THE EFFECT OF EXERCISE ON SERUM IMMUNOGLOBULINS AND INTERLEUKINS IN SECONDARY SCHOOL CHILDREN

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INTRODUCTION

1.2 INTRODUCTION

Epidemiological evidence has shown that regular exercise increases the immune function while strenuous exercise leads to immune suppression (Pedersen & Toft, 2000). Accumulating facts have shown that regular exercise offers some protection against malignancy at an early stage of life (Pedersen & Toft, 2000). In this regard, cytokine released into the circulation have been implicated as a causative mediator of exercise-induced immune perturbation. Suzuki and his colleagues (2000) did a study on marathon runners and reported a significant increase in the concentration of IL-2 while a significant decrease in IL-6, -8 and –10.

Cytokines play a multifunctional role in the immune system. They mediate communication between and within immune and nonimmune cells. They play a major role in initiating the immune responses. Hence, alteration or perturbation in cytokine regulation may produce to a marked impact on the immune system. This may lead to an increase in susceptibility to infection by microorganisms that will impair the individual's life.

The beneficial effects of exercise are very well accepted. Exercise needs to be started from an early age of life and throughout ones life span. Consequently, the habit of doing exercise needs to be promoted earlier especially throughout school life.

The impact of exercise on adolescents and its beneficial effects on health has been a focus of recent research (Murray, 1994). Regular exercise is presumed to play a major role in preventing several leading degenerative diseases of modern societies. The United States Department of Health and Human Service (1992) noted that childhood is a critical time for developing healthy attitudes and behaviour patterns in relation to tobacco use, diet, physical activity and other health-related behaviours that may persist into adulthood (Flectcher *et al.*, 1996). The proper amount of exercise is presumably important for the optimal development and health status of children. Too much or too little exercise may have some adverse effects (McKeag, 1991).

In a recent survey, of more than 13 000 teenagers, only a third said they were moderately to vigorously active five or more times per week (Gordon-Larsen *et al.*, 1999). A study by Sallis & McKenzie in 1991 of 759 children who took achievement test after three different physical interventions, found that students in a health-related physical education (PE) program did as well academically as students who spent half as much time each week in PE.

Consequently, there is a need to focus on the impact of exercise on the immune system in adolescents. There is a paucity of data about this particular issue in Malaysia. Hence, the present study is designed to determine the effect of moderate exercise on the immune system of adolescents with special reference to cytokines.

1.2 STUDY OBJECTIVE

As described above, physical exercise whether acute or chronic, moderate or strenuous affects the immune system. Most previous studies done were focused on athletes or adults. However, no such studies have been done on Malaysian children in secondary school. The purpose of this study, therefore, is to determine the effect of exercise on the immune system of children.

1.2.1 GENERAL OBJECTIVE

To determine the effects of exercise on the immune system in secondary school children.

1.2.2 SPECIFIC OBJECTIVE

To determine the effect of a moderate exercise program on IL-2 and IL-4 levels in secondary school children.

LITERATURE REVIEW

2.1 THE IMMUNE SYSTEM

Immunology is a branch of biomedical science concerned with the response of an organism to antigenic challenge, recognition of self, nonself, all biological, serological, physical and chemical effects of immune phenomena (Dorland's Medical dictionary, 1995). The term immunity refers to all the mechanisms used by the body as protection against environmental agents that are foreign to the body (Benjamini *et al.*, 1996).

The study of immunology as a science or subspecialty of biology has gone through several periods of quiescence and active development. The immune system of our body can be divided into two categories, innate immunity and acquired immunity.

2.1.1 INNATE IMMUNITY

Innate immunity are all the elements with which an individual is born with and which are always present and available at very short notice to protect the individual from foreign invaders. These elements include body surfaces and internal components (Benjamini *et al.*, 1996). The internal components can be further subdivided into two subgroups, humoral and cellular parts. The humoral component include the lysozymes, complements, acute phase proteins while the cellular component include polymorphonuclear (PMN) cells, macrophages, microgial cells and natural killer (NK) cells (Parslow, 1997)

2.1.1.1 PHYSIOLOGICAL AND CHEMICAL BARRIERS

i) Skin

Skin is the first barrier against any microbial agents. Most of the microorganisms and foreign substances cannot penetrate the human skin, unless there are damages. However, some can still enter through the sebaceous glands and hair follicles. Under such condition, acids, fatty acids and enzymes in the sebaceous glands act as antimicrobial agents (Parslow, 1997).

ii) Mucous

Mucous acts as a trap to foreign bodies. It covers the surfaces of many areas in the body such as the gastrointestinal and the respiratory tracts. In the gastrointestinal tract, the presence of a low pH, proteolytic enzymes and bile acid serve as protection

against bacterial infection. A similar function is also served by the low pH of the vagina (Parslow, 1997; Benjamini *et al.*, 1996).

