IMMUNOLOGICAL ASPECTS IN RHEUMATIC FEVER IN CHILDREN

Essay

Submitted in partial fulfillment for the requirements of the Master degree (PEDIATRICS)

BY

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(1984)
ACKNOWLEDGEMENT

I am greatly indebted to professor Dr. AHMED ABD-EL-MONEIM KHASHABA, professor and chairman of pediatrics, Benha faculty of medicine, for his kind supervision, support and continuous encouragement.

I wish to express my deepest thanks and gratitude to Dr. MOHAMED KAMEL RIZK, Assistant professor of pediatrics, Benha Faculty of Medicine, for his kind cooperation, advice, and valuable guidance throughout the whole work.

Finally, I would like to express my greatest gratitude to all members of pediatric departement in Benha Faculty of Medicine.
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AIM OF WORK

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INTRODUCTION
INTRODUCTION AND AIM OF THE WORK
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The immunological system is that part of a host defence mechanism which include the macrophages, the leucocytes, the lymphocytes, the complement system and physical barrier such as motile cilia.

Its primary function is to protect against invasion by infectious agents.

The major cost of this protection are allergy, auto-immunity and rejection of the organ transplanted (Hong, 1983).

Rheumatic fever and consequently rheumatic heart disease are major medical and social problems. Many theories have been postulated for the pathogenesis of rheumatic fever among which is the immunological theory.

Acute rheumatic fever is a delayed, non suppurative sequelae of pharyngeal infection with the group A beta-haemolytic streptococci. In its classic form, the disease is an acute febrile illness characterized by inflammatory lesion of the heart, joints, and subcutaneous tissue. The clinical manifestation are quite variable but ordinarily include carditis, polyarthritis and chorea in varying combination (Markowitz et al., 1965).
Several attempts have been done to explain exact pathogenesis of rheumatic fever. A number of reports published recently have suggested the evidence in favour of an immunological process (Kaplan, 1978).

Our aim is planned to determine the pattern of immunological process and to review immunological basis in rheumatic fever.
REVIEW OF LITERATURE
IMMUNE SYSTEM OF THE BODY

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.

A normally functioning immune system is an effective defence against foreign particles such as pathogenic microbial agents and against native cells that have undergone neoplastic transformation. Defective function of the immune system results in disease (Katz, 1982).

The cellular components of the immunological system:

The versatility of the immune system arises through the action of a number of subpopulation of the T and B cells and macrophages.

The functions of B cells are:

- Synthesize and secrete major classes of immunoglobulin which protect against staphylococcus, streptococcus, hemophilus and pneumococci.
- Neutralize viruses to prevent initial infection.
- Act as Barrier along gastro-intestinal and respiratory tract.
- Initiate killing of the micro-organisms by macrophages.
- Cause secretion of vaso-active amines from mast cells and basophils.
- Actively lyse cells of autologous origin or engage in antigen-antibody complex disease.
- Interfere with killer cell activity directly or indirectly blocking the reaction.

Functions of the T cells:
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There are cellular subpopulation of the T cells, helper, suppressor and killer population.

The helper cells are necessary in the initial antigen response, especially to generate IgG and IgA response. The T suppressor cells serve a homeostatic role in keeping the immune response within a tolerable level. The immune response, because of its great potential for harm as well as good, must be modulated to prevent hyper immune reaction, this process is thought to be accomplished by the T suppressor cells. The T killer cells combine with the
antigen to initiate cytotoxic mechanisms which kill the invading organisms.

The role of macrophage:
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It is the major phagocytic cell of the monocyte-macrophage system, also plays a key role in antigen processing i.e. it presents the antigen for lymphocytes. It also regulate the activity of lymphocyte by soluble factors (Hong, 1983).
THE DEFENCE MECHANISMS AGAINST
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INFECTION
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The healthy individual is able to protect himself from potentially harmful micro organisms in the environment by a number of very effective mechanisms.

These defence mechanisms are both non-specific and specific (Valdimarson, 1975). The non-specific mechanism constitute the first line of defence and are largely responsible for the natural (innate) immunity, while the specific mechanism deal primarily with these organisms which are capable of possessing non-specific barrier. Specific immunity is always acquired and its cardinal feature are the ability to recognize and memorize antigenic experience thus leading to an enhanced capacity to resist infections.

The mechanism of resistance may be separated into two major system (Beisel, 1977); -

I - **Non-specific immunity**:

1. Anatomical barriers.
2. Exogenous body secretion e.g. mucin, lysozyme.
3. Inflammatory reactions.
4. Febrile and metabolic responses.
5. Phagocytic functions.
6. Non-specific factor in plasma i.e. interferon, lysozyme, and iron binding proteins.

II - Specific immunological response or specific immunity:

1. Cell mediated immunity:
   Comprises, T-lymphocytes, lymphokines and macrophages.

2. Humoral immunity:
   Comprises, B-lymphocytes, immunoglobulins, complement and polymorphs nuclear leucocytes.

I - Non specific Immunity

The body possesses a variety of non-specific factors that contribute to host resistance against all types of microorganisms.

1. Anatomical barriers:

   The intact skin and mucous membranes of the body afford effective protection against many organisms (Waldman, 1970). Vitamin A, B complex, C, Proteins and zinc appear to exert their great influence in the maintaining of these barriers (Neumann, 1977).
2. Exogenous body secretions:

Nasal secretion and saliva contain mucopolysaccharides capable of inactivating some viruses (Miller, 1969). The tears contain lysozyme active against gram-positive bacteria.

The sweat and sebaceous secretion of the skin contain bactericidal and fungicidal fatty acids (Waldman, 1970). Protection against infection with many respiratory and enteric viruses has better correlation with the presence of antibody (Secretory IgA) in the mucous secretion than with humoral antibody (Orga and Karzon, 1970). Colostrum and breast milk also contain virus neutralizing antibodies (Adcock and Green, 1971).

3. Inflammatory responses:

Inflammatory responses can provide an early host defensive reaction. It localizes invading microorganisms and prevent their further spread (Movat, 1972).

4. The metabolic responses:

The metabolic response of host cells, involve a wide array of discrete metabolic pathways and molecular functions of individual cells (Beisel, 1972). These mechanisms help the body to meet the stress of generalized
infectious process, including elevated body temperature, the diminished nutrient intake and the initiation of active energy-requiring host defensive reactions.

5. Phagocytosis:

Once microorganisms have established an infection, various elimination mechanisms become involved, of which phagocytic activity.

6. Non-specific plasma factors:

A variety of non-specific plasma substances makes important contribution to the non-specific aspects of host defence:

a) Lysozyme:

It is a protein enzyme found in respiratory and intestinal mucosa, saliva, tear, breast milk, sweat and the cytoplasm of leucocytes and monocytes. It can lyse certain types of gram-negative bacteria by attacking the mucopolysaccharides of their cell walls. Also its activity has been noted against certain viruses (Stiehmn and Fulginiti, 1973).

b) Iron binding proteins:

Certain bacteria as pasteurella septic, E. coli and clostridium welchii require iron to manifest their pathogenicity and they have to compete with iron binding
proteins such as transferrin and lactoferrin for supplying with this element.

Transferrin produced by the liver and lactoferrin released by phagocytic cells, are found in milk, tear, saliva, bile, seminal secretion and in specific granules of leucocytes.

Transferrin and lactoferrin are thought to have an anti-bacterial effect because of their high affinity for iron, and their binding action diminishes the availability of iron for utilization by proliferating micro-organisms. The bactericidal and static effect of breast milk is due mainly to its content of large quantities of lactoferrin and transferrin (Bullen et al., 1972).

c) Interferons:

These are a family of protein, which are released under the stimulus of viruses. They appear to act on other uninfected cells to reduce their susceptibility for colonization by the virus.

d) The concentration of lactic acid in inflammatory foci can exceed the level which kills some bacterial pathogens in vitro. Lactic acid production is decreased in diabetic subjects, hence their ability to localize the infection is diminished (Valdimarson, 1975).
HUMORAL IMMUNITY AND COMPLEMENT

When considering host defences against infection the humoral immune and complement systems are often grouped together because they are soluble proteins found in serum and are involved as effector molecules. This superficial resemblance and functional interaction bind these system together, however they are quite discrete from several standpoints (Root, 1979):

1. The complement system can respond immediately to a variety of activator substance through the involvement of a series of enzymatic reactions leading to changes in vascular permeability, alteration in leucocyte function, and lysis of specific organisms or cells. In contrast, the humoral immune system respond only to specific antigens with the elaboration of immunoglobulins that do not have enzymatic activity but exhibit high specificity for binding with their respective antigens.

