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COUNTERFORCE-NATURE'S DESIGN

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INTRODUCTION

The Vice-Chancellor, Fellow scholars, Great Ife Students, Distinguished Ladies and Gentlemen.

It is a great pleasure and honour for me to give this Inaugural lecture. It is the third to be given by a Professor from the Department of Microbiology, Faculty of Science. The topic is "Counterforce:- Nature's Design".

The balance between man and the many potentially hazardous infectious microorganisms he encounters has often been described as a silent struggle for supremacy. Fortunately for mankind, the battle between host and parasite is usually won by the host. To view the battle more objectively, it is appropriate to examine the types of arment available, the strategies used, and the various factors available to the combatants in this important daily encounter.

Infection may be described as the implantation and successful replication of a microorganism on or in the tissue of a host. If parasitism is to be successful, the infectious microorganism must develop successfully and must replicate in sufficient numbers in the new site to ensure survival of the species. Also, if survival is to be assured, the progeny of the parasite must escape from the original host and survive until additional hosts become available.

For most infections, a balance is maintained between man's defences and the capacity of the microorganism to evolve properties that overcome or bypass them. My lecture today is about the combatants, their structures and the numerous strategies for survival. Counterforce is the survival's kit designed by nature.

Early Notions about Homeostasis

Throughout history, efforts have been made to understand how the human body works. Although many individuals have contributed to generating this knowledge, two in particular stand
out for their contributions to the concept of homeostasis.

The first is Claude Bernard, whose failure to succeed as a playwright led to a career in medicine and research. His many contributions to the field of physiology include the notion that there is an internal environment (milieu interieur) that is important to health and survival. Bernard's concept of the internal environment and the role it played was rather different from the notion that we have today.

To Bernard, all life could be placed into one of three categories: (1) Latent life, (2) Oscillating life, and (3) constant life. Latent life did not actively manifest the features of life. Seeds, spores and the cysts of some invertebrate species fall into this group. Oscillating life was strongly influenced by the external environment include all cold-blooded animals.

Constant life, for which manifestations of life appeared to be free of influence from the external environment, contained all complex higher

organisms. From the language used, it would appear that Bernard might well have considered an internal environment for all three forms of life (definitely for oscillating and constant life). However, it is probable that he expected constancy of the environment only among the more complex organisms.

Nevertheless, Bernard's seminal thinking provided an important framework in which physiological studies were to be conducted. A further major step was provided nearly 50 years later by Walter Bradford Cannon (1973). He introduced the term "homeostasis" to describe the steady-state conditions existing with the internal environment and provided the essential ground rules fo homeostatic control.

The central points of this notion of homeostatic control, first publishe in 1926, are as follows:

(i) In open systems, like our bodies, that are subjected to continued disturbances, constancy is evidence that adaptive mechanisms exist.

(ii) Homeostatic conditions persist because tendencies towards change are resisted by increased effectiveness of adapting factors.

(iii) A homeostatic agent acts in only one way at any given point.

(iv) Homeostatic agents that are antagonistic in one region may cooperate in another.

(v) Regulating systems that determine a homeostatic state may be composed of cooperating factors acting simultaneously or successively.

(vi) When a factor is known that shift the homeostatic state in one direction, it is desirably to seek an automatic control of the factor(s) having an opposite effect.

Although several of these postulates seem rather obvious, their formulation into a coherent scheme provided a significant advancement in our understanding of physiological control. It is a credit to Cannon's insightful genius that these general rules have held fast since they were produced. Advances over the past several decades have been guided by them and have confirmed and refined them (Cannon, 1973).

Regulation

The task of ensuring the smooth and orderly functioning of the human body falls to the nervous, endocrine and immune systems. These systems interact with and direct the abilities of the various organ systems. In doing so, they simply act independently or cooperatively. When the individual is challenged or the internal environment is disturbed, rapid adjustments are sometimes required. Generally rapid response is the nervous system specialty. In contrast to the rapid adjustments produced by neural stimulations, adjustment

to changes in the internal environment can also occur more gradually, over extended periods. Regulations of this nature
are achieved through the actions of chemical messengers that exert influence over metabolic activities. Such control is the province of the endocrine system.

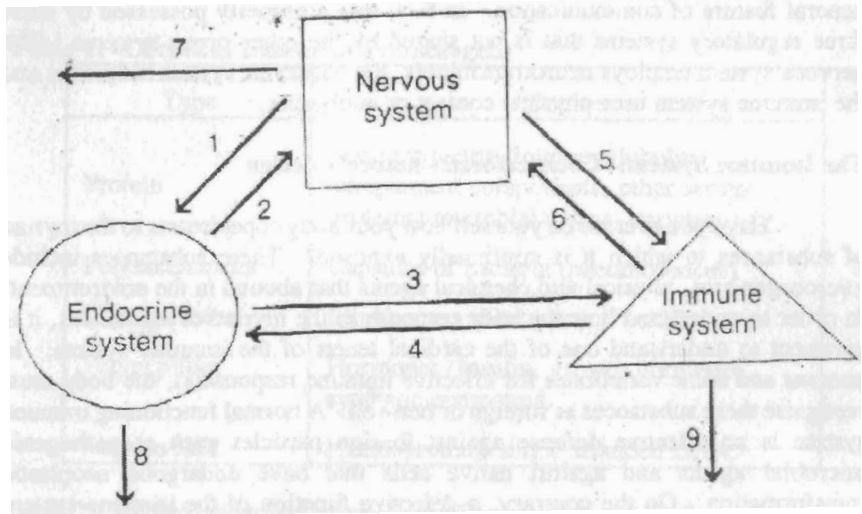

Figure 1: Interaction and Cooperation in Regulation

The immune system is a regulator of homeostasis. It acts as a surveillance factor. The purpose of such surveillance is to ensure that all cells are potential contributors to maintaining the steady state. Cells that are damaged or defective and no longer capable of playing a role in maintaining homeostasis are a liability. Renegade cells (cancer cells) that no longer respond to regulatory signals are a direct threat to the stability of the individual. These upset the balance and can potentially create disease. The function of the immune system is preserving the integrity of the individual and serves, at least indirectly as a regulator of homeostasis.

Interaction and Cooperation in Regulation.

The roles of the three regulatory systems are not as clearly or neatly delineated as shown in figure 1. There is extensive interaction among these three systems. In addition, there is evidence of crossover in execution of regulatory influence. There is also interaction between nerves and endocrine glands, for example, neural stimulation of adrenal glands. The nervous system can indirectly influence the functioning of the immune system through its regulation of blood flow. It can also affect lymphocyte proliferation and release from lymphoid tissues. There is mutual interaction among the regulatory systems that derives from the influence that each exerts independently on any target tissue, there is also overlap in the exercise of regulatory influence that reflects a more general feature of communication. In fact, this a property possessed by these three regulatory systems that is not shared by the other organ systems. The nervous system employs neurotransmitters, the endocrine system hormones and the immune system uses physical contact or antibodies.

The Immune System:- Counterforce:- nature's design

Have you ever asked yourself how your body copes/reacts to the myriad of substances to which it is continually exposed? These substances include microorganisms, physical and chemical agents that abound in the environment. In order to understand how the body responds to the myriad of substances, it is pertinent to understand one of the cardinal tenets of the immune system. In humans and some vertebrates for effective immune response(s), the body must recognise these substances as foreign or non-self. A normal functioning immune system is an effective defense against foreign particles such as pathogenic microbial agents and against native cells that have undergone neoplastic transformation. On the contrary, a defective function of the immune system results in disease. (Williamson and Cornwood, 1978).

The immune system is an extremely complicated one with a variety of roles in maintaining homeostasis and health - Like the endocrine system, it exerts control within the body by virtue of circulating components capable of acting at sites far removed from their point of origin. The complexity of the system derives from an intricate communications network capable of exerting multiple effects based on relatively few distinct cells. The immune regulatory mechanism thus may enormously amplify a given response or markedly diminish it depending on the momentary needs of the organism.

How does the human body react to an invasion by a foreign agent (e.g. bacterium, virus, parasite or cancer cells, transplant tissue or self-antigens). In order to answer the above question properly and adequately it is necessary to understand the organization of the immune system.

A primary function of the immune system is to protect the individual from microbial pathogens and their toxic products. This protection or resistance is made possible by two major defense mechanisms that have evolved in the vertebrate host, the innate or natural immunity and acquired or adaptive immunity. (Barett, 1988).

Antigenic properties

Invasive viruses, bacteria, fungi, protozoa, worms, cancer cells, foreign tissues and worm cells can exhibit, produce or release nonself substances known as antigens. Antigens are substances that can stimulate or drive an immune response and given the opportunity, react

Table 1: Chemical Classes of Immunogens

Type	Source
Protein	Serum proteins (Immunoglobulin, complement components, other serum proteins) microbial toxins, enzymes.
Polysaccharides	Capsules of bacteria (pneumococcus)
Glycoproteins	Blood group substances A and B
Polypeptides	Hormones (Insulin, growth hormones, synthetic compound.
Nuclein acid	Nucleoprotein, single stranded DNA.

Table 2: Distribution and clinical significance of the alloantigens of Man

Type	Example of alloantigen	Clinical significance
Red blood cell	ABH, RhO, blood groups	Hemolytic disease of newborn, transfusion reactions
White blood cell	Histocompatibility HLA_antigen	Transplantation immunity
Platelets	Platet (Pi) antigens	Transplantation thrombocytopenia
Serum protein	Gamma globulin complement component	Immune deficiency (IgA)

specifically by binding with the effector molecules (antibodies) and effector cells (T lymphocytes) produced. This definition of antigen focuses on two important properties that were formally identified by Obermayer and Prick in 1903, namely immunogenicity the capacity to stimulate the formation of antibodies and specifically (the ability to react specifically with these antibodies).

Nature of antigens

Most antigens are proteins but some contain carbohydrates, lipids or nucleic acids. Some antigens are more immunogenic or capable of eliciting an immune response, than others. An antigen, such as a protein, can possess a number of small chemical groupings that are called antigenic-determinant groups (Tables 1&2). Any one determinant group (epitope) under appropriate conditions can stimulate the formation of a particular kind of antibody molecule (or effector cell). Thus a pure protein might give rise to many distinct antibodies and effector cells. Nosal (1987).

Toleragens:

Antigens do not always exhibit immunogenicity or evoke antibody formation, however, in some instances, an antigen presented at one concentration might induce specific immunological unresponsiveness (or tolerance) while at another concentrations it might promote immunity. (Holborow and Reeves, 1983).

The notion of immunological tolerance was proposed in 1944 by Medawar and Burnet and earned them the 1960 Nobel Prize. One important manifestation of tolerance occurs during fetal development. Since an individual's immune system does not normally react against self-components, Burnet suggested the fetal immunocytes were deleted by contact with their specific autoantigens. This process was called clonal deletion and supposedly led to the removal of

immunocytes that would react against self antigens. In this manner an individual became tolerant to self-antigens.