2.1.1.2 CELLULAR DEFENSE

i) Mechanism of cellular defense

When an invading microorganism has penetrated the various physiological and chemical barriers, various types of specialized cells act as a line of defense and destroy the invading microorganism by phagocytosis or killing it extracellularly.

ii) Cells involve with body defense

a) Polymorphonuclear (PMN) cells

PMN cells include such cells as neutrophils, basophils, eosinophils and mast cells. They function by ingesting and destroying invading foreign particles. When the invading particles are detected by the phagocytic cells, they engulfed the foreign invader and destroy it with enzymes called lysozymes (Parslow, 1997).

b) Macrophages

Macrophages originate from monocytes in the blood. They served as phagocytic cells. When macrophages enter the blood stream as monocytes, they migrate to various parts of the body and then differentiate into specific and different cells. These include: differentiation into reticuloendothelial system (RES), Kupffer cells in the liver, alveolar macrophages in the lung and as microgial cells in the nervous system (Parslow, 1997; Weir & Stewart, 1997).

c) Natural killer (NK) cells

Natural Killer (NK) cells recognize the membrane of abnormal cells. Once recognized, they are destroyed by the release of biological potent molecules that kills the target cell within a short time. The NK cells activities are highly enhanced by soluble mediators such as interleukin 2 and 12 (IL-2 and IL-12) and interferons (IFN) (Parslow, 1997; Benjamini *et al.*, 1996).

2.1.1.3 INFLAMMATION

Inflammation is a protective mechanism of tissue response to injury. It serves to destroy, dilutes or walls off both the injurious agent and the injured tissue (Dorland's medical dictionary, 1995). Inflammation is a complex process, comprising of many events. Its is initiated by tissue damage caused by endogenous as well as exogenous factors. The inflammation process tends to bring the injured tissue back to normal. It begins with the activation and increase concentration of pharmacological powerful substances, like the group of proteins called acute-phase proteins. One of the most important members in this group is C-reactive protein.

The cardinal sign of inflammation then appears. These signs are: tumor (swelling), rubor (redness), color (heat), dolor (pain) and loss of function of the inflamed cells (Chandrasoma & Taylor, 1998). The chemical mediators that play a major role in inflammation are; IL-1, IL-6, tumor necrosis factor alpha (TNF-α) as well as IL-8 and IFN-γ (Parslow, 1997).

2.1.1.4 BIOLOGICAL ACTIVE SUBSTANCES

Many tissues synthesize substances that are harmful to microorganisms. Examples of these are, degradative enzymes, toxic free radicals, growth inhibitors, acute phase proteins and interferons.

2.1.2 ACQUIRED IMMUNITY

Acquired immunity is more specialized and supplements the protection provided by innate immunity. Acquired immunity, in evolutionary terms, came into play relatively late, and is present only in vertebrates.

Elements that participate in acquired immunity show specificity against foreign agents in contrast to innate immunity. The response in acquired immunity is greater and faster as compared to innate immunity (Benjamini *et al.*, 1996).

An acquired immunity can be subdivided into two components, involving two types of cells. There are the lymphocytes, T-cells and B-cells as well as two humoral components, immunoglobulins (Ig) and interleukins (IL) (Weir & Stewart, 1997).

A normal adult human body has about a trillion lymphocytes. The T- and B-lineage cells arise from a subset of haematopoietic stem cells in the bone marrow or foetal liver (Weir & Stewart, 1997). A typical lymphocytes is a small, round or club-shaped cell, 5-12 μm in diameter with a roughly spherical nucleus, densely compacted

nuclear chromatin and a cytoplasm so scanty as to be scarcely detectable under the light microscope (Benjamini *et al.*, 1996).