2. The complement system is comprised of components that are available at all times in the circulation of the human host for activation by certain stimuli - in contrast, specific antibody formation takes place after a complex series of cellular events which may
require days or weeks to become clinically detectable and significant. Unless previous experience has been gained with a given or closely related organism, antibody-mediated function are unlikely to play a significant role in host defence until at least several days after an infection has become established. In contrast once mucocutaneous barrier have been breached, the complement system can act in concert with the acute inflammatory defences to play an immediate role.

3. By antigen binding, antibodies can participate in host defence by opsonizing organisms for phagocytosis, by lysis of infectious agent or by neutralization of their infections or toxic capabilities. In a number of these functions antibodies play a cooperative role with components of the complement system, as well as with phagocytic cells, for example, antibodies of IgG or IgM subclass can activate the complement system through the so-called classical pathway. Receptors on both lymphocytes and phagocytes can bind subclasses of immunoglobulins or third and fifth components of complement and thus can be integrally involved in the humoral immune system. Since both the complement and antibodies may use phagocytic cells to complete their effector role in defence against infection, deletion
in either may have similar consequence to the host i.e. recurrent systemic bacterial infection.

The humoral immunity is dependent on antibody production by B-lymphocyte-plasma cell system which are thymus independent and they represent Bursal equivalent or bone marrow derived cells.
ANTIBODY MEDIATED HUMORAL IMMUNITY

Once infected the human host has the capacity of developing a variety of antibodies in response to specific microbial antigens. Such antibodies aid the host to eradicate the organism particularly if it is an obligate extracellular parasite.

Immunoglobulin structure:

All antibodies are glycoproteins known as immunoglobulins (Ig). Immunoglobulins are subdivided into five classes in order of decreasing concentration, IgG, IgA, IgM, IgD and IgE (properties of each class are shown in table (1)). The basis for the distinction between classes can be appreciated from Ig structure. The fundamental structure unit of Ig (Weir, 1983) is shown in figure (1). Each unit consists of four polypeptide chains, two identical light chain (L chains) and two identical heavy chains (H chains). The four chain are held together by disulphide bonds. Light chains may be of two types, designated kappa (K), or lambda (L). In contrast heavy chain are specific for each class of immunoglobulins and named in accordance with the class. Thus,
\[ x = \text{for some value} \]

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*Certain altered reagents*

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Table (1) Properties of Immunoglobulin classes. (Kimball, 1963)
Fig. (1): Diagrammatic view of structural arrangements of polypeptide chains of immunoglobulin molecule. (Weir, 1983).
for IgG, IgA, IgM, IgD and IgE, the heavy chains are respectively designated gamma (\( \gamma \)), alpha (\( \alpha \)), mu (\( \mu \)), delta (\( \delta \)) and epsilon (\( \xi \)). The heavy chains each have a central hinge region at which they are linked in pairs by disulphide bonds and to one half of each heavy chain a light chain is linked also by disulphide bond proximally. This hinge region of various Ig classes had considerable diversity in amino-acids sequence and disulphide linkages endowing each Ig class with its unique characteristics (Stiehm, 1977).

Immunoglobulin molecules can be split in different ways by proteolytic enzymes: papain breaks it below the hinge region resulting in two identical Fab fragments (fragment antigen binding) that retains the capacity to bind but not to precipitate antigen and Fc fragment "fragment crystalline", since it is easily crystallized, it carries no antibody activity but a variety of effector reaction e.g. membrane transmission, macrophage fixation and complement fixation (Porter, 1959).

Immunoglobulins are classified into several classes according to the marked antigenic and structural differences in the region of their heavy chains. There are immunoglobulins subclasses, four subclass for IgG which
are IgG1, IgG2, IgG3, IgG4, two subclass for IgA, which are IgA1, IgA2 and two subclass for IgM which are IgM1 and IgM2 (Kunkel, 1982).

Immunoglobulins classes:
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1. IgG:

It consititute approximately 75% of the total serum immunoglobulins. It is the only class that can cross the placenta, so it is responsible for protection of the newborn during the first months of life. It is also capable to fix serum complement.

2. IgA:

It is the predominant immunoglobulin class in body secretions, so its main function not to destroy the antigens but prevent the access of these antigens to the general immunological system. It provides primary defence mechanism against local infection.

3. IgM:

It is the most efficient complement fixing immunoglobulin. it is also prominent in early immune response to most antigens.

4. IgD:

It is predominant immunoglobulin on the surface of human B-lymphocytes, and it has been suggested that IgD
may be involved in the differentiation of these cells.

5. IgE:

It trigger the release from mast cells of pharmacologic mediators responsible for the characteristic wheal and flare skin reactions evoked by the exposure of the skin of allergic individual to allergens (Goodman, 1982).

Role of Antibodies in Protection against Infection:

Specific antibodies can be involved in this process by promoting the following (Root, 1979):

1. Opsonization of organisms for destruction by phagocytic cells.

2. Activation of cell for lysis of susceptible organisms by the complement system.


4. Inhibition of attachment of organism to host cells.

5. Inhibition of the infectivity of extra cellular viruses (Virus neutralization).
COMPLEMENT SYSTEM IN HOST

DEFEENCE

The complement system was originally defined as those factors present in fresh serum which are responsible for the lysis of antibody coated (sensitized) bacteria and cells (Rapp and Borsos, 1970). It is now thought that one major function of the system is to mediate opsonization and to induce and modulate certain feature of the inflammatory response (Atkinson and Frank, 1980). It consists of at least 15 chemically and immunologically distinct serum proteins which are capable of interacting with each other, with antibody and with cell membrane leading to generation of biologic activity. The individual proteins of this system exist in plasma in an inactive or native state. The native precursor molecules are designated by numerals $C_1$, $C_2$, $C_3$, ..., $C_9$, ... etc. $C_1$ is unique among these proteins in that it is a tetra molecular complex bound together by calcium ion and designated $C_{1q}$, $C_{1r}$, $C_{1s}$, and $C_{1t}$ (Assie and Painter, 1975).

When activated, the complement components interact in an orderly sequential fashion and this has been referred to as "cascada", in that the activation of each component (except the 1st) depends upon the activation of the prior
component in the sequence. Fragments derived from cleavage of components during reaction are designated with small letters following the number or capital letter of the parent protein as in C_{3a}, C_{3b} ... etc. When one of these protein assumes enzymatic activity a bar is placed above it e.g. C\textsubscript{1} or C\textsubscript{3} to distinguish it from the native or inactive molecules.

The different activator of the complement system for both classic and Alternative pathways are demonstrated in table (2).

The sequential activation of the complement components follow two main pathway, the classical and the alternative pathways.

I The classical pathway:

Activation of the classical pathway usually requires initiation by the intraction of specific antibodies of the IgG, IgG\textsubscript{3} or IgM subclasses with an antigen usually cell bound.

The efficiency of IgM antibody to bind and activate C\textsubscript{1} is greater than IgG, so only one molecule of the former is required. Two molecules of the latter for each molecule of C\textsubscript{1} (Borsos, 1971).
Table (2): Activation of the complement (C) system (Cooper, 1982).

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<th>Alternative</th>
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<tr>
<td>Immunologic</td>
<td>IgG, IgM</td>
<td>IgA, IgG</td>
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<tr>
<td>non-Immunologic</td>
<td>Trypsin like</td>
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<td>DNA</td>
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<td></td>
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Under certain circumstances products of microorganisms (e.g. lipid A of endotoxin, staphylococcal protein A) or plasmin may activate $\text{C}_1$ directly without the participation of antibody.

Also C-reactive protein, an acute phase reactant which is often increased in concentration in some disease and during inflammatory states, is capable of binding and then activating $\text{C}_1$ e.g. the reaction of this protein with pneumococcal $\text{C}$-polysaccharide in the presence of calcium causes the activation of $\text{C}_1$ (Kaplan and Volanakis, 1974).

When IgG or IgM antibody is complexed to an appropriate antigen such as foreign bacteria, the reaction begins by fixation of $\text{C}_1$ by the way of $\text{C}_1q$ to the Fc portion of the antibody molecule.

In the presence of calcium ions a trimolecular complex, $\text{C}_1qrs$, is then rapidly formed with the generation of an enzyme with esterase activity from $\text{C}_1s$ portion of $\text{C}_1$ (Valet and Cooper, 1974).