Histocompatibility antigens

Immunological tolerance has become an exciting and active area of research that is especially relevant to the problems of tissue and organ transplantation. Unless the tissue proposed for transplantation is antigenically identical to that of the intended recipient, the patient's immune system attempts to reject it as we shall examine later. (Carpenter and Strom 1980).

The antigens of tissues that are responsible for evoking immunological responses against grafts are called histocompatibility antigens. They are coded for by genes known as histocompatibility genes, which collectively constitute the major histocompatibility complex (MHC).

The normal immune response to bacterial infections

Normal resistance to Infection

How does our body react to a antigen that it is encountering for the very first time? The immune response is composed of two major arms- termed natural or innate immunity and adaptative (acquired) immunity. When an antigen is encountered by the host for very first time, antibodies/T cells are generally not found in the system, therefore the innate immunity is primarily responsible for curtailing any adverse effect(s) of the "invader/Ag". How does this happen?

The ability to resist, without previous exposure almost any substance that threatens the body and to do so without discrimination (i.e. - nonspecifically) are notable features that distinguish natural immunity from acquired immunity.(Mata, and Wyatt, 1971; Weiss, 1977).

There are a number of host resistance factors that further characterize natural immunity. These include:

A. Physical barriers: The anatomical features of the intact skin and the mucous membranes, the bacteriocidal nature of the saturated and unsaturated fatty acids secreted by the sebaceous glands; the viscous slimy nature of mucous membrane and the presence of Lysozyme. All inhibit the colonization of microbes.

B. Mechanical barriers. Salivary flow, urination, tearing and persistalsis are mechanical means of preventing adherence of bacteria to epithelial tissue. Hydrolytic and proteolytic enzymes are also present in these body fluids which degrade bacteria and other invaders.

C. Chemical barriers. The acid pH of the stomach, the lactic acid of the vagina, lysozyme in the body fluids and proteolytic enzymes of the intestine all contribute to an unfavourable environment for some microorganism thereby preventing colonization.

D. Microbial antagonism; competition for nutrients by the members of the indigenous microflora antagonises the growth of many species. The anaerobiosis of the gastrointestinal tract inhibit such pathogens as *Salmonella* and *Shigella* species from colonising the host.

E. Biologically active substances

Complement: The complement system involves a group of serum proteins that are activated by antigen-antibody complexes.(Frank, 1989). Following activation, the complement system functions in two major ways.

Complement modifies foreign membranes as its components swam onto microorganisms, such as bacteria and viruses. While this may lead to disruption of the membrane's integrity (lysis), the more important function of complement is to promote opsonization which refers to the coating of membranes or particles with complement components. **Host cell receptors for these proteins** subsequently bind and help clear complement-coated complexes.

Complement promotes inflammation by releasing anaphylatoxin and chemotactic factors. They work primarily by triggering the release of histamine and other mediators from mast cells and basophils. The resulting contraction of smooth muscle and dilation of blood vessels, facilitate the exudation of plasma and cells into an area of infection. This is nature's design of eliminating infectious agents.

Chemotactic factors serve to attract phagocytic cells to a site of inflammation. In this way, the complement system promotes the desolution of microorganisms. In autoimmune disease, however, complement can similarly produce inflammation and destroy host cells and tissue through phagocytosis or lysis. This is nature's design.

F. Inflammatory response:

Inflammation is the body's reactions to an injury such as an invasion by an infectious agent. In just the same way as it is necessary to increase the blood supply to active muscles
during exercise, to provide glucose and oxygen, so it is also necessary to direct elements of the immune system into sites of infection (Ehrlich, 1910; Metchnikoff, 1968). This is counterforce - Three major things occur during this response namely:

1. An increased blood supply to the infected area.
2. **Increased capillary permeability caused by** retraction of endothelial cells. This permits larger molecules to transverse the endothelium than would ordinarily be capable of doing so and thus allows the soluble mediators of immunity to reach the site of infection.
3. Leucocytes, particularly neutrophil polymorphs and to a lesser extent macrophages, migrate out of the capillaries and into surrounding tissue. Once in the tissue they migrate towards the site of infection by process known as chemotaxis, these three events manifest themselves as inflammation. Inflammation is an effective counterforce, it is nature's design in containing microbial infection as well as repair of damaged tissue.

G. Phagocytosis, Polymorphonuclear leucocytes (PMNs) and macrophages are "professional" phagocytes. They are the primary cells involved in phagocytosis as a nonspecific mechanism of host defence (Oppenhein and

Jacobs, 1986). **The cellular events in phagocytosis are as follows:**

(i) Chemotaxis: Directed migration in response to chemical stimuli of bacterial and host origin.

(ii) Attachment: via opsonins (antibodies, C3b) and cell surface receptors (Fc and C3b).

(iii) Ingestion; Formation of phagosome and phagolysosome containing the ingested particle.

(iv) Killing: Elimination of the ingested bacteria is achieved by two mechanisms.

a. **Oxy**gen independent killing which involves the release of a variety of secretory products such as hydrolytic enzymes, proteases and plasma proteins active in the inflammatory response.

b. Respiratory burst
Respiratory burst: Increased consumption of oxygen and activation of membrane associated oxidase which is dependent on NADPH, Reactive metabolites: for example superoxide anion, singlet **oxygen, hydrogen** peroxide and hydroxyl radical all **kill bacteria - These** agents are powerful counterforce designed by nature and the effective against gram-positive cocci.

As I have earlier indicated, macrophages are actively involved in killing/destruction of "invaders" Macrophages represent the first line of defence against microbial infections and thus present a formidable force in host natural resistance. Although many activities associated with these cells are nonspecific, their responses as antigen processors and presenters is remarkable (Allen, 1987).

Dozens of products may be secreted by macrophages/monocytes depending upon their status. These include a host of enzymes active at neutral and acidic pH. Among these enzymes are plasminogen activators (which dissolves clots) lysozymes (which digest bacteria, and collagenases and acid hydrolases (which act on tissue products. Macrophages also produce and secret several critical plasma proteins, including coagulation proteins and complement components. In addition, macrophages secrete a variety of bioactive substances grouped into three categories. (1) Reactive metabolites of oxygen such as hydrogen peroxide, (2) bioactive lipids such as prostaglandins and (3) factors regulating cell activities (eg) Interleukin-I (Il-1) immune interferon (IFN) and angiogenesis factor that promote neovascularization of tissues (Allen, 1987). Table 3.

Activated Macrophages

Macrophages can be activated by lymphokines produced by Ag or antigen-stimulated lymphocytes and by complement components. When this happens, they become morphologically and functionally modified. Activated macrophages as they are called are "angry macrophages" so to say. As a result, these cells are dramatically more microbicidal and more tumoricidal than quiescent or nonactivated macrophages (Vernon-Roberts, 1972; Nossal, 1987). Table 3.

Table 3: Complement components

Protein	Serum Concentration (μg/mL)	Physical Characteristics: Molecular Weight	Physical Characteristics: Sedimentation Rate	Immunological Function
C1	75	410,000	11.0S	Stabilizes immune complexes
C1q				Binds to Fc portion of Ab (1gG, 1gM) molecules
C1r	34	190,000	7.0S	Links C1q and C1s: enzymatically activates C1s
C1s	30	87.000	4.1S	Enzymatically activates C4 and C2
C2	25	115,000	5.5S	Cleaved to C3a and C3b-C3a has anaphylatoxic, chemotactic, and opsonic properties, C3b forms C5 convertase and when associated with C4b22b has opsonic properties.
C4	450	210,000	10.0S	Cleaved into C4a and C4b-C4a has anaphylatoxic properties, C4b binds C2b and can neutralize viruses.
C5	75	190.000	8.7S	Cleaed into C5a and C5b-C5a is phagocytachomoattractant and has anaphylatoxic properties; C5b binds avidly to membranes and initiates MAC.
C6	60	128,000	5.7S	Serine protease-forming part of MAC
C7	60	121,000	5.6S	Forms part of MAC
C8	80	163,000	8.0S	Forms part of MAC
C9	58	79,000	4.5S	Forms part of MAC

Mr. Vice-Chancellor Sir, Ladies and Gentlemen I have spent the last few minutes to describe the importance of innate/natural immunity the body possesses in combating invading microorganisms. All these activities are carried without the involvement of lymphocytes specifically antibodies and T cells. The next few minutes will be spent on describing the role of lymphocytes in immune response: As I have indicated earlier the immune system protects individuals against microbial pathogens and their toxic products - the adaptive or acquired immunity is composed of cellular components.

Cellular components of the immune response.

Three major cell types participate in acquired or adaptive immunity of host defence. They are B-lymphocytes, T-lymphocytes and macrophages. Knowledge of the distribution of these cells in the vasculature and among the mucosal epithelium and their arrangement in lymphoid tissues and organs is essential to understanding the complexity of the immune response (Table 4).

In contrast to innate immunity which is non-specific and an attribute of every living organism, acquired immunity is not present at birth but develops subsequent to neonatal stage only after encounter or exposure to a foreign substance. This type of protection in the host is mediated by two physiologic mechanisms that exhibits specificity, diversity, memory and adaptability. The two mechanisms are humoral immune response, this type of defence is accomplished by means of serum antibodies. The second is cell mediated immunity which involves physical participation by cells of the immune system.

Mr. Vice-Chancellor sir, ladies and gentlemen you will recall I defined what antigens are - It is time to describe its counterpart - the antibody (Ab) or immunologlobulin.

The *immunogobulins* are among the most intriguing genetic systems in all of biology (Edelman, 1973; Porter, 1973). The capacity to specifically bind a given antigen constitutes the basis of humoral immunity. Moreover, immunoglobulins have the ability to perform many different effector functions designed to activate B-cell growth, lyse foreign invaders, protect mucosal membranes, or clear antigen-antibody complexes (Landsteiner, 1948). The genes that encode the immunoglobulin protein chains are among the most instructive genes ever analysed (Dreyer and Bennett, 1963). While most proteins are designed to perform a single repetitive function, the major goal of immunoglobulin is to dispaly diversity so that an individual can generate 10^5 to 10^8 different antibodies (Kabat *et al*, 1970; Tonegawa, 1983). The immunoglobulin genes utilize a fascinating gene-shuffling mechanism

Table 4: Lymphoid organs and their functions

Lymphoid Organs	Functions
Primary Lymphoid Organs	
Bone marrow	Is major site of hemopole production of all major blood cell types, provides microenvironment for antigen-independent differentiation of B-cells, provides antigen-processing environment, may be the possible equivalent of bursa of Fabricius.
Thymus	Provides environment responsible for antigen-independent differentiation of t cells; provides humoral factors important for T cell maturation.
Bursa of Fabricius	Provides environment responsible for B cell maturation (found only in birds)
Secondary lymphoid organs	
Spleen	Acts as temporary reserve site for lymphocytes; provides antigen-processing environment; is auxiliary site of hemopoiesis (in extraordinary circumstances)
Regional lymph nodes, adenoids, tonsils, peyer's patches appendix	Are temporary holder sites for recirculating lymphocytes; provide antigen-processing environment.

to ensure this breadth of immunity (Dreyer *et al*, 1963; Engleman *et al*, 1980; Tonegawa, 1983). This is nature's design.