There is considerable evidence for the existence of a committed marrow progenitor, called the lymphoid stem cells, that serves as a common precursor for both T- and B-cells. The progeny of this stem cell undergoes different pathways of maturation to be T or B-cells (Benjamini *et al.*, 1996; Roitt *et al.*, 1989).

2.1.2.1 T-CELLS

The T-cells account for about 75% of all lymphocytes. This group of lymphocytes developed from an immature precursor cells that leave the marrow and travel through the blood stream to the thymus. In the thymus they mature and become mature T-cells. These thymus-derived cells are the source from which the word T lymphocytes are derived (Weir & Stewart, 1997).

i) Site of maturation

The maturity of T lymphocytes occur mainly during foetal development and for a short time after birth. Removal of the thymus gland in the neonate results in a severe reduction of the quantity and quality of the T lymphocytes. However, removal of the thymus in an adult results in a less undesired affect, since the T lymphocytes have already matured and populated the secondary lymphoid organ (Roitt *et al.*, 1989).

ii) Cells types

a) T-lymphocytes

T-cells can be classified into two subsets known as CD4 and CD8. Mature and functional T-cells always express either one of these surface proteins. The cells that express CD8 have the capability of being cytotoxic or the ability to kill target cells. CD8 T-cells is synonymous with T_C cells or cytotoxic T-lymphocytes (CTLs) and they play a major role against viral infection (Weir & Stewart, 1997).

The T lymphocytes that express CD4 protein on their surface are known as T-helper cells. Helper cells, CD4 T-lymphocytes, do not have cytotoxic capability but instead function as helper T-cells (T_H cells). Roughly, 70% of T-cells in human blood are $CD4^+CD8^-$ (equal to CD4 cells) whereas 25% are $CD4^-CD8^+$ (CD8 cells) the remaining 5% form double positive or double negative ($CD4^+CD8^+$ or $CD4^-CD8^-$) (Table 2.1, Benjamini *et al.*, 1996).

T-lymphocytes detect foreign bodies by way of surface proteins called T-cell receptors. These receptors are not secreted into the blood stream, hence T-cells lack the ability to strike at long distance targets (Weir and Stewart, 1997).

T-cells can detect foreign bodies only by making a specific contact and after the foreign substances are cleaved into small peptides. This cleavage is carried out by the so called antigen-presenting cells (Benjamini *et al.*, 1996).

Table 2.1: Major T–cell subsets found in normal blood and peripheral tissues (Parslow, 1997).

SURFACE PHENOTYPES	PREDOMINANT FUNCTION	PROPORTION OF TOTAL LYMPHOCYTES	RECEPTOR TYPE
$CD4^+ CD8^-$	Helper	70%	α/β
$CD4^- CD8^+$	Cytotoxic	25%	α/β, rarely γδ
$CD4^- CD8^-$	Cytotoxic	4%	γ/δ
$CD4^+ CD8^+$	Unknown	1%	α/β

2.1.2.2 B-CELLS

The major difference and defining feature of cells in the B-cell lineage is their ability to produce immune protein called immunoglobulin, where no other single cells produce this protein. In embryonic life, B-cells differentiate from haemetopoietic stem cells in the liver. After birth and the rest of the human life, this function shifts into the bone marrow. The bone marrow is considered as a primary lymphoid organ that is equivalent to the Bursa of Fabricius (DeFranco, 1997).

All mature B-lymphocytes express antigen specific receptors that have a structure and specificity identical to the antibody. The mature B-cells are transported to the secondary lymphoid organ by circulating blood. During the transfer, when they encounter a foreign antigen, they are activated and respond to it. When an activated B-cell divides, some of its progeny becomes memory B-cells while the rest will differentiate into plasma cells (DeFranco, 1997; Benjamini *et al.*, 1996).

The main function of B-lineage cells is to secrete antibodies into the blood and other body fluids thereby making these fluids inhospitable for foreign invaders. They are the principal cell types involved in humoral immunity. B-cells also function as antigen-presenting cells and as a source of lymphokines. These are important mediators that are involved in cell maturation and immune response (DeFranco, 1997).