The activity of $\text{C}_1$ is modulated by a natural humoral inhibitor, the $\text{C}_1$ inhibitor. The fourth ($\text{C}_4$) and the second ($\text{C}_2$) components are the natural substrate of $\text{C}_1$. Cleavage of $\text{C}_4$ result in a large fragment of ($\text{C}_{4b}$), and a small fragment ($\text{C}_{4a}$).
The next step is cleavage of $C_2$ by $C_4^-$ into two fragment $C_{2a}$ and $C_{2b}$. The two fragment $C_{4b}$ and $C_{2a}$ combine to form bimolecular complex $C_{42}^-$. 

Activation of $C_3$ (Schultz, 1980): (Fig. 2)

In relation to host defense, the products of $C_3$ activation by the $C_{42}^-$ enzyme or the alternative pathway $C_3$ convertase, are the most important in the entire sequence of reactions.

Cleavage of $C_3$ results in small fragment $C_{3a}$, and larger fragment $C_{3b}$. $C_{3a}$ has a potent anaphylatoxin activity, and in this capacity cause the contraction of smooth muscles, and the release of histamine from mast cell and basophils.

Cell-bound $C_{3b}$ (e.g. on microbial cells) promotes the adherence of these cells to receptor on other cells (immune adherence). In addition, bound $C_{3b}$ on microbial cells reacts with membrane receptors for $C_{3b}$ on phagocytic cell such as polymorphnuclear leucocyte and macrophage to enhance the process of phagocytosis.

Thus $C_{3b}$ is the major opsonin of the two C pathways. $C_{3b}$ also is involved in the feedback activation of the alternative pathway, it potentiate the haemolysis of red
blood cells and it appears to be involved in the induction of lymphokines by bone marrow-derived (B) lymphocytes.

Cleavage of \( C_3b \) results in two additional fragments \( C_{3c} \) and \( C_{3d} \). \( C_{3c} \) is converted to \( C_{3e} \), and now it is thought that this fragment may stimulate and mobilize polymorph nuclear leucocyte from bone marrow. The fragment \( C_{3d} \) also has membrane receptor on various cell membranes, including lymphocytes, and when bound to microbial cells, it may enhance the adherence of immune complexes or cells to other receptor containing cells.

An additional action of \( C_{3b} \) is to bind to the \( C_{4b} - 2a \), enzyme to form trimolecular complex, which now cleaves \( C_5 \) to \( C_{5a} \) and \( C_{5b} \).

This enzyme is termed the \( C_5 \) convertase - \( C_{5a} \) is a potent chemotactic factor, and is the second anaphylatoxic fragment of the C system. Thus, \( C_{5a} \) promotes directed migration of phagocytic cells such as leucocytes to sites of pathogen activity in the host, provided the C system is intact and is activated at these sites.

\( C_{5b} \) binds to \( C_6 \), then to \( C_7 \) and the \( C_{5b667} \) complex also has chemotactic activity.
Fig. (2): The full complement sequence using the classical pathway, the complement sequence is initiated by the binding of antibodies to determinants on a cell surface and ends with lysis of the cells. Cl inhibitor (C1INH) blocks the proteolytic activity of Clr andCls. (Kimbali, 1983).
This complex may bind to other cells in close proximity even though the cells have been sensitized with antibody, and bind to C₈ and C₉.

The C₅b to C₉ in a dimer form is responsible for the ultimate lysis of the cell (Muller-Eberhard, 1976).

II - Alternative Pathway: (Fig. 3)

The alternate pathway does not have a specific requirement for antibody to initiate its activation. It is probably the major initiating pathway for activation of the terminal complement components under most conditions when pre-existing antibody activity against offending antigen is absent (Gotz and Muller-Eberhard, 1976).

This mechanism bypasses C₁, C₂ and C₄ and enters the classical pathway at the C₃ reaction step.

The pathway is initiated by complex polysaccharide such as endotoxin, lipopoly-saccharide, some bacteria such as Escherichia coli and by aggregate of IgA or IgE; these activating substances interact with an enzyme in this unit designated initiating factor (IF), resulting in the conversion of properdin (P) and factor D to their enzymatic form P and D. The major cleavage of C₃ occurs after generational factor D which permits activation
Fig. (3): The alternative pathway of complement fixation. (Kimball, 1983).
Fig. (4): Simplified view of activation of complement pathways and activities of components. (Weir, 1983).
of factor B in the presence of Mg$^{++}$ and C$_{3b}$, a major
fragment B6 and a minor fragment Ba are formed and the
complex C$_{3b}$ Bb becomes the alternative pathway C$_3$
convertase (Vallotta et al., 1974).

One of the function of the activated properdin (P)
is to bind to C$_{3b}$ in the bimolecular complex to prevent
the rapid decay of C$_{3b}$- Bb. Now, this convertase is ca-
ble of cleavage C$_3$ to C$_{3a}$ and C$_{3b}$.
Thus the fragment C$_{3b}$ which is a constituent of the alter-
native pathway C$_3$ convertase is generated by the action
of C$_{3b}$- Bb on native C$_3$, by the step described above for
the action of C$_1$, C$_4$ and C$_2$ of the classical C pathway
(Schultz, 1980).

Importance of complement in infection:

Bacteria frequently produce chemotactic factors that
attract leucocytes directly and in the absence of serum,
but this attractive effect of bacteria is often weak, and
a strong effect is seen only in the presence of serum.
The complement peptide C$_{5a}$ or related peptides derived
from C$_5$ is the major chemotactic factor generated in the
presence of serum.

There are considerable advantages in such indirect
system for chemotaxis:
1. They allow the generation of chemotactic gradient from solid source. The complement-mediated chemotaxis is essential for detection of bacteria by leukocytes.

2. A gradient of a factor that is being generated continuously at its source (bacterial surface), i.e., by means of complement activation, will not decay rapidly and thus will permit stronger and more continuous stimulation of directed leucocyte locomotion (Wilkinson, 1980).
NEUTROPHILS FUNCTION

Neutrophils play a major role in the body defense against acute infection process. In order to accomplish this action they must be capable of series of complex functions that collectively make up the phagocytic process (Cline and Territo, 1980).

Effective phagocytosis is important in limiting the spread of infection and prevent invasion of microorganism.

Phagocytosis:
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It is composed of four interrelated phase chemotaxis, opsonization, ingestion and killing (Drutz and Mills, 1983).

(A) Chemotaxis:
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The initial phase in the inflammatory response involves the margination of neutrophils to the capillary endothelium and their eventual migration to the site of infection, a process known as chemotaxis (Zigmond, 1978).

Neutrophils show direction migration under the influence of chemotactic agents but a concentration gradient is needed for migration to occur. However
even in the absence of gradient but with chemotactic factors present random migration is enhanced and localization or trapping of phagocytes occur ( Wintrobe et al., 1981 ).

Despite microorganism are capable of elaborating chemotactic factors in the absence of serum, complement system appears to be the most important source for chemotactic activity.

Antigen-antibody complex, bacterial products, certain bacteria, certain enzymes and lysozyme from neutrophils or macrophages can indirectly produce chemotactically active fragment, by activating the classical or alternative pathway of the complement system ( Becker and Ward, 1980 ).

B) Opsonization:

The function of serum opsonin is to react with microorganisms and make them more susceptible for ingestion by phagocytes ( Drutz and Mills, 1983 ).

This may occur by one of 3 mechanism ( Fudenberg, 1978):

1. Specific antibody alone ( IgG\textsubscript{1} and IgG\textsubscript{3} ):

Under conditions of abundant antibodies, specific
antibody combines with the surface antigen through antibody combining sites located on the Fab portion of Ig molecule. The Fc portion of the molecule is then free to attach to Fc receptor site on surface of neutrophils, thus completing a bridge between bacteria and phagocytic cell.

2. Specific antibody acting in contact with complement via classic pathway:

Here, a quantity of antibody apparently insufficient to opsonize. So, it may react with bacteria and activate sequentially the haemolytic complement sequence. Receptor sites for activated C₃ are present on the surface of neutrophil. The activated C₃ on the bacterial surface apparently serves as a bridge between bacteria and phagocytes promoting ingestion.