Antibody protein structure

Immunoglobulin molecules constitute a substantial portion of the plasma proteins. When they display the capacity to bind to antigens, immunoglobulins are called antibodies. Immunoglobulins are complex, multichain proteins composed of two identical heavy (H) chains and two identical light chains (Burton, 1985). Each heavy and light chain is also bipartite (Fig.2). The amino-terminal portion is the variable (V) region and differs markedly from one

immunoglobulin molecule to the next while the carboxy-terminal portion is the constant (C) region and is invariant. This pattern parallels the functions of these regions: the variable regions must interact with myriad of antigens, and the constant regions perform invariant functions, such as generating stabilizing disulfide bonds, bonding to cell-surface receptors and fixing complement. The structure of the antibody molecule was eludicated in the late 1950s by Porter, Edelman and others when these workers observed that reducing agents would break the interconnecting disulfide bonds and release free H and L chains. Moreover, papain and pesin two enzymes were subsequently discovered. Papain cleaves the molecule at the amino-terminal side of the disulfide bonds between the heavy chains. This cleavage generates three fragments: two Fab (fragment antigen binding and the Fc (so named because it is readily crystalizing) fragment (Fig.3).

Immunoglubulin classes

There are five different classes of immunoglobulins: IgG, IgA, IgM, IgD and IgE. All classes of immunoglobulins share the same variable region repertoire. However, each class has an entirely different heavy chain constant region that is responsible for the different functions of the molecules. The H chain classes designated y, ά, δ, and for IgG, IgA, IgM, IgD and IgE respectively (Tonegawa, 1983). - Tables 5 & 6.

B Lymphocytes

A central lymphoid organ for B cells was first discovered in birds. It is the cloaca-associated organ known as the Bursa of Fabricius - hence the term B cell. The bone marrow of mammals is regarded as the principal central lymphoid organ for B cells.

During differentiation and maturation, a B cell undergoes a succession of changes in location, morphology, immunocompetence and function. B cells possess immunoglobulins as antigen receptors. It also has receptors for F_c, hormones, mitogens and others.

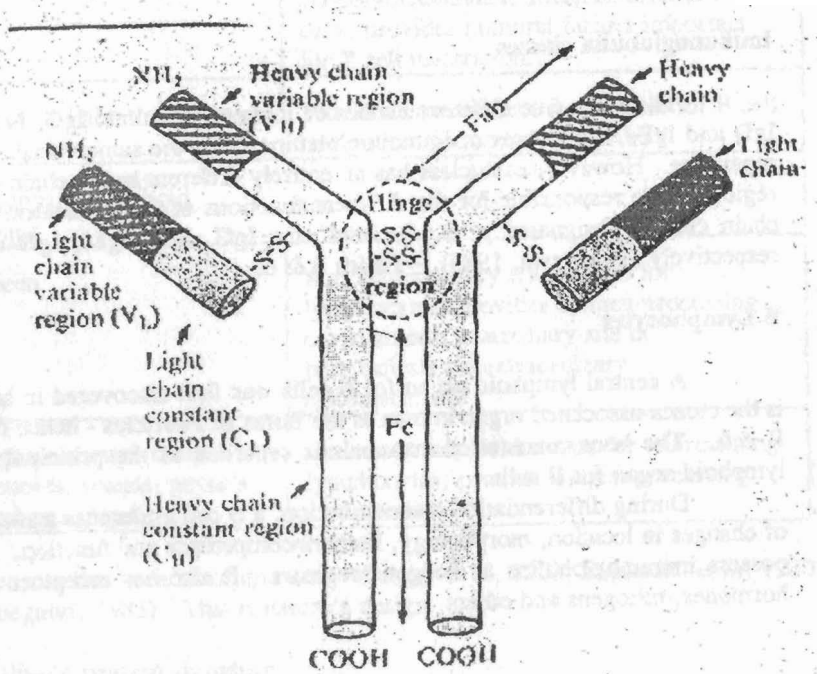

Figure 2: Schematic Structure of the Immunoglobulin Molecule (IgG)

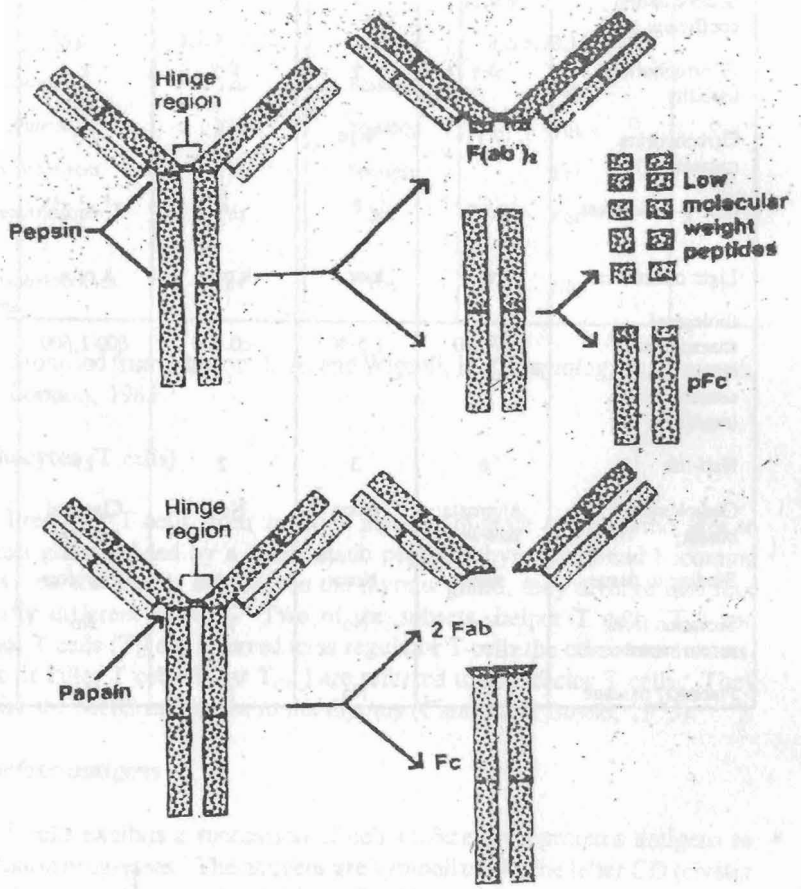

Figure 3: Effects of Papain and Pepsin on IgG Molecule

Table 5: Physical and Biological Characteristics of Human Immunoglobulin Isotypes.

Biophysical and chemical traits	IgA	IgD	IgE	IgG	IgM
Molecular weight (KD)	385	160-184	160-200	188-190	146-970
Sedimentation coefficient (Sw)	7-9,11*	7	8	7	19
Electrophoretic mobility	β-γ	γ	β-γ	γ	β
Carbohydrate content (%)	7-11	9-14	12	2-3	12
Heavy chain class	α_1, α_2	δ	ε	$\gamma^1,\gamma^2,\gamma^3,\gamma^4$	μ
Light chain class	k or ∝	k or ∝	k or ∝	k or ∝	k or ∝
Biological characteristics serum concentration (mg/dL)	50-100	1.5-40	≤0.005	800-1,600	50-200
Half-life	6	3	2	21	5
Complement binding	Alternate pathway	None	None	Classical pathway	Classical pathway
Binding to tissue	none	None	Humal	Heterology	None
Secretion from serous membrane	Yes	No	Yes	No	No
Placental passage	No	No	No	Yes	No

Table 6: Characteristics of Human IgG Isotypes

Characteristics	IgG Isotype			
	IgG1	IgG2	IgG3	IgG24
H chain type	γ^1	γ^2	γ^3	γ^4
Number of disulphide bridges	2	4	13	2
Allotype (Gm group)	1,2,4,17,22,	24	3,5,6,13,14,15,16	-
Crosses placenta	Yes	Possibly	Yes	Yes
Binds complement	Yes	Possibly	Yes	Yes
Binds to macrophages	Yes	Possibly	Yes	No
Binds to heterologous tissue	Yes	No	Yes	Yes
Binds to Staphylococcus aures protein	Yes	Yes	No	Yes

Source: Modified from Hanson, L.A. and Wigzell, H. *Immunology* Butterworth, London, 1983.

T-lymphocytes (T cells)

Precursor T cells from the bone marrow migrate as prothymocytes to the thymus gland guided by a chemostatic peptide, thymotaxin and becoming receptors. As the T cells different in the thymus gland, they diverge into four functionally different subsets. Two of the subsets, helper T cell, (T_H) and suppressor T cells (T_s) are referred to as regulator T cells the other two subsets, cytotoxic or killer T cells T_C or T_{CTL}) are referred to as effector T cells. They are acquire the MHC molecules in the thymus (Cantor and Boyse, 1975).

T cell surface antigens

T cells exhibits a succession of cell surface glycoproteins antigens as differentiation progresses. The antigens are symbolized by the letter CD (cluster designated) and a number or by the letter T and a number.

Thus T lymphocytes with CD7, CD2, CD3 and CD4 markers (one abbreviated just, CD4) represent the circulating T cell that have helper (inducer) and delayed hypersensitive function; lymphocytes with CD7, CD2 and CD3 and CD8 markers abbreviated, CD8) are T cells with cytotoxic and suppressor

The Immune Response

The preceding section considered the major elements involved in an immune response, namely, antigens, macrophages, immunoglobulin B lymphocytes, T lymphocytes and their subsets (T_H, T_S, T_C, T_D) MHC restriction, cytokines and the complement system. Let us now see how these elements interplay in the sequence of events of an immune responses (Fig. 4). It is important to recall that before an immune response takes place - before there is antigen recognition - there already exist millions of lymphocytes, each of which possesses receptors only for small portions of the antigen for which they are specific (Lanzavacchia, 1985).

A precise event initiates the immune response. A receptor molecule (Abba, 1988) on the surface of a B cell or a T-cell recognises the antigen to which the cell is programmed to respond and binds to some small part of it. It is however the nature of the antigen that determines whether it is the B cell or the T cells that will have the effector function; how the antigen is presented to trigger the immune response, and the pathway of the immune response. The proliferation of B cells and T cells that leads to the production of Abs and effector T cells does not result simply by binding of antigen with receptor (Milgram et al, 1985).