2.1.2.3 IMMUNOGLOBULINS

Immunoglobulins are globular protein that serves as critical ingredients at every stage of humoral immunity. There are two types of immunoglobulins:

i) Immunoglobulin expressed on the surface of resting B-lymphocytes that serve as receptors

ii) Immunoglobulins that are secreted into circulation to function as antibodies.

(Parslow, 1997; Weir & Stewart, 1997)

The immunoglobulins are a related family but nonidentical glycoproteins. The biologic attributes of immunoglobulins are determined by its polypeptide components. Secreted immunoglobulins, known as antibodies are bifunctional molecules in that they bind specifically to antigens and also initiate a variety of secondary phenomena such as activation of complement, opsonisation or signal tranduction.

Every immunoglobulin molecule is made up of two different types of polypeptides, the larger, heavy (H) chains and smaller, light (L) chains. The chains are held together by noncovalent forces as well as covalent interchain disulfides bridges to form a bilaterally symmetrical structure. All light chains proteins have a molecular weight of approximately 23 000 D and can be classified into two distinct types, called kappa (κ) and lambda (λ). On the other hand, heavy chains proteins have a molecular weight of about 50 000 to 70 000 D. There are also five different classes or isotypes (Parslow, 1997).

The five classes of the heavy chains polypeptides are designated μ, δ, γ, α and ε and immunoglobulins that contain these heavy chains are designated the IgM, IgD, IgG, IgA and IgE respectively (Parslow, 1997)

i) Immunoglobulin G (IgG)

IgG accounts for approximately 75% of the total serum immunoglobulin in normal adults and is the most abundant antibody produced during secondary immune responses in the blood. IgG is the only immunoglobulin that can cross the human placenta and it is responsible for providing the newborn with protection during the first month of life (Parslow, 1997; Benjamini *et al.*, 1996).

ii) Immunoglobulin A (IgA)

IgA is the predominant immunoglobulin produce by B-cells in Peyer's patches, tonsils and other submucosal lymphoid tissues. It accounts for only 10 to 15% of total serum immunoglobulin, it is by far the most abundant class of antibody found in saliva, tears, intestinal mucus, bronchial secretion, milk, prostatic fluid and other secretions (Parslow, 1997)

iii) Immunoglobulin M (IgM)

IgM constitutes about 10% of normal serum immunoglobulin and it is normally secreted as J-chain-containing pentamer with a molecular mass of approximately 900 kD. IgM predominates in early primary immune responses to most antigens. IgD often accompanies IgM. These are the most common immunoglobulins expressed on the surface of the B-cells, particularly virgin B-lymphocytes (Parslow,1997; Weir & Stewart, 1997).

iv) Immunoglobulin D (IgD)

IgD molecule is a monomeric four-chain unit with a molecular mass of approximately 180 kD and commonly found on the surfaces of B-lymphocytes. It is rarely secreted in significant amounts. The physiologic function of IgD is still unknown. It is relatively labile and is easily degraded by heat or proteolytic enzymes (Parslow, 1997; Weir and Stewart, 1997).

v) Immunoglobulins E (IgE)

IgE represents only a minute fraction of all serum antibodies, IgE is extremely important from a clinical standpoint because of its central involvement in allergic reactions (Parslow, 1997).

2.1.2.4 CYTOKINES

All communications need a medium to transfer the information. In the body, the medium is through chemical mediators. In the immune system most of the critical interaction among cells is controlled by soluble mediators called cytokines.

The cytokines are a diverse group of intercellular-signaling proteins that regulate local and systemic immune response, inflammatory response, wound healing, haematopoiesis and many other biological processes (Oppenheim & Ruscetti, 1997). Benjamini *et al.* (1996) defined cytokines as antigen-nonspecific soluble factors.

There are over 100 structurally different and genetically unrelated cytokines that have been identified. These are polypeptides or glycoproteins with molecular

weight (MW) of 6000 to 60 000 D. These mediators are highly potent and act by binding to specific surface receptors at concentrations of 10^{-9} to 10^{-15} M. Most of the cytokines act either as paracrine or autocrine. They are not produced by a specific gland like endocrine hormone but they are produced by a variety of different tissues and individual cells (Oppenheim & Ruscetti, 1997).