3. Via the alternative pathway:

Although antibody is absolutely required for opsonic activity mediated by the classical pathway, the alternative pathway does not require antigen-antibody reaction. Instead, this pathway is activated directly by bacteria or fungal polysaccharides, resulting in fixation of C₃ to the surface of organism. Ingestion by phagocytes is therefore mediated by cellular receptor for activated C₃.
phils and opsonized par-

lished cohesive forces usually pre-

ent detachment ( Allison, 1982 ).

The pseudopodia form and surround the particles resulting in complete internalization of the organism. These pseudopodia eventually fuse resulting in complete internalization of the particles within a membrane bound vacule, the phagosome ( Gabig, 1980 ).

D) Killing:

The mechanisms by which neutrophils kill microorganisms are not fully understood. However, it is clear that multiple interlocking microbial system are present ( Drutz and Mills, 1983 ). These system can be divided in two broad categories:

Those system that require oxygen and those which do not ( Klebanoff, 1975 ).

1. Oxygen dependent antimicrobial systems:

These can be further divided into those which are myeloperoxidase mediated and those are myeloperoxidase independent.

Myeloperoxidase mediated antimicrobial system is responsible for the normal intracellular rate of
bacterial killing (Gabig, 1980).

2. Oxygen independent Antimicrobial system:

This system is capable to kill some organism under anaerobic conditions:
lysosome is capable of hydrolysing the cell wall of certain bacteria, thus affecting their death (Wintrobe et al., 1981).
CELL-MEDIATED IMMUNITY

It is the immunity in which participation of T-lymphocyte and macrophage is predominant.

Cell-mediated immunity occurs particularly in infection by agents which enter the cell such as viruses and tubercle bacilli. It can also develop after skin contact with certain chemical substance.

The sequence of steps leading to this form of immunity is essentially not different from that leading to the antibody response, but the response is initiated in different area of the spleen and lymph nodes (Para cortical areas of lymph node and white pulp around central arterioles of the spleen); these area are under the control of the thymus gland (Kimball, 1983).

Mechanism of cell-mediated immunity:

When an individual is exposed to antigen such as virus, its own lymphocytes become activated or sensitized. Cell mediated immunity dependent on these activated lymphocytes is usually recognised by means of a skin test (e.g. intradermal injection) with antigen that, in an individual who has developed a cell mediated response,
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results in inflammatory reaction at site of injection.

The lymphocytes that have previously been sensitized to antigen are capable of production of soluble products called lymphocyte activation products or lymphokines (Weir, 1983).

Lymphokines:

These are soluble products produced by exposure of sensitized lymphocyte to the sensitizing antigen. These products are shown in table (3) (Rocklin, 1982).

They are believed to serve three main functions:

1. Recruitment of uncommitted lymphocytes.
2. Retention of such cells and phagocytes at the inflammatory site.
3. Activation of the retained cells so that they can take part in the inflammatory response. Some of function of these products are shown in table (4) (Weir, 1983).

These products can be thought of as chemical messengers that allow communication between the cells and also as agents that amplify the response. They act on macrophages, polymorphs, lymphocytes and also on other non-lymphoid cells.

The overall contribution of these factors in the cell-mediated immune response has not yet been clearly
Table (3): Products of activated lymphocytes.

Mediator affecting macrophages

migration inhibition factor
macrophage activation factor
chemotactic factor for macrophages

Mediator affecting leucocytes

chemotactic factor for neutrophils, basophils
leucocyte inhibitory factor,
histamine releasing factor

Mediator affecting lymphocytes

mitogenic factor
transfer factor
factors affecting antibody production

Factors affecting other cell types

Cytotoxic factors
interferon
tissue factor
immunoglobulin binding factor

( Rocklin, 1982 )
Table: (4) (Weir, 1983).

<table>
<thead>
<tr>
<th>Lymphokine activity</th>
<th>Possible role in vivo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage 'migration inhibition'</td>
<td>Retention of emigrated macrophages at site of inflammation.</td>
</tr>
<tr>
<td>Macrophage 'chemotaxis'</td>
<td>Emigration of macrophages to site of inflammation</td>
</tr>
<tr>
<td>Macrophage 'activation'</td>
<td>Enhanced metabolic, phagocytic and antimicrobial activities.</td>
</tr>
<tr>
<td>Macrophage 'aggregation'</td>
<td>Aggregation and localization of macrophages at inflammatory site.</td>
</tr>
<tr>
<td>Macrophage 'arming'</td>
<td>Enhanced extracellular cytotoxic effects of macrophages.</td>
</tr>
<tr>
<td>Macrophage 'spreading-inhibition'</td>
<td>Brings about cell surface changes possibly facilitating passage of cells through blood vessel walls.</td>
</tr>
<tr>
<td>Lymphocyte 'mitogenesis'</td>
<td>Induces non-committed lymphocytes to become metabolically active at inflammatory site.</td>
</tr>
<tr>
<td>Lymphocyte 'potentiation'</td>
<td>Augmentation of lymphocyte activation by specific antigen.</td>
</tr>
<tr>
<td>Lymphocyte 'suppression'</td>
<td>Limitation of DNA synthesis by lymphocytes.</td>
</tr>
<tr>
<td>Lymphocyte 'co-operation'</td>
<td>Facilitation of B cell response to T-dependent antigens.</td>
</tr>
<tr>
<td>Granulocyte 'migration inhibition'</td>
<td>Similar effect as on macrophages.</td>
</tr>
<tr>
<td>Granulocyte 'chemotaxis inhibition'</td>
<td>Similar effect as on macrophages.</td>
</tr>
<tr>
<td>'Cytotoxic' effects</td>
<td>Induces lymphocyte cytotoxicity on certain cell types.</td>
</tr>
<tr>
<td>Inhibition of 'proliferation'</td>
<td>Inhibition of cell proliferation without lysis;</td>
</tr>
</tbody>
</table>
established, nor has their chemical identity or mode of action. However, it is widely believed that the lymphokines are the main effector mechanisms in the cell mediated response.
ACUTE RHEUMATIC FEVER

Rheumatic fever is a multisystem disease of obscure aetiology. The evidence of recent streptococcal infection is found in over 70-80% of cases of acute rheumatic fever and is generally required for diagnosis of rheumatic fever (Markowitz et al., 1965).

Acute manifestation include migratory arthritis, carditis, chorea, erythema marginatum and subcutaneous nodules as well as a number of less prominent symptoms and signs. Multiple focal aseptic inflammatory lesion are the basis for the acute manifestation (Markowitz et al., 1965).

Recurrent of rheumatic fever is a characteristic feature of the disease following an untreated streptococcal infection in a patient with previous history of the disease. The acute illness is of limited duration but it is the carditis that can lead to permanent valvular damage. For this reason, extensive studies have been concerned with methods to prevent the occurrence of rheumatic fever (Wannamaker, 1979 & Krause, 1979).

Aetiology:

Acute rheumatic fever occurs secondary to pharyngeal
infection with group A beta-haemolytic streptococci. It only occurs following upper respiratory tract infection with group A - streptococci and not following cutaneous infection.

The extra-cellular products of streptococci:

These can be summarized in table (5). Many studies suggest that these toxins have primary toxic action on tissues as well as secondary hypersensitivity action, so it is conceivable that these toxins could play an important role in initiating the pathologic damage seen in rheumatic fever (Watson, 1960).

Pathogenesis:

Despite many years of intensive investigation the precise pathogenic mechanism of rheumatic fever is still obscure. The overriding clinical importance of carditis in rheumatic fever had led to most theories of the pathogenesis of the disease being restricted only to a consideration of the involvement of the heart (Tagg and McGivent, 1972).

Yet most investigators now favor the concept that this disease is a consequence of an unusual immunologic
### Table (5)

<table>
<thead>
<tr>
<th>Extracellular product</th>
<th>Inhibition by specific antibody</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptolysin O</td>
<td>+</td>
<td>Measurement of antibodies to streptolysin O is the most common serologic test for diagnosis of streptococcal infection.</td>
</tr>
<tr>
<td>Streptolysin S</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>DNAse</td>
<td>+</td>
<td>Antibodies to this antigen is useful for serodiagnosis of both throat and skin infection.</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>+</td>
<td>&quot;</td>
</tr>
<tr>
<td>NADase</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Streptokinase</td>
<td>+</td>
<td>Activate plasminogen to plasmin.</td>
</tr>
<tr>
<td>Erythrogenic toxin</td>
<td>+</td>
<td>Cause rash of scarlet fever.</td>
</tr>
<tr>
<td>Proteinase</td>
<td></td>
<td>Digest M protein.</td>
</tr>
</tbody>
</table>

(Parker, 1980).
Several clinical, pathologic, and epidemiologic observation have long suggested that with or without toxic tissue injury, rheumatic fever is largely a manifestation of the host's immune response to the streptococcus or to his own tissue. These are some observation:

1. Infants and very young children, whose capacity to respond to many types of antigenic challenge is limited, rarely get rheumatic fever despite of common occurrence of streptococcal infection in that age group.