Table 7: Classes of Lymphocytes

Lymphocytes	Role
T cells	
T_H	Provide "resistance" or potentiate expression of immune function by other lymphocyte.
T_S cells	Suppress or impair express ion of immune function by other lymphocytes.
T_C cells	Bring about cytolysis and cell death of "targets"
T_D cells	Recruit and regulate a variety of non specific blood cells, macrophages in expression of delayed (Type IV) hypersensitivity.
B cells	
B-lymphocytes	Proliferate/mature into antibody-forming cells.
Plasma cells	Are mature-active antibody-producing cells.
Nucleus various killer cells types, K, NK, NC, LAK	Bring about cytolysis and death of target cells.

Table 8: Characteristics of Various Lymphocyte Classes

Lymphocyte	Surface Markers or Features of T & B Cells Human:	Mouse
T cells immature	CD5 (T1) CD1(T6) CD(T11)	Thy-1, Ly1,2,3 and TL
Mature subset		
T_H cell and T_D cells	CD4 (T4)	Thy-1, Ly1, L3T4 Qa1
T_S cells and T_C cells	CD5(T1):CD8(T80	Thy-1, Ly+-2,3
Activated T cells	HLA-DR, CD5 (Tac)	Ia
B cells		
B. Lymphocytes	CD19-22, CIR, sIg	Lyb-2,3,5, sIg.
Plasma cells	?	PC-1
Null Cells		
K,NK, NC, LAK	display neither T nor B cell markers	

Table 9: Lymphocyte Surface Receptors.

Receptor	Features	Distribution
Antigen receptors	Are sIg that react against specific foreign.	B cells
	Are non-Ig protein heterodimers that bind specific foreign antigen	T cells
MHC receptors	Recognise particular "self" antigen	B and T cells
Complement receptors	Bind active fragments of C3 of complement system	Mature B cells, Phagocytes
F_C receptors	Recognize FC fragment of Igs	B and T cells null cells, phagocytes.
Lymphokine/monokine receptors	Bind lymphocyte or monocyte factors such as interlocking	B and T cells
Nitrogen receptors	Recognise Lipopolysaccharide or plant lectins (non-specific) nitrogenic factors	B and T cells

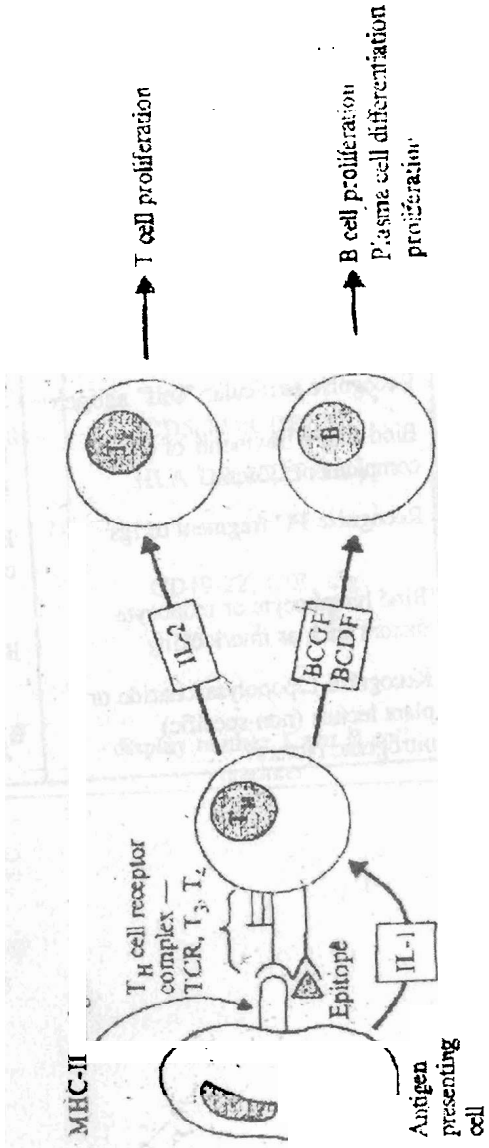

Figure 4: Cellular Interactions Involved in an Immune Response

Cross-linking of several receptors usually is required, as is collaborative cellular interactions and projection of an immune response most often involves protein antigen recognition by T_H cells (Greaves et al, 1974; Unanue, 1980).

The production of antibodies or of effector T cells involves three cell types (a) antigen-processing/presenting macrophages called accessory cells (b) helper T cells and either B cells or effector T cells.

The macrophages ingest, process and present on their cell membrane antigen fragments.

In order for a given T_H cell to recognise and respond to its specific small part of the antigen present on the macrophage, (a) the macrophage must have on its surface a self marker, a Class II-MHC glycoprotein. The requirement for this marker is called MHC-restriction.

The T_H cell, activated by the two signals from macrophage, produces interleukin-2 (IL-2). IL-2 initiates clone formation of the activated T_H cell in an autocatalytic manner other lymphokines (interleukins) (Cantor, and Boyse, 1975).- Table 10.

Mr. Vice-Chancellor sir, the preceeding section has enumerated the beneficial effects of the immune system, however, there are several instances where the immune system is deleterious to the host. As we have seen earlier the immune response is a powerful weapon against disease, but it sometimes goes awry. For some of us, the immune system reacts to certain foreign substances in a way that is not beneficial and so it is responsible for diverse group of pathological states, such as atopic allergic diseases and asthma (Beall, 1973; Karenblast and Wedner, 1984). Why does an individual react to dust, ragweed, penicillin, food, other products to which the individual had previously been exposed? The answer lies with allergy or hypersensitivity.

Whenever the immune system acts excessively or inappropriately to an Ag and pathological changes occur, the person is said to be hypersensitive. Historically, hypersensitivity reactions were divided originally into two classes based on the relative amount of time for immunological response to develop in a sensitized host. Immediate hypersensitivity describes
reactions develop in less than 24 hours after exposure to an Ag, whereas delayed hypersensitivity reactions occur within 24 to 48 hours.

Table 10: Representative of Lymphokines and their Actions

Lymphokine	Designation	Actions
Chemotactic factor	CTF	Stimulates chemotaxis of macrophages
Interleukin 2	IL-2	Stimulates clonal expansion and maturation of T and B cells and NK cells
Macrophage stimulating factor	MSF	Stimulates macrophage migration to site of Ag
Macrophage-active factor	MAF	Restricts macrophage movement and increases phagocytic activity
Migration-inhibiting factor	MIF	Inhibits migration of macrophages
Interferon (gamma	IFN-y	Stimulates NK activity

However, in 1963 Coombs and Gell refined the classification, identifying four classes or types. Within the category of immediate hypersensitivity reactions, there are three subdivisions namely Type 1 (anaphylaxis), type II (cytotoxic), Type III (immune-complex-mediated) reactions which are all Ig-mediated hypersensitivities involving B-lymphocytes. type IV is cell mediated or delayed hypersensitivity reaction and is mediated by T-lymphocytes (Austen, 1974).

Mechanism of IgE-mediated hypersensitivity

The first phase of Type 1 immediate hypersensitivity is *sensitization stage*. It starts with the first exposure to the *allergen,* which initiates the biosynthesis and release of humoral antibody, in this case, primarily IgE.(Table 11). A subsequent exposure may liberatre mediators.

Mediators

The contents of the mast cells secretory vesicles include a variety of substances with similar physiological effects on inflammation. *Histamine* is the most abundant and faster acting of these substances. It induces smooth muscle contraction, release of mucus, vasodilation and increases capillary permeability.

All these actions can have profound effects. For example excessive smooth muscle contraction and release of mucus in the respiratory tract can close the air passages of the traechea and bronchi, causing asphyxiation and death by suffocation. Another target area is the uterus. Pregnant women who are severly allergic can abort the fetus during an attack of histamine release and subsequent smooth muscle contractions in the uterus. Histamine can also lead to edema in which excess fluid accumulates in the tissues. This is due to histamine-induced increase in capillary permeability. Vasodilation through histamine release also ensures that the area has increased blood flow. thus, there can be excessive loss of blood fluids into the tissues. This can lead to circulation shock, when cells no longer are supplied with the proper levels of oxygen and glucose from the blood. Under these conditions, cells, tissues, organs and eventually organ systems begin to fail and death can occur. There is counterforce -and it is nature's design.

Blood Groups

Experiments in blood tranfusions were first undertaken during the seventeenth century but were so unsuccessful that they were outlawed. It was in 1904 when Landsteiner discovered that the serum of some human donors clumped, or agglutinated the red blood cells of other normal donors that the mystery of incompatibility was resolved. Since that time, it has been found that there are serum IgG Abs that can react with Ags present on the red blood cells. These erythrocyte Ags, called agglutinogens number over 100 and comprise some 20 blood group

Table 11: Comparison of Hypersensitivity Reactions

Characteristic	Type 1	Type II	Type III	Type IV
Approximate time to develop clinical signs	30 min	5-12 hours	3-8 hours	24-48 hours
Reaction mediators	IgE, histamine SRS-A, ECF-A etc	IgG, IgM complement	Igg, IgM, complement eosinophil neatrophil lysosonal enzymes	T cells macrophages lymphokines
Reaction to intradermal injections	Wheal and flare		Erythema/oedema	Erythema/ inoburtion
Passive transfer with serum from sensitized donor	Yes	Yes	Yes	No
Examples	Asthma allergies anaphylaxis	Transfusion reaction drug induced allergies hemolytic disease of newborn	Arthus reaction serum sickness	Graft rejection contact dermatitis, tumor immunity

systems. Antibodies to these Ag, called agglutinins, can be encountered in two clinical situations (1) during pregnancy if the fetus has an erythrocyte Rh-Ag which the mother erythrocytes lack and (2) in blood transfusions of the transfused blood is mismatched and has red cell Ags different from those of the recipient's blood. The ABO blood group was discovered by Landsteiner by mixing the red cells of one set of donors with the serum of others and checking for agglutination.

From the results, he defined the blood groups as O, A, B, AB, which was based on the distribution of two serum agglutinins (IgG) and two agglutinogens (Ags) on the erythrocytes surface. The agglutinins are known as anti-A and anti-B. The Ags of the ABO blood groups are inherited characteristics.

Rh factor or D antigen

This Ag can be found on the surface of human erythrocytes. It was named Rh since similar Ag was detected in serum produced in rabbits immunized with *rhesus monkey* red blood cells. Approximately 85% of the population possess this Rh(D) Ag and are said to be Rh+. Persons who do not have the Rh factor on their RBCs are Rh-. The plasma of Rh- persons does not contain agglutinin against the Rh factor, but such Abs can develop if blood transfusions of Rh+ blood are given to these people.