Most of the activities of cytokines are redundant or extensively overlap. One cytokine may induce the secretion of another cytokines. Due to the redundancy and complex interactions, it is quite perilous to extrapolate from an *in-vitro* study of cytokines and use it to assess its role in an intact organism (Moldoveanu *et al.*, 2001; Oppenheim & Ruscetti, 1997).

Cytokines nomenclature has little to do with structural relationship among molecules. Cytokines produced by lymphocytes are known as lymphokines, whereas those produced by monocytes or macrophages are called monokines. Some of them, known as interleukins (IL), have been assigned numbers in sequence from IL-1 to IL-16. Many of the rest of the cytokines still retain their descriptive and frequent misleading historical name (Oppenheim & Ruscetti, 1997).

Cytokines act over both short and long range, with consequent systemic effects. They play a crucial role in amplification of the immune response. The release of cytokines from just a few antigen-activated cells results in the activation of multiple different cell types (Moldoveanu *et al.*, 2001).

2.1.2.4.1 INTERLEUKIN 2 (IL-2)

Interleukins belong to the cytokine groups. Interleukins are referred to as cytokines that are produced by one type of leukocyte and affect other leukocytes. IL-2 is an autocrine and paracrine growth factor that is secreted by activated T-cells and is essential for clonal T-cell proliferation.

IL-2 molecule is a polypeptide, that is made up of about 133 amino acids and has a molecular weight of 15 400 D. It is encoded by a single gene on the human chromosome 4. Its amino acids sequence shows no similarity with any other known cytokine. It can be also glycosylated to multiple degrees to produce higher molecular weight species. IL-2 is a globular protein with two alpha (α) helices that are arranged to form hydrophobic planar faces around a very hydrophobic core. This configuration is maintained in part by a single interchain disulfide bond, that is essential for biologic activity (Oppenheim & Ruscetti, 1997; Benjamini *et al.*, 1996).

IL-2 is one of the most critical immunoregulatory cytokines that is essential for the T-cell proliferation. It affects cytokine production and the functional properties of B-cell, macrophages and NK cells (Oppenheim & Ruscetti, 1997; Weir & Stewart, 1997).

Resting T lymphocytes do not synthesize or secrete IL-2 but can be induced to do both by an appropriate combinations of antigen and costimulatory factors or by exposure to polyclonal mitogens. Antigen-induced IL-2 production occurs mainly in

CD4 T_H cells. CD8 lymphocytes and some NK cells can however, also be induced to secrete IL-2 under certain conditions (Oppenheim & Ruscetti, 1997; Weir & Stewart, 1997).

IL-2 has a very dominant effect on T-cells. When normal human T lymphocytes are exposed to a T-cell mitogen, IL-2 mRNA expression becomes detectable after four hours, reaching a peak after twelve hours and then declines rapidly (Moldoveanu *et al.*, 2001).

IL-2 also has an effect on NK cells. The unique characteristic of NK cells is that they express the IL-2 receptor (IL-2R) on its surface. This enables NK cells to response to IL-2 even during their resting state. However, this response is weak. Once NK cells have been activated, they express the IL-2α chain. This requires a high affinity receptor unlike that of its resting state. IL-2-stimulated NK cells have enhanced cytolytic activity, secrete numerous cytokines, including interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα). These are potent activators of macrophages. IL-2 also induces lymphokine-activated killer (LAK) activity that is predominantly due to the NK cells (Moldoveanu *et al.*, 2001; Oppenheim & Ruscetti 1997; Benjamini *et al.*, 1996).

On the other hand, activated B-cells express high-affinity IL-2R of about 30% the density found on T-cells. IL-2 enhances proliferation and antibody secretion by normal B-cells at concentrations of two to threefold higher than that required to obtain T-cell response. It also influences the heavy-chain class switch, biasing B-cells towards expression of IgG2 antibodies (Oppenheim & Ruscetti, 1997).

Human monocytes and macrophages express low levels of IL-2R β. This is a low affinity receptor that continuously but inducibly expresses high affinity receptors containing all three chains on exposure to IL-2, IFNγ or other activating agents. Continued exposure of an activated macrophage to a higher concentration of IL-2, enhances its microcidal and cytotoxic activities, promotes hydrogen peroxide production, TNFα, IL-6 and activation of neutrophils (Oppenheim & Ruscetti, 1997; Benjamini *et al.*, 1996).