2. Rheumatic patient typically have high titres of antibodies to streptococcal antigen during acute attack and react intensely to intra-dermal injection of streptococcal somatic antigen.

3. Most patient have circulating autoantibodies to several tissue during their attack and in some cases long afterward.

4. The heart of patient dying of severe acute carditis have widespread deposits of immunoglobulins and complement in the myocardium and heart valves.

(Parker, 1980).

Many theories have been suggested for the etiology of rheumatic fever. These include:
(I) Immunologic Theories:

These theories suggest that, the immune system is involved in the pathogenesis of rheumatic fever by different ways:

(A) Auto-immune theory:

At present this is the most widely accepted theory of the pathogenesis of rheumatic fever.

Two mechanisms were suggested:

1) Humoral mechanism:

In up to 80% of patients with acute rheumatic fever, autoantibodies against cardiac tissue have been demonstrated. Those with acute carditis or recurrence tend to have the highest titres. Immunofluorescent staining demonstrates that serum from rheumatic patients contains autoantibodies against cardiac myofibrils, smooth muscle of cardiac vessels and endocardium. These autoantibodies cross-react with group A streptococcal antigens, many of which closely associated with M-protein. Immunofluorescence techniques reveal that 18% of patients with inactive rheumatic heart disease have focal deposits of immunoglobulins throughout the myocardium.

Patients with active rheumatic fever has diffuse myocardial deposition of Y-globulin and complement as well as
valvular deposition of IgG, but not IgA, IgM or complement. It is not known whether the immunoglobulins deposited in the myocardium cross-react with streptococcal antigens (Fig. 5).

2) **Cellular mechanism**: 

Streptococcal cell wall antigens are lymphocyte mitogens. Patient with rheumatic fever show decrease mitogenic response during the first attack, but this response is normal in the subsequent attack. Streptococcal M protein can induce delayed hypersensitivity in humans, however the lymphocyte of normal children, as well as patient with rheumatic fever are stimulated by streptococcal cell wall antigens. This suggest that cellular hypersensitivity to these antigen is not a major immunologic determinant of the disease (Caldwell and Kaltreider, 1982).

(B) **Immune complex (allergic) Disease**: 

Because of clinical similarity of rheumatic fever to serum sickness, it has been suggested hypersensitivity in the pathogenesis of rheumatic fever, but there are arguments against this view. First, serum sickness or allergic disease manifest shorter latent period. Second, patient with serum sickness has decreased serum complement
Fig. (5) : Autoantibodies as mediators of carditis in rheumatic fever.
(Basic and clinical immunology, 1982).
owing to increased consumption by immune complexes. In rheumatic fever, serum complement is often elevated
( Caldwell and Kaltreider, 1982 ).

However studies on synovial fluid of rheumatic fever have shown that decrease C1q, C3 and C4 suggest local consumption
( Svartman et al., 1975 ). These findings add new support to this theory at least as far as arthritis is concerned.

(C) Exaggerated antibody response :

It has been suggested on the basis that level of anti-streptolysin O and other streptococcal antibodies in patient with acute rheumatic fever are usually higher than those in patient after uncomplicated streptococcal infection.

(D) Delayed Hypersensitivity :

Several observation support the idea the delayed hypersensitivity is involved in the rheumatic process.

- The fact that the disease rarely occur in children under four years of age suggest that several infection with streptococcus are necessary to sensitize the child ( Rantz et al., 1953 ).

- Streptococcal antigens can be shown to induce delayed hypersensitivity in animals and Humans( Francis et al., 1957 ).
Examination of human heart from acute rheumatics reveals a lymphocytic infiltrate both perivascular and between muscle bundles (Murphy, 1960).

(E) Immune reaction to streptococcal antigens:

A specific streptococcal products could bind to tissues and the antibody response against it could damage the underlying tissue.

(II) Non-immunologic theories:

There are old theories and became out of date. These include:

(A) Toxic theory:

It has been hypothesized that the manifestations of rheumatic fever are secondary to the action of streptococcal toxins. Streptolysin O might exert a direct toxic effect on host cells and thus provoke rheumatic fever (Thompson et al., 1970).

The objections to this theory are the immunologic nature of streptococcal products which will prevent recurrence of the disease. And the latent period would not be necessary to develop the direct toxic effect which is not the case in rheumatic fever (Taranta, 1979). Secondly, the histologic damage
produced by these toxins in general does not mimic the chronic granulomatous lesions seen in rheumatic fever. Although a variety of cellular and extracellular structure of streptococcus when injected into experimental animals may cause necrosis and vasculitis, non of these lesion is analogous to the lesion seen in acute rheumatic fever (Ginsburg, 1972).

(B) Infection theory:

It has been suggested that the disease is caused by the direct invasion of involved tissue either by group A streptococci or their "L" forms. However, neither of these has been isolated from involved tissue (Caldwell & Kaltreider, 1982). Despite an extensive clinical trial, there was no evidence that this treatment resulted in clinical improvement in the acute disease or reduced the development of permanent damage (Mortimer et al., 1959).

(C) Viruses:

The possible role of viruses was also introduced. There is much evidence to indicate an active role of viruses in the production of heart disease.
Pathology:

As regard rheumatic carditis, rheumatic process may cause endocarditis, myocarditis, or pericarditis, but these lesion may exist single or in combination.

Macrosopically, the heart is pale, flabby, dilated and covered with a fibrinous pericardial exudate, there are also tiny vegetations near the line of closure of the mitral valves mainly and the aortic valves. "McCallum's patch", which is roughening of the endocardium, may be seen on the posterior wall of the left atrium.

Microscopically, there is diffuse interstitial myocarditis with widespread oedema and foci of necrotic and degenerating myocytes.

If the illness has lasted longer than a week or two, there will be small distinctive inflammatory lesion called Aschoff's bodies, the mature Aschoff's body is the only lesion specific for rheumatic fever and is considered pathognomononic. It comprises a central area of "fibrinoid" surrounded by lymphocytes, plasma cells and large basophilic cells, some of them multinucleate. The nuclei of many of these cells are elongated and have a distinctive pattern of centrally clumped chromatin with
as caterpillar nuclei. Cells containing these nuclei are called "Anitschkow myocytes" (Stollerman, 1975).

The pathology of chorea is unknown, since chorea is not fatal. However, there are scattered foci of inflammation and necrosis have been seen in the cortex, cerebellum and basal ganglia in patient dying with chorea, but these lesion are non-specific.

As regard rheumatic arthritis, there is effusive synovitis without proliferation or erosion, so there is no residual damage in the joints after recovery. There is swelling of articular and periarticular structures; cellular infiltrate into the synovial membrane, and there is serous effusion into the joint space (Parker, 1980).

The subcutaneous nodules look rather like large Aschoff lesions, with central zone of lattice-like fibrinoid material surrounded by Histiocytes, fibroblasts, and lymphocytes. These lesion heal completely. The cells of these lesion not form the palisade appearance which is seen in the nodules of rheumatoid arthritis (Markowitz & Gordis, 1972).

Clinical Manifestations:

Rheumatic fever manifest itself as a variety of signs and symptoms that may occur singly or in combination.
Certain manifestations which are particularly characteristic of acute rheumatic fever and are thus helpful in diagnosis have been termed the "major manifestation". These include arthritis, carditis, chorea, subcutaneous nodules and erythema marginatum. Other findings which are non-specific to be of major importance in diagnosis have been designated as "minor manifestation", these include arthralgia, fever, previous history of acute rheumatic fever, certain laboratory findings namely prolonged P-R interval on E.C.G., elevated E.S.R., leucocytosis and presence of acute phase reactant in the blood i.e. +ve CRP, in addition epistaxis, abdominal pain and anorexia may be present (Parker, 1980).

Carditis:

Carditis is common in childhood, its incidence decreases progressively with increasing age. It is the most serious manifestation of rheumatic fever, because it is the only one that can cause permanent structural damage to host tissue. If carditis is not present at the onset of attack, it seldom appears thereafter (Taranta, 1979). The inflammatory process may involve endocardium, myocardium and pericardium. The hallmarks of cardiac involvement are:

- Organic heart murmur not previously present.
- Cardiac enlargement.
- Congestive heart failure.
- Pericardial friction rub or signs of effusion.