Rh Incompatibility

The condition occurs if a Rh- mother carries a fetus which is Rh+. Normally the fetal-maternal circulation does not mix, but small hemorrhages can occur, especially during the last trimester when the fetus is relatively large. if this happens, there is an intermingling of fetal and maternal blood. In this situation, the Rh+ blood cells of the fetus would cross the protective placental barrier and enter the blood circulation of the mother. The antigenic Rh+ red cells of fetus would then trigger the production of anti-Rh ab by the mother's immune system. This is counterforce - it is nature's design. The maternal Ab produced is IgG which able to cross the placental barrier and enter the fetal circulation. Once the anti-Rh Abs have bound to the fetal Rh+ erthryocytes, complement is activated and fetal red cells are destroyed. As a result, the baby may be born with a disease called *erythroblastosis fetalis*, or *hemolytic* disease of the newborn. The disease is manifested in the fetus before it is born or within the first few days of neonatal life. The clinical symptoms include severe anaemia, jaundice, edema and enlargement of the infant's spleen and liver. Unless the baby receive a total blood transfusion, death due to shock rapidly occurs. This is nature's design.

Mechanisms of protozoal survival

If parasites elude the host's immune response and are sufficiently virulent, they kill the host upon whom their own survival depends; however if they are too easily destroyed by the immune response, their own survival is similarly jeopardized. The survival of any parasite therefore represents a balance between induction of immunity in the host and escape from surveillance (Bloom, 1979). Parasites may even have induced mutations in man which enable him to resist the parasite. The protozoan causing malaria is an example. The sickle cell haemoglobin gene confers partial resistance to *Plasmodium falciparum* and limits its multiplication within erythrocytes. Thus, people with the normal haemoglobin genotype (HbAA) are highly susceptible to falciparum malaria; those with the homozygous sickle cell genotype (Hb SS) suffer serious and usually lethal sickle cell anaemia, but those with heterozygous sickle cell trait (Hb AS) have a survival advantage in endemic malarial areas (Cohen, 1979). This is counterforce - it is nature's design.

There are many ways in which protozoa can evade or modify the host's immunological attack. Antigenic variation is the most striking example of successful adaptation and is exemplified by sleeping sickness caused by *Trypanosome brucei* that is spread by the bite of the tsetse fly. After infection, the number of parasites in the blood fluctuates periodically; this cycle of parasitemia, remission and recrudescence is due to destruction of trypanosomes by host antibody, followed by the emergence of parasites of a different antigenic constitution. Antibodies produced after each wave of parasitemia are specific for one antigen variant only. It is probable that the parasite possesses a number of genes that code for its surface antigen and can switch these genes on and off in sequence. Other protozoa can rapidly change their surface coat to elude the immune response, a process known as antigenic modulation (Gray and Luckin, 1980; Vickerman, 1978). Within minutes of exposure to antibodies, leishmania parasites can remove (`cap off') their surface antigens, so becoming refractory to the effects of antibodies and complement (Vickerman, 1978). - Table 12.

Suppression of the immune response is one of the most obvious adaptive mechanisms for protozoal survival. The most striking examples occur in malaria and visceral leishmaniasis during which soluble antigens released by the parasite may inhibit the host's immune response by acting directly on lymphocytes or by saturating the reticuloendothelial system. Such antigens may also effectively remove specific antibody, so preventing antibody from eradicating the parasite (Lewis and Peters, 1977). This is nature's design.

Table 12: Parasites Immunity

Mechanism	Examples of diseases due to: Protozoa	Helminths
Host variation		
Genetic factors	Malaria	
Suppression of host immunity	Malaria, leishmaniasis	Schistosomiasis
Parasite variation		
Antigenic variation	Trypanosomiasis	
Antigenic modulation	Leishmaniasis	
Antigenic disguise		Schistosomiasis
Premunition		Schistosomiasis
Resistance to macrophage killing	Leishmaniasis, toxoplasmosis, trypanosomiasis	

Mechanisms of helminth survival

Antigenic variation is also important in helminth survival. Adult schistosomes `disguise' their surface antigens The parasite may synthesize host-like antigens, such as α_2 macroglobulin, to mask its own foreignness (Vickerman, 1978). Alternatively, it may absorb host molecules onto its surface; red blood cell antigens, immunoglobulins and complement all of which have been demonstrated on the outer layer of schistosomes (Phillips *et al.* 1978).

The term concomitant immunity or `premunition' is used to describe a form of acquired immunity in which the established infection persists but new infection is prevented by immune mechanisms (Bout *et al,* 1977). This is nature's design. Schistosomiasis is again the best example: adult schistosome worms can live in the host for many years, often with little or no evidence of any immune response. However, adult schistosomes do stimulate a response that prevents reinfection of the same animal with immature forms of the parasite, called cercaria. The disguise adopted by the adult worms may play an important role. It is counterforce and its nature's design.

HIV/AIDS AND THE IMMUNE SYSTEM

AIDS is described as the greatest public health challenge of our time. By the end of 1998 more than 33 million adults worldwide were estimated to be infected with HIV, the virus that causes AIDS, a fatal condition that has no cure. Of these, about 21 million were men and 12 million were women. 14 million have died. An estimated 16,000 new cases occur every day. About 10% of African adults infected with HIV live in Nigeria, the region's most populous country (UNAIDS, 1998) Nigeria's adult infection rate is now about 4% and it continues to rise (UNAIDS, 1998).

According to a report in (Time, July 17, 2000) twenty-four million people in sub-Saharan Africa are HIV-positive, 70% of the world total. Thirteen million people have already died of AIDS and 10 million more are expected to die within five years. In Kenya, one in seven people is HIV-positive. In Botswana, the rate of infection is one of four people, in Zimbabwe, it is heading toward one in three. The World Bank estimates that AIDS could shrink some African economies by up to 25% over the next 15 years. According to Simon Robinson in his (Time, July 17, 2000) report, the American Central Intelligence Agency (CIA) recently described the spread of AIDS in Asia, the former Soviet Union and particularly Africa a **threat** to US national security and said that it could trigger ethnic wars and genocide and undermine democratic governments. Peter Hawthorne in his own report (Time, July 17, 2000) stated that South Africa the most developed economy in the subcontinent is facing a devastating onslaught of the disease, with 4.2 million people infected - 10% of the population. According to a recent survey by ING Barings, the international corporate and investment bank, one third of South African's semiskilled and unskilled work force will be HIV-positive in 2005. Apart from the immediate human cost, researchers say productivity could slump by 50%. "AIDS will define the future structure and shape of society and the business environment in Africa". say Alan Whiteside, one of South African's leading AIDS experts.

An estimated 1 million children in developing countries also are infected with HIV or have AIDS. The epidemic is spreading so rapidly and so widely that it may jeopardise many previous gains in child survival, warms Peter Piot, executive director of the Joint United Nations Programme on HIV/AIDS. Currently, according to the United Nations Children's Fund (UNICEF); about 1,000 children die from AIDS every day. Millions more are left without support when their parents die of AIDS, or they suffer because their parents have AIDS-related diseases such as tuberculosis and cannot properly care for their children.

About 4 of every 5 women and nearly 9 of every 10 children infected with HIV live in Africa. Because HIV/AIDS epidemic in sub-Saharan Africa has from its start spread primarily through heterosexual relations, women and children have been the more affected than in

countries where HIV initially spread largely through male-to-male sex or intravenous drug injecting equipment (UNAIDS, 1998).

Why is this virus so devastating - come into the world of counterforce. How does the AIDS virus take over the immune system and make if unresponsive to invasion by pathogenic
cells or agents? To answer this question, we need to first understand the characteristics of the HIV virus.

Lymphocyte infection

AIDS appears to be caused by a RNA retrovirus - This type of virus, instead of storing its genetic material in DNA, uses RNA (Fig.5). This viruses consists of a protein coat and an RNA core. While infecting a cell, the virus first sheds its protective protein coat (Fig.6). Then using an enzyme called a *reverse transcriptase*, the viral RNA is translated to DNA. This DNA can now be integrated into host's chromosomal DNA. The retroviruses, thus, have a profound effect on the genetic composition produced by the virus enables the infected cell to transcribe and translate the viral genes. These genes now can be used to assemble new viruses that can be released to infect more cells. This is nature's design.