High-dose of IL-2 has been tested as an immunostimulatory agent in the treatment of a variety of cancers. This produced a partial remission in about 20% of patients with renal carcinoma or metastatic melanoma (Oppenheim & Ruscetti, 1997; Benjamini *et al.*, 1996).

2.1.2.4.2 INTERLEUKIN 4 (IL-4)

IL-4 has a molecular weight of 15 000 to 20 000 D. It is a glycoprotein secreted by activated CD4 T cells of the T_H2 subset and by mast cells. It was initially identified as a helper factor for B-cell proliferation and was known as B-cell growth factor-I. IL-4 was also previously known as B-cell stimulatory factor-I because of its ability to induce class II MHC expression on resting B-cells (Oppenheim & Ruscetti, 1997).

IL-4 is a major regulator of the heavy-chain class switch. It promotes switching to IgG4 and IgE. IL-4 can induce the expression of low affinity Fcε receptors (Oppenheim & Ruscetti, 1997).

IL-4 also promotes the induction of T_H2 cell that controls the proliferation and activities of eosinophils and mast cells. In contrast, IL-4 suppresses the induction of T_H1 function, which controls many facets of cellular immunity. Besides that, IL-4 also promotes cytotoxic T-cell activity, enhances IL-3 mediated mast cells growth and acts synergistically with colony stimulating factors (CSFs) to enhance the growth of various hematopoietic cells. It also induces vascular cell adhesion molecule 1 (VCAM-1) on endothelial cells (Oppenheim & Ruscetti, 1997).

IL-4 produces multiple effects on macrophages. It activates macrophage cytocidal functions and increases macrophages class I MHC proteins. It also suppresses the synthesis of proinflammatory cytokines such as IL-1, IL-6, IL-8 and TNFα that has been produced by activated monocytes (Oppenheim & Ruscetti, 1997). The IL-2 and IL-4 have various effects on immune function especially on T-cells and B-cells respectively (Figure 2.1).

Both innate and acquired immune systems are related and supplement each other, this relationship is shown in Figure 2.2.