The mitral regurgitation is the most common lesion of rheumatic heart disease and oftenly accompanied by mitral stenosis or aortic valve disease.

Arthritis:

The joint involvement is the most common clinical manifestation of rheumatic fever. It starts as arthralgia without objective signs of inflammation, however it is rapidly followed by arthritis with objective signs of inflammation as hotness, redness, swelling or at least limitation of movement. (Feinstein and Spagnuolo, 1962).

Arthritis involves mainly large joints and this takes migratory form. Each joint is involved maximally for few days, so that the affection of several joints overlap partly in time (Taranta, 1980). Arthritis becomes increasingly frequent with age and tends to be of shorter duration and less severity in children than in adults (Mc Donald and Weisman, 1978).
Chorea:
-----

Chorea is characterised:
(a) Rapid, purposeless involuntary movement
(b) Muscle weakness, and
(c) emotional lability.

Chorea occurs over the most limited age range, it does not occur under three years of age, and become rare again after puberty. It can occur unaccompanied by other major manifestation, with normal acute phase reactant and low A.S.O. titre. The latent period between streptococcal infection and chorea may be as long as several months which makes it difficult to explain the connection between the two events (Taranta, 1980).

Patient who develop chorea as an apparently isolated manifestation, have a relatively high incidence of rheumatic heart disease (Bland, 1962).

Subcutaneous nodule:
---------------------

Subcutaneous nodules of rheumatic fever are firm and painless. The overlying skin is not inflammed, can be moved over them. Their diameter varies from few millimeters to one or two centimeters, they are mostly located over bony surfaces. They are more common in patients with carditis, but seem to be very rare nowadays (Taranta, 1980).
Erythema marginatum:
---------------

It is a non-pruritic, pink, evanescent skin rash which occur mainly on the trunk, buttocks, or the proximal parts of the limbs (Feinstein and Spagnuolo, 1962). The skin lesions expand centrifugally while the skin in the centre return to normal.

Diagnosis:
--------

There is no single laboratory test that can establish or confirm diagnosis of rheumatic fever, for this reason clinicians have to apply their own clinical judgement using a set of finding known to be common in this perplexing disease - The revised Jone's criteria.

According to Jone's criteria, there must be two major criteria or one major and two minor criteria plus evidence of preceding streptococcal infection (anti-streptolysin O titre or other streptococcal antibodies, antihyaluronidase and anti DNAs) (Kaplan, 1978).

Major criteria include carditis, poly arthritis, chorea, erythema marginatum and subcutaneous nodule. Minor manifestation include fever, arthralgia, previous rheumatic fever or rheumatic heart disease, leucocytosis, prolonged P-R interval, positive acute phase reactants
i.e. elevated E.S.R. and positive test for C-reactive protein, supportive evidence of streptococcal infection. Those together with other finding as anaemia, pallor, abdominal pain, epistaxis, tachycardia, weight loss and malaise.

However there is no specific immunologic test for the diagnosis of rheumatic fever. Virtually all rheumatic patients have antibodies to streptococcal antigens, although the height of the antibody titre bears no relation to the severity of the disease. Most normal individuals also have low titres of antistreptococcal antibodies, since antistreptolysin O is so common among the normal population only high titres - 333 units in children - constitute evidence of recent infection. Therefore, decisive evidence of recent infection rests on showing a rise in antibody titre (Caldwell and Kaltreider, 1982).

Treatment:

Therapy of rheumatic fever consists primarily of anti-inflammatory agents, bed rest, general supportive care, Aspirin and corticosteroids are the two anti-inflammatory drugs ordinarily administrated. Aspirin is used in treatment of polyarthritis in dosage 75-100 mg/kgm.
The fundamental mechanism is inhibition of synthesis of prostaglandins, especially type E, which increase capillary permeability causing oedema as well as produce fever, inflammation and pain (Casaky, 1979).

Prednisone is favoured over other steroids, and is used in severe carditis, in dosage 2 mg/kgm. The rational choice of anti-inflammatory agents depends on cardiac status. If there cardiac enlargement, pericarditis, and signs and symptoms of heart failure steroids should be utilized, otherwise the salicylate therapy is the best choice (Gersony, 1983).

The anti-inflammatory agents do not cure acute rheumatic fever, but merely suppress its manifestation. Neither steroids nor salicylate alter the duration of the attack or affect its ultimate course, however, signs of acute inflammation measured by ESR and CRP are suppressed more readily with steroids than aspirin. The steroid and aspirin have effect in lowering lymphocyte proliferation (Gray et al., 1981).

With respect to heart-reactive antibody titer, there is evidence for preferential diminution of this antibody with steroid as opposed to salicylate (Read and Zabriskie, 1981).
The management of chorea is supportive. Symptomatic care include quiet environment and protection against tongue-biting and other self-injuries due to violent movement. Phenobarbital, Chlorpromazine, or Diazepam may be helpful.
IMMUNOLOGICAL ASPECTS IN RHEUMATIC FEVER

After concluding the relationship between group A streptococci and rheumatic fever as the sole initiating factor, much time was spent to consider the possible role of immunological mechanism in the disease.

First, the latent period between streptococcal sore throat and the onset of rheumatic fever, a period that fits well with the time required for the development of an antibody response. Measurement of actual antibody response to several of the extracellular products of group A streptococci in patient who developed rheumatic fever showed a sharply rising antibody titre at first appearance of symptoms of the disease, reaching their peak one or two weeks later (Mc Carty, 1977).

Second, the finding that antibody response to a number of different streptococcal antigens is higher in patient who develop rheumatic fever, than in patient in the same pandemic, who have uncomplicated streptococcal infection (Mc Carty, 1952).

A third type of evidence came from the demonstration that effective penicillin therapy of established streptococcal sore throat will prevent rheumatic fever.
The suggestion is that if one stops the antigenic stimulus, the risk of rheumatic fever is greatly reduced.

Studies on the pathogenesis of rheumatic fever, however, have been successful in identifying new antigens of the group A streptococci, than in discovering which is directly involved in initiating the rheumatic process and how does this occur. In addition to the M protein and carbohydrate of the cell wall, there is antibody response to other surface proteins, peptidoglycan and to lipoteichoic acid (Van de Rijn et al., 1977).

The diversity of manifestation of rheumatic fever cannot be explained on the basis of a single type of immune reaction. One can look upon the cross-reaction between group A carbohydrate and a component of cardiac valves as a possible factor in endocarditis. Also between the membrane antigen and heart muscle as a possible cause in myocarditis. With these points in mind, let us now examine in detail the immunologic data that tend to support the immunological concept.
HUMORAL IMMUNITY IN RHEUMATIC FEVER

A number of reports published recently have suggested the evidence in favour of an immunological process. In immunological disorders serum immunoglobulins are frequently altered (Fahey, 1965).

Changes of Immunoglobulin and their types:

Serum IgG, IgA and IgM all were elevated in rheumatic heart patient. The increased immunoglobulins in rheumatic fever occur variably, IgM is the first immunoglobulin to rise in serum after exposure to an antigen. Patient of acute rheumatic carditis have marked increase in serum IgM as compared to chronic rheumatic case (Fahey, 1965).

The mean serum IgA in rheumatic cardiac patient in chronic condition is more elevated (Carlisle et al., 1972).

It is interesting to note that subjects with cardiac decompensation have marked elevation of serum IgA as compared to compensated subjects. It is possible that association of elevated IgA to cardiac decompensation may be related to more severe cardiac damage due to immunologic disturbance. The duration of heart disease does not alter IgA level significantly (Carlisle et al., 1972).
The alteration in serum immunoglobulins of patient with rheumatic heart disease, thus suggests an immunologic disturbance related to disease process. Serum immunoglobulin A is marked increase in rheumatic fever than in other streptococcal sequelae, and total antibody to M-associated protein (assessed by complement fixation) is the only antibody found to be of higher titer in patient of acute rheumatic fever (Potter et al., 1972). The anti-group A carbohydrate, anti-hyaluronidase and anti-DNase B titers have been increased in acute rheumatic fever (Shulman et al., 1974).

Local immunological reaction play a major role in some infectious disease, based on this idea immunoglobulins are studied in saliva of rheumatic patient, because some believe that rheumatic fever may be due to unusual immune response of the host to pharyngeal streptococcal infection.