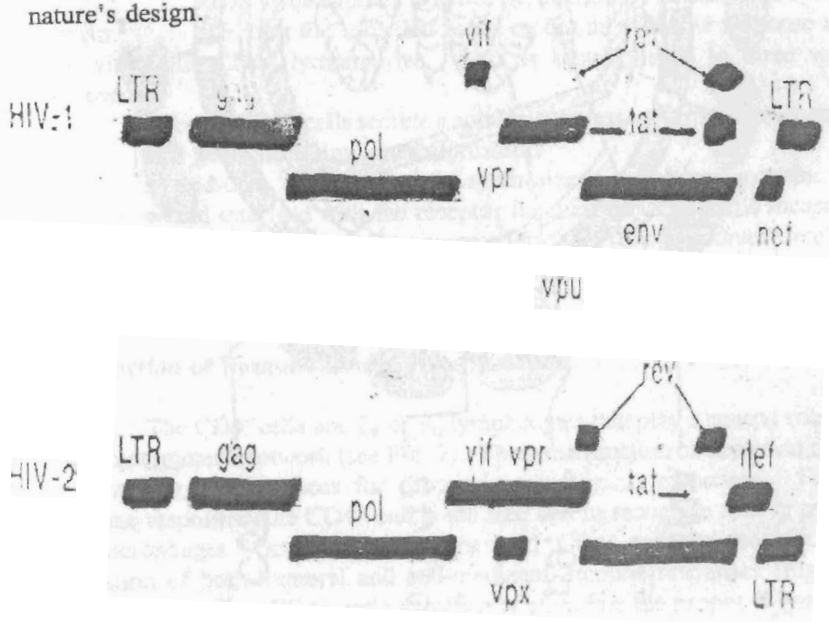

Figure 5: Human Retrovirus Genomes

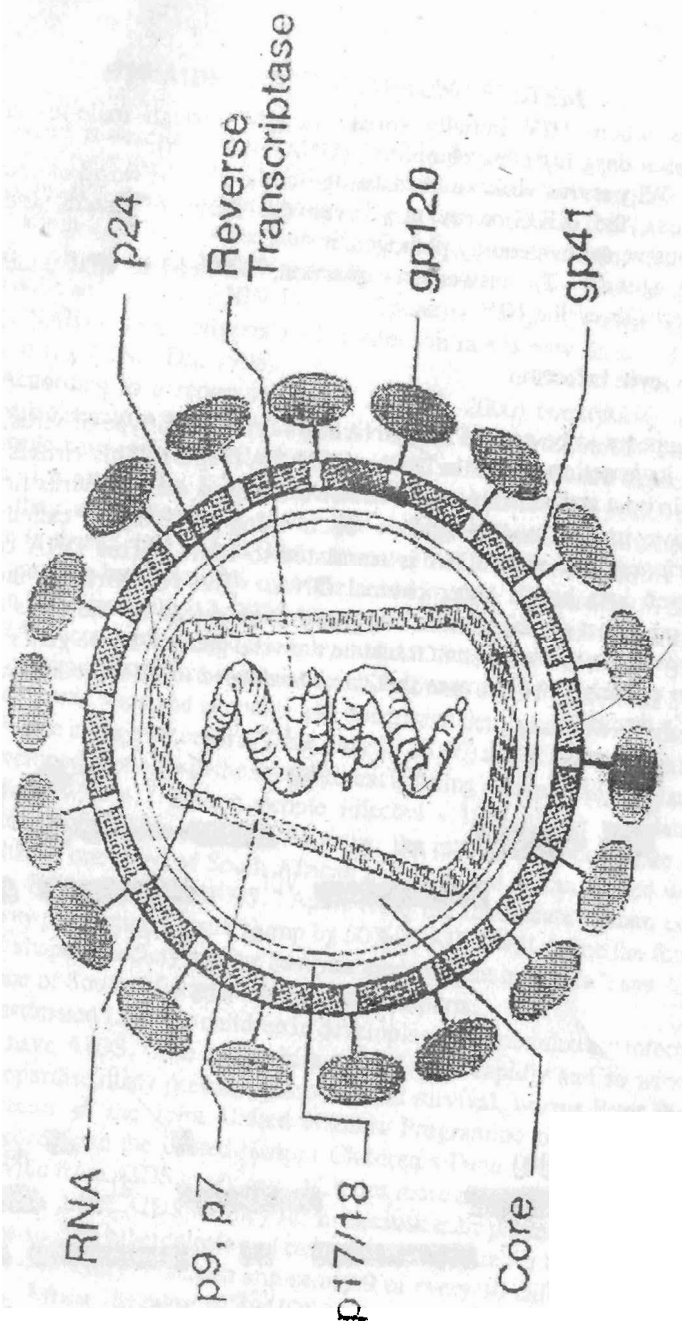

Figure 6: Schematic Structure of HIV Surface Proteins

The HIV-1 viruses, upon encountering permissive T helper/inducer lymphocyte ($CD4^+$), bound to specific receptors, the $CD4^+$ Ags, on the cell surface. Particular HIV-1 coat glycoproteins for example, gp-41 and gp-120 (stands for 41 and 120 kDa glycoprotein) and bind directly to the $CD4^+$ Ags. Upon gaining entry, the viral genes are inserted ultimately with the $CD4^+$ cell's own chromosomal DNA. The virus might remain "silent" for years, entering a latent state, until it is triggered to begin replication and expression.

One trigger for this virus is the T cell protein, nuclear factor KB, which is produced when $CD4^+$ cells are activated by Ag. Once activated, the HIV DNA directs the $CD4^+$ cell to make copies of the virus, assemble the viral parts and release (by "budding") the completed infective HIV-virus. Eventually, the host cell dies. However, before this occurs, it remains alive for a long period, serving as an AIDS virus factory.

Although HIV primarily infects and kills $CD4^+$ cells it can also infect other cell tissues including macrophages, Ab-producing B cells, endothelial cells of blood vessels, and glial (non neuronal brain) cells. Interestingly, the $CD8^+$ (suppressor/cytotoxin) cell is not attacked by HIV. This is nature's design.

Evading Immune Destruction

The AIDS virus appears to avoid destruction by the immune system by detrimentally affecting the cells that could mount an effective response against the virus, the $CD4^+$ lymphocytes. This is accomplished in three ways as follows:

1. Infected $CD4^+$ cells secrete a soluble suppressor, lymphotoxin, that acts as a generalized immunosuppressant.
2. In addition, the virus might synthesize a membrane protein, which would interfere with the receptor function of $CD4^+$ cells incapable of recognising foreign Ags presented to them (this is counterforce).
3. Moreover, the virus eventually kills the $CD4^+$ cells, thereby reducing their numbers in the immune network.

Destruction of Immune Competence/Network

The $CD4^+$cells are T_H or T_D lymphocytes that play a central role within the intact immune network (see Fig. 7). Their malfunction or depletion can have far-reaching consequences for proper immunological responses. For most immune responses, the $CD4^+$ cell is the first cell to recognise the Ag presented by macrophages. Once the Ag is recognised, $CD4^+$ cells are essential for the activation of both humoral and cell-mediated immune responses (Fig.7). In humoral immunity, $CD4^+$ cells specifically stimulate the proper B lymphocyte to clone into

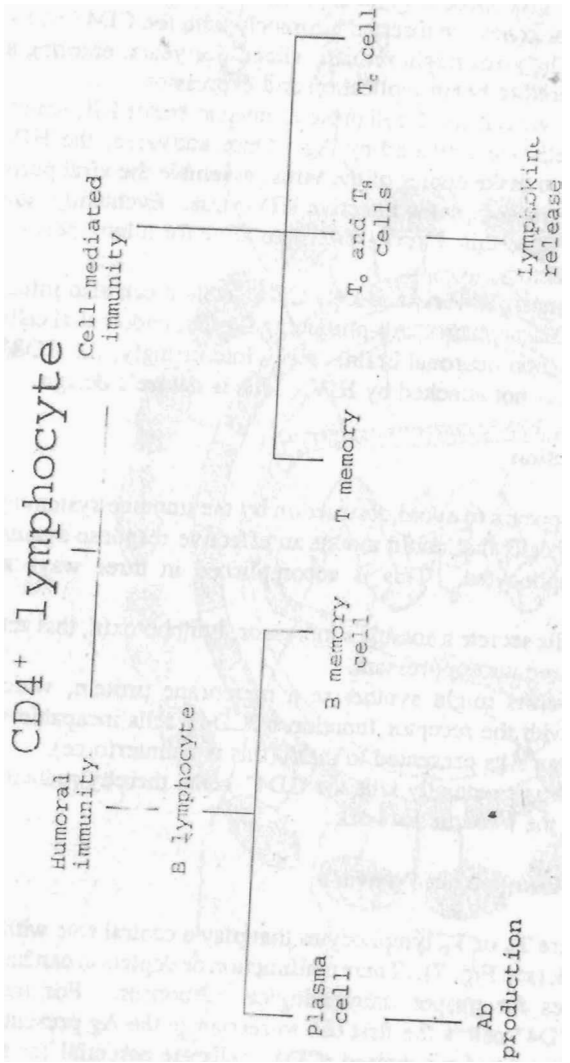

FIG. 7 INTERACTIONS WITHING THE IMMUNE NETWORK THAT CAN BE AFFECTED BY HIV.

Ab-producing plasma cells and memory B cells. The Ab (with or without serum complement) can specifically attack and kill (or inactivate) the foreign (transformed) cells or virus that is attacking the host. In cell-mediated immunity, $CD4^+$ cells are responsible, in part, for the clonal formation and expression of T_C cells, other T_D cells, and T memory cells. These activated T cells can directly battle the foreign cells either by direct killing (T_C cells) or recruitment of phagocytes (T_D cells). Therefore, the malfunction or depletion of $CD4^+$ cells cause a breakdown of the entire immune network. The only cells that are left relatively unscatched are $CD8^+$ (suppressor/cytotoxic cells). These cells are responsible for inhibiting specific immune responses by suppressing T_H, B lymphocyte, and T_C cell expression.

Transplantation Immunology

Mr. Vice-Chancellor sir, Experiments in transplantation during the last century have given rise to new medical era. Many situations have arisen in which clinicians have wanted to replace damaged tissues or organs of patients with similar healthy tissues organs. It is now possible to surgically transfer a variety of tissues or organ from a healthy donor to an ailing recipient or from one site to another in the same individual.

Organ transplantation involves manipulating a complex collection of tissue and cell types. These cells of an individual express as a unique set of membrane Ags called alloantigens (allo-Ags), which immunologically define a person's cell type or specifically as do fingerprints. The information about the synthesis of these unique proteins is stored in each person's chromosomal DNA.

The uniqueness of "self" is associated with a highly sensitive immune mechanism for sensing any foreign cell. Unfortunately this also includes organs donated to a person whose life depended upon accepting the new, healthy replacement for the diseased one. Since the cells of the transplanted organ have a set of allo-Ags that are unique and different from the recipient, the transplanted organ is seen as foreign and destroyed. The fact that the organ is needed for the host's continued survival is overruled by the body's immune defence system, which does not allow any foreign cell to prosper in the body. This is nature's design.

Artificial Hearts and Joints:- Attempts to Fool Mother Nature

With the advent of the Jarvik-7 artificial heart, artificial joint, and other prosthetic devices, many advances have been made in substituting biological body parts with artificial, man-made body parts. However, unexpected complications have inevitably arisen. One of these is a phenomenon called *biomaterial-centered infection*. The biometerials used in artificial devices do not

create smooth surface as living tissue. This provides a focus for bacterial adhesion. Bacteria are able to scale out the irregularities of the biometerial surface, adhere to them, and colonize the surface. Pathogens that easily adhere to biometerial surface include *Staphylococcus aureus, S. epidermidis Pseudomonas, Streptococcus* and *Proteus* species.

In addition, there seems to be poor tissue integration of biomaterial surfaces. For a transplant to be successful, the tissue cells must form a bond with the biomaterial surface that is comparable to the bond formed between adjacent cells in a tissue. The process ic currently a slow one at best. Yet it can and must happen in order for the artificial organ to become compatible with the body's tissues.

These two phenomena, of microbial adhesion and tissue integration of biomaterials, interact as the two forces compete with one another for the surface of the artificial organ. If the rapidly dividing bacteria colonise first the implant is doomed, but if the tissue cell integrate with the biomaterial surface first, it is vigorously defended by host defenses and bacterial colonization is prevented. Understanding how to tip the balance in favour of tissue integration will prevent the catastrophic infections that doom so many artificial organ transplants.

Immunology of Infertility

Many married couples have agonised on their inability to have children. Quite a number of couples' infertility may be associated with their immune system. Imagine a man whose spermatozoa carry Ags that stimulate anti-sperm antibodies or a woman whose ovum stimulates anti-ovum antibodies! This is nature's design.

Human spermatozoa and seminal plasma contain strongly immunogenic material: Some of these antigens are unique to sperm or seminal plasma (Semen-specific antigens) but others are shared with other fluids, secretions, and organs. Five to 14% of infertile coupling show evidence of sperm antibodies. These antibodies may be produced by the man, the woman or both.

Escape of Tumour from Immune System

One of the most dreaded diseases by man is cancer. The immune response to cancerous or neoplastic transformation is not very different from what have been described earlier. However, some cancer cells have evolved mechanisms to elude the immune systems - welcome to the world of counterforce.

"Sneaking through"

The simplest way to avoid death at enemy hands is to avoid capture. One way cancer cells can avoid immune cytolysis/destruction is by sneaking through enemy lines until they are strong enough to resist attack. Some tumors are only weakly immunogenic, so in small number they do not elicit an immune response.