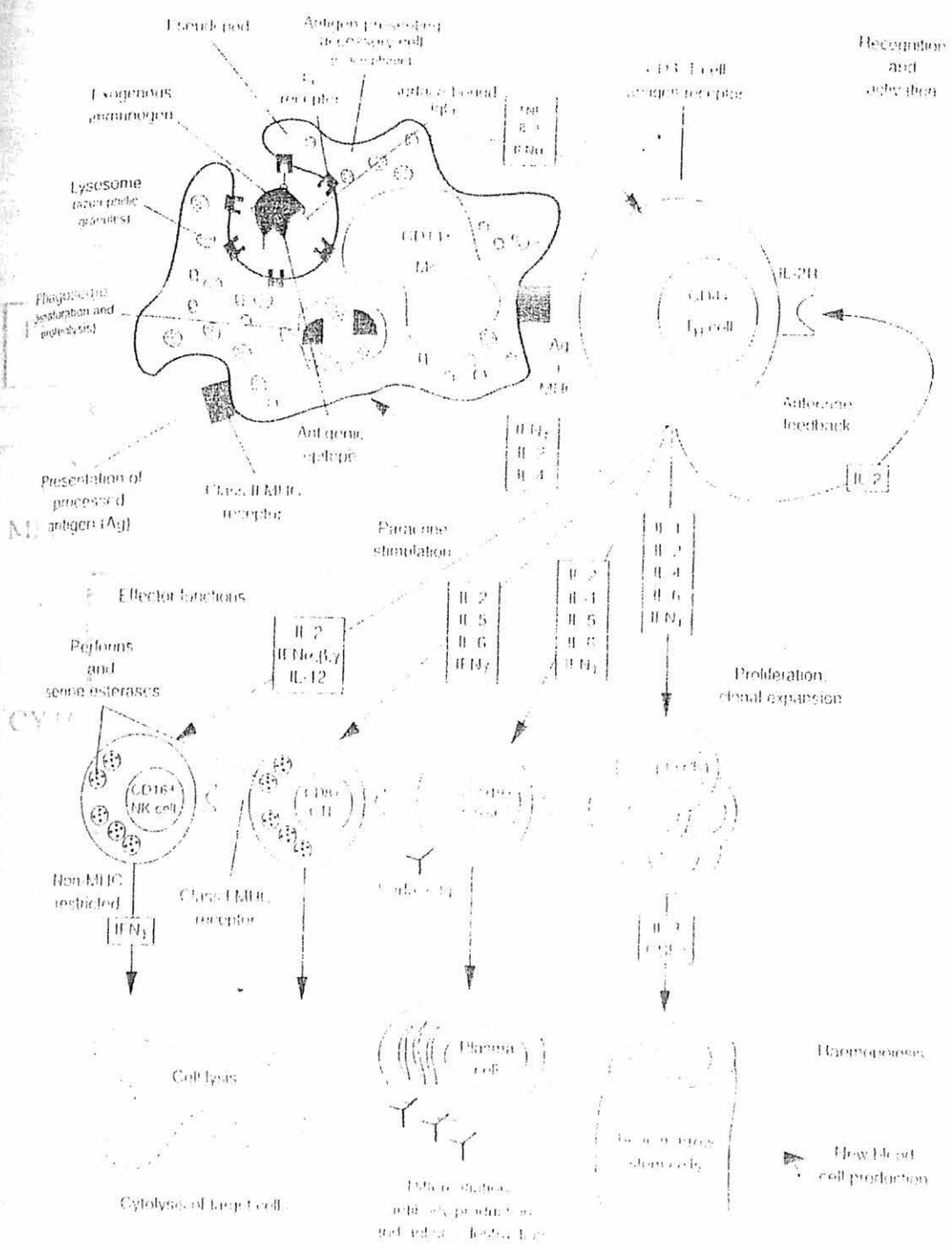

Figure 2.1: The numerous functions of cytokines in immune system (Shephard *et al.*, 1994)