Neither immunoglobulin nor streptococcal antibodies were increased in saliva of rheumatic patient, thus no evidence for local immune response to streptococci in saliva of rheumatic patient, thus no abnormalities are present in saliva of rheumatic patient (Waldman et al., 1968).
Antineuronal antibodies in chorea:

Until recently studies of cross-reactive antibodies in rheumatic fever were limited to reaction with muscle, blood vessels, and glycoprotein antigens. Very little information was available concerning the presence or nature of antibodies in rheumatic chorea.

The studies demonstrate the presence of IgG antibodies - in sera of rheumatic patient - reacting specifically with neuronal cytoplasmic antigens in caudate and subthalamic nuclei of the human brain, there is direct correlation with the presence of these antibodies and the length and severity of the chorea attack and recent studies show disappearance of antibodies after subsidence of chorea (Husby et al., 1976). The relation to rheumatic state is further emphasized by the relative absence of this antibody in post streptococcal nephritis. It is conceivable that IgG antibody to cytoplasmic structure in subthalamic and caudate nuclei is some how involved in the genesis of chorea, but that the clinical syndrome itself is modulated by other factors than merely the presence of antibody itself. Thus the extracellular streptococcal products and genetic background may also be involved. The incidence of chorea in Egypt is higher than in other
parts of the world, so it is possible that the occurrence of chorea itself may be conditioned or somehow modulated by genes related to HL-A phenotype. Such situation might explain the presence of subthalamic and caudate nuclear cytoplasmic antibodies in both chorea and active carditis.

The higher titers recorded in sera from children with chorea as compared to those with carditis, with clear correlation of positive reaction with duration and severity of chorea, point to significant relation of antibody to disease process. The precise nature of the cross-reacting antigens in caudate and subthalamic nuclei and group A streptococci remains unknown. In rheumatic chorea, anti-neuronal antibody appeared to represent cross-reaction with antigen shared by group A streptococcal membrane (Kingston et al., 1976).

Heart-reacting antibodies:
------------------------
Many studies have suggested the presence of heart-reacting antibodies, by immunofluorescence antibodies reacting with the sarcolemmal and intermyofibrillar regions of mammalian heart tissue, (Zabriskie et al., 1970). Heart-reactive antibodies in patient with rheumatic fever appear to result from antigenic stimulation of streptococcal antigen share with mammalian tissue (Kaplan and
Fremgley, 1969). The highest titers of heart-reacting antibodies occur in patient with carditis and this may be due to response to stimulation by antigens released from damaged heart muscle. These antibodies present in acute phase of disease cross-reacting with streptococci, while in chronic case are not cross-reacting (Zabriskie, et al., 1970).

The presence of high titre heart-reacting antibodies is useful aid in diagnosis and helpful in excluding other condition associated with painful joint as rheumatoid arthritis.

It is of special interest that patient with valvular disease have higher titers of these antibodies as compared to patient without valvular disease. These antibodies persist for years after initial attack, in contrast the patients without valvular disease, in whom the titers fall off rapidly after the initial attack. The persistence of these titers in patient with rheumatic valvular disease may be related to slow and sustained release of valvular cross-reactive glycoprotein, thus perpetrating valvular damage (Buddy and Ayoub, 1968). It is not known whether the presence of these antibodies is peculiar to rheumatic patient or not. However, it is
still not known whether the antibodies present in rheumatic fever patient are primarily streptococcal induced or the result of initial heart insult with release of cardiac antigens giving rise to cardiac-induced antibodies that happen to cross-react with streptococcal antigen (Read and Zabriskie, 1981).

The presence of higher titers of heart-reactive antibodies in patients with acute rheumatic fever is significant and may provide additional tool for differential diagnosis of rheumatic fever. The titre of these antibodies declines slowly over a period of 2-3 years following acute attack of rheumatic fever, but reappear with subsequent recurrence. It is possible in each case, without prior knowledge of the clinical history, to determine whether a patient have uncomplicated strepto-coccal infection and acute rheumatic fever. These antibodies are absent in unrelated arthritis (Kaplan, 1964). The fact that the decline of heart-reactive antibodies parallels the clinical course of recovery in acute rheumatic fever is of interest and suggest causal relation of this antibody to rheumatic fever. The fact that heart-reactive antibodies appears to correlate closely with the time of greatest susceptibility to rheumatic recurrence may also be of value in long-term management of rheumatic patient.
These patient may be placed on injectable penicillin until heart-reactive antibodies become negative. Oral penicillin may be instituted and these antibodies titers are checked every 6 months. With reappearance of heart-reactive antibody in serum of patient, injectable penicillin may be given until the titers becomes negative again (Markowitz & Gordis, 1968).

Streptococcal antibodies in Rheumatic fever;

The strepto-coccal antibody response to extracellular antigens is generally higher in rheumatic patient than in patient with uncomplicated streptococcal infection (McCarty, 1954).

The most common streptococcal antibodies is Anti-streptolysin O which are not type specific and rise after infection with any one of 50 types of group A streptococcus and return to normal level after 2 - 6 months. The only antibody indicative of a type-specific streptococcal infection is the one directed against the M antigen. These type-specific antibodies develop slowly and are usually not detectable until one or two months after an infection.
The studies have suggested that these antibodies (anti-M antibody) disappear from the blood within two to three months in most patients and that titre can be recalled by small dose of cell wall vaccine of homologous types (Potter et al., 1960).

It has been also suggested the presence of circulating antibody to group A carbohydrate in patient with streptococcal infection. This antibody, like other streptococcal antibodies declines to normal levels within a year follow the acute stage of the disease, except in patient with chronic rheumatic valvular disease. The elevated level of antibody reacting with group A carbohydrate persists for many years may be as long as 25 years following last streptococcal infection, while antibodies to streptococcal extracellular products decline to normal level following acute episode (Dudding & Ayoub, 1968).

In absence of evidence for antecedent group A streptococcal infection, the level of the A-antibody remains normal even if there valvular damage as in congenital heart or bacterial endocarditis. This association to streptococcal infection suggest that valvular damage does not contribute to the elevated A-antibody level in patient with chronic rheumatic valvular disease. This elevation of A-antibody is absent in congenital heart with
or without bacterial endocarditis. Also, the additional damage of heart valves inflicted by bacterial endocarditis with underlying rheumatic disease not produce significant elevation of A-antibody (Goldstein et al., 1968).

There is also significant rise in antibodies to group specific polysaccharides in patient of rheumatic fever and these antibodies can be critical constituent in the induction of rheumatic fever, these antibodies are more useful as marker for severe infection (Ilkka et al., 1981).

It has been suggested that there are antibodies against M-associated protein (MAP), these anti-MAP antibodies rise in rheumatic fever. This anti-MAP response is influenced by the infecting type of streptococci, so the high titer of anti-MAP may not always be associated with rheumatic fever. Perhaps the generally higher titers seen in rheumatic fever, compared with, for example, nephritis are a reflection of the influence of the type of streptococci (Widdowson and Maxted, 1974).

The studies of streptococci that elicit rheumatic fever and the protective immune response to them and their purified M protein are required to define cross reaction that may aid in the development of broadly reactive M protein vaccines (Bisno, et al., 1982).
The amount of a complement component in serum does not necessarily indicate the amount of its participation in a disease process since serum level depends on synthesis and catabolism of complement as well as its consumption (Cooper et al., 1971).

Increased serum levels of both total complement and C3 have been described in patients with acute rheumatic fever (Hornung and Arquembourg, 1965).

However, the mean value of C3 is reduced in rheumatic heart disease, suggesting that a complement-mediated injury may occur at some stage in the course of the disease (Sapru et al., 1977).

It has been suggested that, the values of CI, C4 and C3 are decreased within the synovial fluid in patients who have rheumatic arthritis. Such local activation of C3 with consequent formation of chemotactic and vasoactive fragments may account for the presence of many leucocytes in these joint in absence of bacteria as well as presence of fluid itself.

The relative decrease in both early and late components of complement within the synovial fluid suggests
local activation by immune complexes. Such activation of complement within the joint spaces may play a primary role in development of inflammatory arthritis of acute rheumatic fever (Swartman, et al., 1975).
CELL-MEDIATED IMMUNITY IN RHEUMATIC
FEVER

The monocellular infiltrates occurring within lesions of rheumatic fever such as the aschoff nodules or focal areas of myocarditis suggest participation of cell-mediated immunity.