(2) Modulation of tumor cell-surface Ags:

Certain tumor cells have also devised clever evasive attacks by circumventing immune activation. One such strategy is the modulation of tumor cell-sruface Ags.

Certain tumor cells can transfer antigens from their surface to the interior (cytoplasm) making themselves immunologically invisible. This is counterforce.

Another strategy is to devise a blocking mechanism that renders an individual invisible to the enemy. This tool is realised in certain cancers by the production of *mucoprotein* that *coats* and *masks the surface tumor antigens*. Tumor cells often produce copious amounts of a mucoprotein called *sialomucin*. This molecule binds to the surface of tumor cells, providing a protective shield against immune attack.

Certain types of tumors are capable of synthesizing varous immunosuppressants.

Cancer cells can also use weapons of their own against the immune system. They do this by somehow invoking the immune system to produce blocking Abs against the tumor Ags. This is counterforce.

Mechanisms of immunity to protozoal infection

Mr. Vice-Chancellor Sir, the infectious agents (Ags) have also evolved a mechanism of evading host immune systems - a number of these will be considered briefly.

Patients react to protozoal infection with a spectrum of responses similar to that evoked by other microbes, but some protozoa have evolved unique mechanisms for surviving in the face of the best the host can offer in the way of natural and acquired immunity.

Furthermore, some protozoa penetrate and survive within host cells; examples include the malarial parasite, plasmodium, which invades erythrocytes and hepatocytes and leishmania which survives inside macrophages. Such intracellular protozoa are not accessible to antibodies unless protozoal antigens are also secreted onto the host cell surface. This is nature's design.

MY CONTRIBUTION

Studies with Breast-milk

My contribution is in the area of pathogenic microbiology and infectious diseases. Infections continue to feature prominently as causes of mortality and morbidity in developing countries and children seem to be the most vulnerable. As a postgraduate student in the United States, I got interested in studies involving the role of human breast milk in protecting newborn/infant against childhood diseases. The initial studies done with other investigators (Afolabi, Grissom and Ako-Nai, *et al.* 1985), analysed breastmilk for the presence of aerobic bacteria from low-income mothers in Nigeria to assess their suitability for use in milk banks. In the study the nutritional and health status of donor mothers and their infant pairs were similarly assessed. The study revealed the presence of aerobic bacteria specifically *Streptococcus salivarius, Bacillus cereus, Klebsiella pneumoniae* and *Streptococcus epidermidis*. Our study also revealed that the bacterial load of these milk samples was acceptable and that such milk samples could be used in milk banks. Traditionally in most tropical African countries, mothers breast feed their infants with no supplementation in the first 1-6 months. Contamination of such samples would be disastrous if they are collected for non-lactating mothers from milk banks.

Having established that milk obtained from Nigerians can be used in milk banks, we then (Kassim, Afolabi, Ako-Nai, *et al*; 1986) proceeded to analyse milk samples from these mothers and the sera of corresponding infant-pairs for the presence of immunoprotective factors.

Studies of Immunoprotective factors in Breastmilk of Nigerian mothers.

We (Kassim, Afolabi, Ako-Nai et al, 1987) analysed breast milk and serum samples from a number of healthy Nigerian mother-infant pairs for concentrations of IgG, IgM, IgA, C3, C4 and lysozyme by single radial immunodiffusion technique using commercial monospecific antisera. The results of the immunologlobulin concentrations showed that the mean maternal serum IgG concentration was 2,767 mg/100ml, compared to the mean infant concentration of 669 mg/100ml. The breast-milk had the lowest IgG concentration of 55 mg/100ml. Similarly the mean maternal serum IgM concentration of 258 mg/100ml was significantly higher than either the mean infant serum or breast milk concentration ($P<0.05$). The mean IgA concentration of 169mg/100ml in the maternal sera was also significantly higher than either infant sera or breast milk ($P<0.05$). However the mean IgA concentrations in both the infant sera (29 mg(%) and milk sample (26.5 mg%) were not significantly different. Unlike the IgM which was measurably absent in 54.5% of the milk samples by radial immunodiffusion, the IgA was

consistently present in all the milk samples.

In contrast to the immunoglobulins in which the maternal concentrations were about four times higher than in either infant sera or breast milk, the concentrations of C3 and C4 were only slightly higher in the maternal sera, although they were significantly less in the breast milk ($P<0.05$). The mean C3 concentrations in maternal and infant sera were 164 and 145 mg/100ml respectively, while the mean milk concentrations was 11.5 mg/100ml. C3 and C4 were also measurably absent in 18.2% and 24.2% of the milk samples respectively.

Our study showed that the mean maternal serum concentrations of C3 and C4 were slightly higher than those of their infant pairs, and that C3 concentrations were approximately four times higher than those of C4 in both maternal and infant sera. Other investigators (Najakima *et al*, 1977, Ballow et al 1974, Mata, 1971) have demonstrated the presence and the functional activities of the complement component in both human colostrum and maternal milk and it has been speculated that these factors may collectively protect the infant against respiratory and enteric infections. Unlike the IgA and lysozyme, our results show that the milk concentration of C3 and C4 were significantly less than those of the maternal and infant sera, an indication of passive maternal transfer. The mean milk IgA concentration was 29 mg(%) compared to 26.5 mg(%) for the infant sera, while the mean lysozyme concentrations in the milk and infant serum samples were 3.24 mg(%) and 2.5 mg(%) respectively.

Our study is important in that most of the investigators dealing with immunoglobulins in milk samples have largely focussed on IgA and to a lesser extent on IgG and IgM. The few available studies on IgG and IgM have reported concentrations of about 1%. But our study found that milk samples from the Nigerian mothers had relatively high concentrations of IgG with a mean of 55 mg(%). Even with 54.5% of the milk samples lacking measurably concentrations of IgM, the mean IgM concentration was 24.8mg(%). It is obvious that the relative unique concentrations of the six immunoprotective components in the breast milk samples of our study population may represent a successful adaptation to an environment with high prevalence of infectious agents.

Some studies have suggested that the maternal - infant transmission of Cytomegalovirus (CMV) may occur perinatally, while others have implicated the maternal breast milk as a significant source of CMV infections for infants. It has been speculated that maternal antibodies may actually modulate CMV infection in infants. Kassim, Afolabi and Ako-Nai, et al; 1987), measured milk and serum samples from maternal-infant pairs for CMV IgG antibodies employing enzyme-linked immunoassay (ELIZA of Voller and Bidwell). Concentration in milk samples of class specific immunoglobulins (IgG, IgM and IgA) were determined by radial immunodiffusion using commercial monospecific antigen standards. Our results revealed that 90 per cent of the mothers were seropositive for CMV

IgG antibodies, compared to 33 per cent of their respective infants. The high prevalence of CMV antibodies observed in our maternal age group is consistent with the data reported in previous investigations. Stek et al (1983), found that 97 per cent of Nigeria school children from Epe South-western Nigeria) were positive for CMV antibodies. Okafor and Marshal, found that 78 per cent of 40 females from Enugu (South-eastern Nigeria were also seropositive for CMV. Stagno *et al* (1982), studied infants born to women who were shedding CMV only in breast milk. They found that none of the children who were bottle-fed acquired CMV, whereas 58 per cent of breast-fed infants became infected. These investigators cited this as evidence supporting the contention that the breast-milk of seropositive mothers may serve as an important source of CMV transmission to their breastfed infants. However, it has been noted that the rates of CMV infection in infancy are very high in populations in which the practice of breast-feeding is very common and where the majority of women of child bearing age are seroimmune to CMV (Numazaki *et al*, 1970, Cruz *et al*, 1977). It has therefore been speculated that the extremely low prevalence in infancy or CMV-related morbidity in such populations may be related to the acquisition of passive humoral immunity, which may serve to modulate the severity of the viral infection.

Available evidence indicates that acute respiratory infections (ARI) are a leading cause of infant mortality and childhood morbidity worldwide. They account for 10-15% of the 10 million infant deaths each year and for 30-40% of outpatient attendances. (Leowski, 1986), *Haemophilis influenzae* type b, *Neisseria meningitidis*, *Steptococcus pneumoniae* and *Bordetella pertussis* are species of bacterial that are not only responsible for a significant proportion of the clinical spectrum of ARI, but also account for more than three-quarters of all cases of acute bacterial meningitis (ABM).

While these four bacteria differ in their morphology and cultural characteristics, they share common properties of possessing a capsule and producing an IgA protease. The pathogeniticity of *B. pertussis* has been shown to result from toxin production (Morese and Morese, 1976). While it is the capsule that determines the virulence of the other three bacteria (Macleod, Hodges, Heidelberger, 1945; Robbins, 1978). Whole-cell vaccine is at present the major means of immunization against *B. pertussis* and effective immunization with the other three bacteria is accomplished with capsular polysaccharide vaccines. But infants who are less than 18-24 months of age and who are the most susceptible to ABM do not respond to capsular polysaccharide vaccine (Greenwood, 1984). Nevertheless, relatively few studies have examined and characterized the immunoproctive factors against the four bacterial species in human breast milk. We (Kassim, Afolabi, Ako-nai *et al*, 1989) demonstrated the relative concentrations of IgG, IgM and IgA antibodies to these four species of bacteria in paired maternal/infant sera and in breast milk samples of their respective mothers. We also compared the relative titres of the antibodies in

breast-milk obtained from Nigerian mothers and those obtained from breastfeeding mothers in Washington, D.C. Results from our study showed that the mean maternal serum IgG antibody to *B. pertussis* was about twice as high as the mean serum titre in the infants. The pertuss s IgG titres in many milk samples were just as high as those in maternal sera. Anti-pertussis IgA levels were also fairly high in the breast-milk samples. Such high antibody titres indicate its synthesis in the mammary glands. Our findings corroborate earlier reports indicating that microbial infections of the mucosal surfaces may lead to production of IgA antibodies in breast-milk (Glass *et al.*, 1983, Yolken *et al*, 1978; and Fubara and Freter, 1973) In their study of pertussis antibodies in Indonesian mothers, Oda *et al* (1985) separated pooled colostrom samples by affinity chromatography with class-specific immunoglobulin fractions. They reported that the IgA-enriched and IgG-enriched fractions were equally effective in protecting mice against respiratory challenge with *B. pertussis*. Their experimental evidence was relevant to our study since our results conclusively showed that anti-pertussis IgG and IgA were both prominent in breast-milk samples and therefore collectively enhance an infant's immunity to pertussis.

