches. In contrast, **tolerated antigens** are more

likely to be **soluble** and absorbed directly across the **enterocyte surface**. This tolerance may not

be absolute, as most normal individuals have detectable serum IgG or IgA antibody specific for

dietary antigens.

It is now known that oral tolerance is probably an active immunological event. The tolerizing

antigen must be processed and presented by dendritic cells , but the consequence of such

presentation may be variable. Some T cells that recognize processed antigen may undergo

**apoptosis** (clonal deletion) and others might recognize antigen but fail to become fully activated,

as not all three signals required for T-cell activation are received. Such T cells are not deleted,

but remain non-functional or **anergic**.

IV. Self tolerance

The final form of tolerance is self-tolerance (the ability of the immune system to tolerate the self

antigens that comprise the tissues of the body). Failure of self-tolerance leads to autoimmune

diseases. In order to achieve self-tolerance, potentially autoreactive T and B lymphocytes must

be brought under control.

Knowledge abounds on how self-tolerance is achieve for T-cells. One mechanism involves

elimination of T-cells by **negative selection** during intrathymic maturation. However, if this

process was full-proof, there would be no such thing as autoimmune disease, so a proportion of

autoreactive T cells must ‘escape’ clonal deletion and be allowed to enter the peripheral T-cell

54

pool. Circulating autoreactive T-cells are readily identified in man and have also been

demonstrated in the dog. These cells must clearly be controlled in order to prevent autoimmunity

and a range of mechanisms are probably employed to achieve this aim. Some autoreactive Tcells

may recognize antigen presented to them in peripheral lymphoid tissue. This cells may

either undergo apoptosis (‘**peripheral deletion’** as opposed to ‘central’ intrathymic deletion) or

may become **anergic** if they fail to receive appropriate costimulatory signals. Other stimulatory

T cells may be kept away from their target autoantigens in a process known as ‘**immunological**

**ignorance’**. This may work at different levels; for example, some body tissues are normally kept

at distance from the adaptive system behind a ‘blood-brain barrier’ or ‘blood-testis barrier’, so it

is relatively difficult to induce autoimmunity to brain or testicular tissue. Alternatively, this may

work at the level of the APC, which processes self-antigen but fails to present it. Although all of

these mechanisms might be at play, the single most important means of controlling autoreactive

T cells is via regulatory T cells.

Autoreactive B cells must also be kept in check in order to prevent those autoimmune diseases

caused by autoantibody production. The development of B lymphocytes is less well defined than

that for T cells, but also involves a form of clonal deletion. The control of autoreactive B cells

within the periphery likely relies on the regulation of those autoreactive T cells that would

normally be requires to provide help for activation of the B-cell response. Lack of T-cell help

renders the autoreactive B cell anergic. Autoreactive B cells within the periphery may also be

‘ignorant’ of their cognate antigens if these antigens are normally kept sequestered away from

the immune system.

**IMMUNOSUPRESSION AND IMMUNODEFICIENCY STATES**

**(Dr. Michael Agbaje)**

Immunodeficiency is defined as the presence of impairment in function any part or parts of the

immune system that results in the immunodeficient individual being vulnerable to infectious

disease. Two broad types of immunodeficient states are recognized;

a. Primary immunodeficiency – this occurs when immunodeficiency is occasioned by a mutation

in a gene encoding a molecule of the immune system. Such diseases are inherited and congenital,

with clinical signs manifesting early in life.

55

b. Secondary immunodeficiency- this occurs in adults that have previously had normal immune

function and may be related to age, infection, medical therapy or the presence of chronic disease.

Causes of secondary immunodeficiency are discussed below;

MEDICAL IMMUNOSUPPRESSION

Secondary immunodeficiency can be deliberately induced by veterinarians when

**immunosuppressive drugs** are used to control autoimmune disease or when chemotherapy is

used to control autoimmune disease or when **chemotherapy** is used in managing cancer. The

ultimate side-effect of these drugs is secondary immunosuppression and increase susceptibility to

infection.

i. Specific Infections

The best example to illustrate infection associated secondary immunodeficiency is feline

Immuniodeficiency Virus (FIV) infection. FIV is a **T lymphotropic retrovirus** that infects

lymphocytes and APCs and has been extensively investigated as an animal model of human

immunodeficiency virus (HIV). Infected cats have an acute phase of mild illness during which

there is progressive decline in blood CD4+ T cells. The cat will then become asymptomatic, but

during this second phase of disease there is a continued decline in circulating CD4+ T cells that

may occur over several years. During the third stage of the disease, there is recurrence of mild

illness that progresses to a more severe terminal stage 4-5 disease. The terminal illness is similar

to human AIDS and is a **chronic , multisystemic disease** that may include gingivostomatitis,

respiratory tract infection, enteritis, dermatitis, weight loss, pyrexia and lymphoadenomegaly.

Neurological disease and lymphoma may also develop and a range of secondary infections have

been reported. Concurrent Feline Leukaemia virus (FeLV) should also be considered and FeLV

may be immunosuppressive in its own right due to depletion of infected T cells.

ii. Chronic disease

Animals afflicted by chronic infectious, inflammatory or neoplastic disease will likely have a

degree of secondary suppression of the immune system and increased susceptibility to infection.

Some infectious agents (e.g canine distemper virus [CDV], canine and feline parvovirus, FIV,

and FeLV, porcine circovirus-2 as the cause of postweaning multisystemic wasting syndrome in

this species, equine herpesvirus-1, bovine viral diarrhoea virus) may cause **direct depletion of**

**lymphoid tissue**. Other infections are associated with the production of circulating

56

immunosuppressive factors that appear to inhibit lymphocyte blastogenic responses. Such

inhibition of lymphocytes function has been demonstrated in diseases such as demodicosis, deep

pyoderma, pyometra and disseminated aspergillosis in the dog.

iii. Stress

Chronic stress is also immunosuppressive and follows elevation in endogenous glucocorticoid

production. A similar effect is seen in hyperadrenocorticism, in which there is circulating

lymphopaenia and increased susceptibility to secondary infection. Stress-induced immune

suppression is likely to play a major role in susceptibility to infectious disease in intensively

reared livestock. Animals housed indoors in high density rearing units or animals transported for

long distances in close confines are considered at risk for such immune suppression. Highintensive

exercise is also immunosuppressive, although milder exercise can enhance a range of

immune functions.

iv. Malnutrition

Severe malnutrition leads to increased susceptibility to infection due to **impairement of T-cell**

**function**, but with sparing of B-cell activity and immunoglobulin production. These effects are

thought to be related to **leptin,** adipokine (cytokine produced by adipocytes) related to body fat

mass. An animal suffering malnutrition will have loss of body adipose tissue reserve and reduced

concentrations of leptin. Leptin is also immunostimulatory (macrophages and Th1 function) and

proinflammatory, starvation is associated with immune suppression.