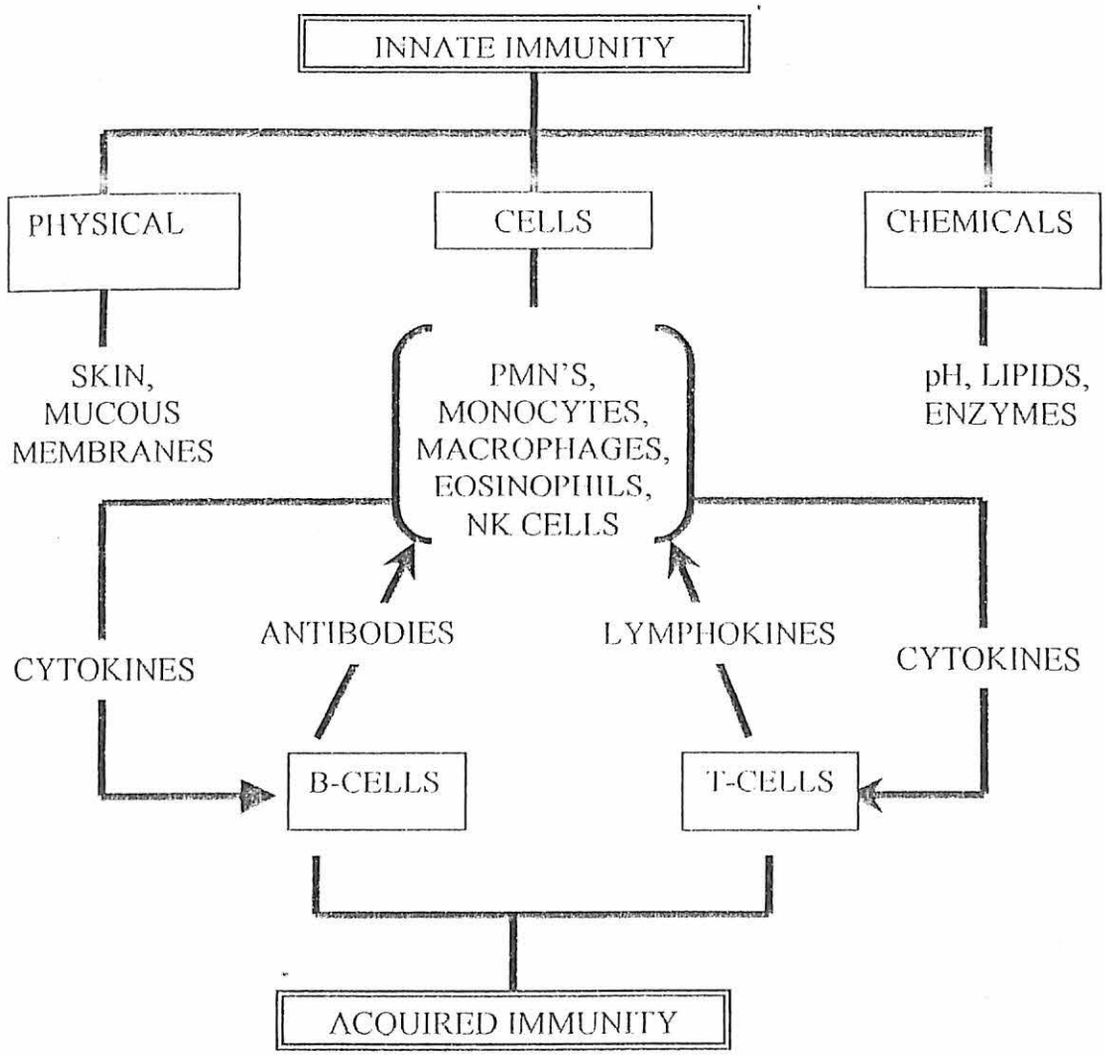

Figure 2.2: The interrelationship between innate and acquired immunity (Benjamini *et al.*, 1996)

2.2 PHYSICAL ACTIVITY

Physical activity, exercise and physical fitness are often used interchangeably (LaPorte *et al.*, 1985). Physical activity is any bodily movement that results in energy expenditure above basal rate. It is an inclusive term that includes both static and dynamic skeletal contraction as well as aerobic and anaerobic metabolism (Hoffman-Goetz, 1998). Physical activity is frequently measured in populations as occupational, household, leisure time, recreational and activities of daily living.

Exercise on the other hand, is a subset of physical activity and is defined as planned, structured, repetitive activities that improve or maintain the components of physical fitness (Caspersen *et al.*, 1985). Exercise is usually measured in clinical and experimental setting along the dimensions of intensity and duration using measures of maximal oxygen uptake (VO_2 max), heart rate and time to exhaustion. On the other hand, physical fitness is conceptualised as the ability to carry out daily task, including exercise with vigor, alertness and without undue fatigue (Robbins *et al.*, 1999).

Physical fitness, which reflects interactions between the environment (exercise training) and genetic capacity, is often measured by cardiorespiratory endurance, changes in body composition, skeletal muscle strength, power, speed, flexibility, agility, balance and reaction time (Hoffman-Goetz, 2000).

The goals of an exercise is to improve oxygen delivery and metabolic process, build strength and endurance, decrease body fat and improve movement in joints and muscles. All of these benefits are essential for health.

Exercise should not be used or applied to a specific group of people, and should be used as a preventive rather than corrective tool. The American Heart Association recommends that individuals engage in 30 minute or longer workouts at least three or four times per week. Exercising more than five times a week for 20 to 24 minutes each session may be closer to optimum.

2.2.1 TYPES OF PHYSICAL ACTIVITY

There are a few types of exercise or physical activities that can be applied to obtain different benefits. This can be divided into three general categories, which are aerobic, strength and flexibility exercises. It is also recommended that a well balance exercise must contain all these three categories.

Jogging, swimming, cycling, stair climbing and aerobic dancing are a few examples of aerobic exercise. Aerobic exercises build endurance and keep the heart pumping at a steady but elevated rate for a longer period. On the other hand, for a physical activity pyramid (PAP), the desired effect is achieved if the aerobic exercise is done for about 25 to 30 minutes, three to six times per week (Simon *et al.*, 1999).

Strength or resistance training is more on muscle strength. With reference to PAP, strength training is recommended two or three times per week, one to three set with eight to twelve repetitions per set. The American College of Sports Medicine has recommended at least two times per week of strength training. Precautions need to be taken if some one has cardiovascular disease and are not advised to do isometric training (Robbins *et al.*, 1999; Simon *et al.*, 1999)