The results showed that the mean anti-Hib IgG antibody in maternal sera was about twice as high as in infant sera and about three times as high as in breast-milk. It has previously been shown that transplacentally acquired maternal antibodies decline over a 3-month period, after which infants became susceptible to Hib. The appreciable levels of anti-Hib IgG in infant sera would suggest that those antibodies were mostly likely produced in response to Hib exposure or to antigenically related organisms. On the other hand, the higher anti-Hib IgA concentrations in breast-milk relative to maternal sera are a good indication that the milk IgA was locally synthesized in the mammary glands. Similarly, our study shows that a number of milk samples particularly those from Nigeria contained anti-Hib-IgG levels that are just as high as those in maternal sera. With appreciable levels of anti-Hib IgA in breast-milk, it could be said that the milk anti-Hib antibody titre may be adequate for protection against the development of Hib disease.

In our analysis of serum and milk samples for specific antibodies to *S. pneumoniae* we used a polyvalent capsular polysaccharide vaccine as the antigen. We found similar levels of anti-pneumococcal IgG antibody in both maternal and infant sera. It is possible that the high IgG titres in infant sera either indicate on early development of immunocompetent responses to *S. pneumoniae* or represent an augmented response to various pneumococcal serotypes. Unlike previously published findings, our results conclusively demonstrate that anti-pneumococcal IgA and IgG are equally prominent in human breast-milk. Some studies have shown that newborn infants who developed invasive disease owing to *S. pneumoniae* type III had low or unmeasurable levels of serum IgG antibody to capsular polysaccharide (Christensen *et al*, 1980). The presence of high anti-

pneumococcal IgG and IgA titres in breast-milk may therefore serve to augment an infant's level of protection against the development of pneumococcal disease.

We used a polyvalent capsular polysaccharide vaccine containing serogroup A, C, Y and W135 of *N. meningitidis* as our assay antigen. The mean IgA level in maternal sera was about twice as high as that of infant sera while the distribution and the mean titres of the IgG antibodies in the two sets of milk samples were remarkably similar. It should be noted that the consistently high anti-bacterial IgG milk titres in our study are in contrast to previously published findings that indicate IgA to be the only predominant antibody in milk. (Yolken *et al.*, 1978, Glass *et al.*, 1983). Our results enable us to suggest that the anti-meningococcal antibodies present in breast-milk may enhance protection against meningococcal disease in early childhood.

Diarrhoea Research and Findings

The study of diarrhoeal diseases is of considerable epidemiological significance because according to Synder and Merson (1982) diarrhoeal diseases are the major killers of children under 2 years of age in developing countries. Apart from the mortality associated with diarrhoea diseases, there is also a very high level of morbidity with up to 4.8 annual episodes of diarrhoea incidence as reported for children in a peri-urban community in Manaus, Brazil (Guerrant *et al*, 1981). Although some reported episodes of diarrhoea are due to viruses, several bacterial species are associated with infantile diarrhoeas.

Our studies of diarrhoea diseases were informed because of the following

-Diarrhoea is a disease of poverty
-Overcrowding living conditions, personal hygiene and others are predisposing factors.
-*E. coli* is a normal flora of GIT.
-Careless disposal of sewages/wastes - is common in our urban centres.
-Contamination of sewage and non-treatment by standard methods - are prevalent in our living centres.

The incidence of enterotoxigenic *Escherichia coli* (ETEC) was investigated at oral rehydration (ORT) clinics in Ibadan and Ile-Ife. Our study revealed (ETEC) strains played a significant role in the etiology of diarrhoea in both communities and children aged 18 months or lower were the most susceptible. (Ako-Nai *et al*, 1990).

Our studies suggests *Escherichia coli* strains are responsible for a large proportion of microbes involved in diarrhoeal diseases at least in Southwestern Nigeria. The results show that as many as 21.3% of diarrhoeal subjects were infected with heat-labile toxin-producing strains alone. In a parallel study conducted (Ako-Nai et al,1990) reported EPEC incidence rate of 37.1% in this sample population making a total of 58.4% for Ibadan and Ile-Ife. The fact that

only 3.5% of healthy control subjects were carriers of ETEC reinforces the view that *E. coli* strains are responsible for a significant proportion of cases of infantile diarrhoea in Nigeria. **Antibiotic resistances of etiologic agents of diarrhoea.**

Diarrhoea diseases are generally not treated with antibiotics except in special cases. Application of oral rehydration salts seems to the mainstay of therapy. However, there is ample evidence that extensively use of antibiotics in the treatment of a large variety of bacterial infections has undermined the usefulness of these drugs because of the development of resistance to them by microbial agents. This is especially the case in developing countries where as reported by (Murray *et al*,1985 and Koh 1986), antibiotics are not only available on demand, but can be obtained from many diverse unmonitored and indeed unmonitorable sources (Lamikanra, Ako-Nai and Ogunniyi, 1996). Our work have shown that there is a high level of resistance to a broad spectrum of antibiotics by microorganisms in infantile diarrhoea. From the results of transconjugation studies, it is apparent that there is a large reservoir of transmissible antibiotic resistances among children in Ile-Ife, such that the use of antibiotics within this locality may be severly compromised by the rapid emergency of resistant organisms in the course of treating an infection.

Studies involving Staphylococcus aureus

Infections caused by *S. aureus* became prominent in hospitals in the 1950s because of the emergence of *S. aureus* strains that were resistant to penicillin alone or to several antimicrobial agents including streptomycin, tetracycline and chloramphenicol. Some of these strains were also highly invasive and had the capacity to spread; they belonged to the phage-type 80/81 complex, which included types 52A/80/81 and 52/52A/80/81. Therefore, it became apparent that phage typing was an important epidemiological tool in the identification of virulent strains of *S. aureus*. In a pioneering effort in 1990, I together with a number of colleagues (Ako-Nai *et al*, 1991) and in collaboration with a Danish Scientist Dr. V.T. Rosdahl of the phage-typing laboratory of the Statens Seruminstitut, Copenhangen, Denmark undertook a study of phage-typing of *S. aureus* strains obtained from various sources in Ile-Ife. We also determined the *in-vitro* antibiotic sensitivity testing of these clinical isolates. Our results showed that a large proportion (32%) of the isolates were untypable under the conditions of the phage-typing tests. However, 68% of the isolates were typable and several different groups were identified. The biggest group, group 11, contained 25% of the isolates. We compared our *S. aureus* phage-types with that reported by Dr. V.T. Rosdahl in Denmark. 18.8% of the isolates belonged to phage group II. The percentages of organisms in several other groups were also similar when comparisons were made between isolates from Nigeria and Denmark. 11% of Nigerian isolates and 12.3% of Danish isolates were in group

I and figures for group III were 15% and 11.7% for Nigeria and Denmark, respectively. Furthermore, 10% of Nigerian isolates and 7.1% of the Danish isolates belonged to the mixed group. Nigerian isolates were in the 94/96 complex whereas 13.3% of Danish isolates belonged to this group, and only one Nigeria isolate but
8.1% of the Danish isolates were of type 95. These results indicate that there are some noticeable differences in the distribution patterns of the phage-types in both localities but that the similarities may be more important than the differences. The large percentage of untypable strains (32%) highlights the importance of isolating local strains of *S. aureus*. Our results also indicate that resistance to penicillin, tetracycline and streptomycin is fairly evenly distributed amongst isolates from different sources, whereas methicillin, erythromycin and gentamicin resistances are associated with phage groups I and 83A (also 94/96 and NT) and are more likely to be found on nasal isolates than in isolates from skin lesions.

S. aureus strains have also been associated with septicaemia (Ako-Nai et al, 1999). In a study recently carried out in Ile-Ife, over 33% of the bacterial isolates cultured from neonates blood were *S. aureus* strains. In another study done in this environment, (Ako-Nai *et al*, 2000) reported staphylococci were the predominant organisms that colonised the skin of newborn infants. Although the predominant organisms encountered in the study were coagulase-negative staphylococci, *S. epidermidis* led this group. Unlike studies reported in Europe and the US (Hanson, 1996, Serra *et al*), *S. aureus* strains represented the principal organisms involved in cases of acute otitis media in a study recently reported (Ako-Nai *et al*, 2000). The bacterial isolates characterized were similar to those reported by (Cisse *et al*, 1995) in Senegal, West-Africa - underscoring a possible regional variation of aetiologic agents associated with this condition.

Recently (Ako-Nai *et al*, 1995) undertook a study of the incidence of pathogenic microorganism isolated from various clinical specimens in four university teaching hospitals in South-western Nigeria. The results showed that of the total number of seven hundred isolates cultured from various specimens, *E. coli* was the most single frequently isolated organism.
S. aureus strains accounted for over 28.4% of total number of isolates cultured from wound specimens and were the predominant isolates that colonised the wounds in the four centres. Our results corroborated others reported elsewhere (Shija, 1976, Gediokoglu, 1980). The reasons for the predominance of *S. aureus* in wounds are a complex combination of several factors. Scott-Emuakpor, (1970) associated the frequency of *S. aureus* in wounds with the intrinsic nature of the organism and its ability to survive in its hosts hostile environment. While Cooke and Gibson (1983) have expressed the view that autoinfection of wound by nasal carriers of *S. aureus* strains may be an important factor in the frequency of wound infections, our studies (Lamikanra *et al*, 1985, and Ako-Nai *et al*, 1992) showed that relatively high nasal carriage of the organism (20-40%) among apparently healthy individuals may in part account for the frequency of recovery in clinical specimens.

Frequent exposure of humans to infectious agents does not augur well for the effectiveness of the immune system. The recent increase in the incidence of HIV/AIDS in Nigeria has led to resurgence of pulmonary tuberculosis (TB) - A study conducted by Onipede, Ako-Nai *et al*.(1999) suggests tuberculous patients are more likely than others to be susceptible to HIV/AIDS. The reason being in part due to the compromised nature of the immune system in these patients.

Finally we have seen that a functioning immune system is an effective barrier to invading microorganism. There are a few suggestions that can be useful for maintaining an effective immune system which can be practised by each individual. These include:

-The maintenance of a general state of well being through regular medical checkups and healthy sanitary living.
-Maintenance of healthy dietary habits that reduce fats and carbohydrate intake but maintain a relatively high mineral and vitamin intake.
-Avoidance of excessive exposure to parasitic infections - like malaria, schistosomiasis and other debilitating diseases.
-Avoidance of exposure to hard drugs, physical and chemical mutugens (e.g. living in the vicinity of high tension electrical installations).
-abstinence or low alcohol consumption.
-Regular exercise and adequate rest/relaxation.
For HIV/AIDS - faithfullness to your partner, avoiding promiscuity, practice of safe sex -through the use of condom/abstinence and avoiding pre-marital sex.

Before I close I wish to remark that carrying out any meaningful and productive research requires adequate funding which has recently become quite inadequate in the university system. There is no serious nation that can advance technologically without investing in its educational system. The current paltry funding of education in the country is appalling and unacceptable. If our leaders are to be taken seriously and want Nigeria to advance to any technological height or status, they must adequately fund education. There is no excuse, the nation possesses the resources but lacks the political will.

Thank you and God bless.

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