The studies have been suggested the presence of cell-mediated response in patients with rheumatic fever to membrane fraction derived from group A streptococci. These data provide a model for possible mechanism involved in pathogenesis of rheumatic fever (Read et al., 1974).

Cellular Reactivity to streptococcal antigens:

The question of whether hypersensitivity to streptococcal antigen plays a role in the pathogenesis of the non suppurative sequelae of streptococcal infection remains unclear.

The rheumatic patients exhibit exaggerated cellular reactivity to streptococcal membrane antigens. This increased cellular reactivity to membrane structure persists in rheumatic patient up to 5 years after the initial attack without any evidence of an intercurrent streptococcal
infection or rheumatic recurrence during this period. After 5 years the majority of rheumatic individuals lose this altered sensitivity to membrane structure and respond in normal fashion to these antigens.

This persistent heightened reactivity of lymphocytes to streptococcal cell membrane is of particular interest as this antigen cross-reacts with sarcolemma of mammalian heart and the walls of blood vessels.

This cross-reactive properties of these antigen result in auto-sensitization to tissue antigen producing cytotoxic effects in the tissue of the host. This concept is in agreement with the histological finding of a large number of lymphocytic cells in the pathological heart lesion of rheumatic fever (Read et al., 1974).

Cell-mediated immune response in rheumatic fever:
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Several reports indicate altered lymphocyte transformation response to streptococcal antigen in post-streptococcal disease.

The rheumatic heart patients clearly have a depressed cellular immune response to the streptococcal antigens. The response of lymphocytes from rheumatic heart patients to phytohemagglutinin is normal, while the response to extra-cellular products of streptococci is
significantly lowered (Gary et al., 1981).

Several reports show that T-cell population is reduced in patient with rheumatic heart disease, furthermore is strongly stimulated by streptococcal membrane antigen. Such a response is not elicited by other components of these organism. The susceptibility of patient may be related to specific sensitization of lymphocyte. Persistence of enhanced antigen sensitization, even when the T-cell count improve at the end of six weeks, suggest that this abnormality may persist for along time and account for the well-known recurrence after streptococcal infection in these patients (Sapru, et al., 1977).

In acute rheumatic fever, there is also impaired cellular reactivity of lymphocytes. It is clear that immune or sensitized lymphocytes are capable of mediating tissue damage through the production of various lymphokines such as migration inhibition factor or cytotoxic factors (Lueker and Williams, 1972).

It has been suggested that the persistence of streptococcal antigens in tissue of rheumatic heart disease patients may promote antibody production at the expense of dalyed hypersensitivity, this leads to cellular hyporesponsiveness. The actual mechanism for this; is due
to high dose tolerance due to chronic exposure to high
doses of the antigens (Francis and Oppenheim, 1970).

The cell-mediated immune response to cardiac anti-
gen have been studied using leucocyte migration inhibition
test. These studies show that cell-mediated immune res-
ponse is present only in cases who have rheumatic carditis
suggesting that it is heart specific and is produced only
when the heart is involved. The leucocyte migration inhi-
bition test have higher incidence in case of acute rheumatic
fever with carditis as compared to chronic valvular heart
disease with acute rheumatic activity. This suggest that
migration inhibition test is more specific in initial attack than
in recurrence (Agarwal et al., 1980).

Lymphocyte binding C-reactive protein in acute rheumatic
fever:

The several reports have indicated that C-reactive
protein (CRP) may bind to lymphocytes and in particular,
may actually adhere to T-cells or B-cell activated by
antigen. It has been suggest that a marked increase in
cell binding CRP occurs during the course of acute rheuma-
tic fever (Winchester et al., 1975).
It seems possible that CRP may bind to lymphocyte in diseased patient perhaps on a different basis from those of normal. It is conceivable that CRP binding may, instead of reflecting an immunological mechanism, merely be related to lymphocyte membrane damage of some kind. If CRP is indeed capable of preferential binding to antigen-activated T-cell or natural killer cell, it is conceivable that such CRP binding may serve to attenuate self-directed cellular responses possibly to the host (Croft et al., 1976).

It is important to recognize that proportion of CRP binding cell may directly influence several expressions of the immune response. CRP-binding lymphocytes may represent a marker for immunologically committed cell in acute rheumatic fever. These findings indicate that streptococcal antigens produce an altered cell-mediated immune response in patient with rheumatic fever (Williams et al., 1978).

The binding of CRP to lymphocytes during rheumatic fever is part of host's own protective reaction against possible ongoing immunological injury. Therefore, it is possible that fixation or adherence of CRP to B-cell occur as natural reactive phenomenon destined to turn off continued binding of potentially harmful streptococcal antigen to B-cell, perpetuating Humoral immune response to cross-react self constituents such as myocardial sarcolemmal membrane and heart valves, i.e.; CRP serves to attenuate
harmful effects during acute rheumatic fever (Williams et al., 1980).

Tissue distribution of lymphocytes in rheumatic heart valves:

Recently, several reports provide information on tissue distribution as well as relative proportion of T-cells, T-cell subsets, B-cell and Tissue mononuclear cells in rheumatic heart valves using immunofluorescent techniques.

The studies show intense focal mononuclear cell collection of lymphocytes and plasma cells, the most of lymphoid cells involved in such infiltrates are helper/inducer T cells and only occasional B-cells.

These T-cell are juxtaposed in close proximity to fibroblast and area of collagen fibrils. This suggests that Helper T cells may somehow be involved in the long term sequelae of contracture, fibrosis, and thickening, well known to be associated with rheumatic valvular deformities. Conceivably, therefore Helper T cells may secrete or elaborate lymphokines or humoral products that are capable of inducing fibroblasts and possibly cells of
macrophage-monocyte type to secrete collagen or induce chronic scarring that occur in end-stage of rheumatic valves.

The finding of helper/inducer T cells predominance within chronic rheumatic valvular lesion appears to be of more fundamental importance than parallel studies of lymphocyte cell surface marker profiles during acute rheumatic fever (Raizada et al., 1983).

Suppressor-lymphocyte function in rheumatic heart disease:

Recent attention has been directed to the importance of suppressor-lymphocyte function in the normal regulation of both cellular and humoral immune response.

Several diseases with auto-immune features have recently been shown to be characterised by defects in suppressor cell immune regulation.

The patient with rheumatic heart disease has normal immune-regulatory function, thus immune-regulatory defect has no role in the development of rheumatic heart disease (Anderson et al., 1981).
Non-T cells in rheumatic heart disease:
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The non-T cells (i.e. non-sheep red blood cell rosetting) are essential for T cell response to blastogen A (an antigen prepared from the extra cellular products of group A streptococci).

The functions of the non-T cells in patient with rheumatic heart disease are impaired in their ability to modulate the T cell proliferative response to blastogen A. This functional alteration of the non-T cell in rheumatic heart diseased patient may be related to the pathogenesis of the disease (Gray et al., 1982).
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IMMUNE COMPLEXES IN RHEUMATIC FEVER

Because the patient with acute rheumatic fever develop antibodies to multiple cellular and extra cellular streptococcal antigens, a potentially large number of immune complexes can be developed. These patients have high circulating level of immune complexes in their serum.

These immune complexes persist for several weeks after the initial appearance of the clinical symptoms. Whether or not these complexes play a role in the cellular response (i.e. high cellular reactivity related to high level of immune complexes) is still unknown. The fact that patients, who have post streptococcal sequelae either nephritis or rheumatic fever, have circulating immune complexes suggests that the nature of the complexes may be more important than the presence of these complexes in a given disease state (Van de Rijn, et al., 1978).

Recent studies define the potential role of circulating immune complexes in pathogenesis of certain manifestation of rheumatic fever. It is possible that localised immune complex mediated disorder may occur within the joint in acute rheumatic fever, similar to rheumatoid
arthritis. The synovial fluids of patients with rheumatoid arthritis contain immune complexes as well as decreased complement and activated complement components.

If the immune complexes are directly responsible for certain manifestations of rheumatic fever such as the polyarthritis, this may be through modulating the immune response to streptococcal antigens (Yang et al., 1977).

There is increased frequency of immune complexes in rheumatic patients who are HLA-B5 positive. This may suggest a more heterogeneous immune response with the development of multiple antigen-antibody systems in these patients. However, the pathogenic importance of these complexes remain unsettled (Yoshinoya and Pope, 1980).
SUMMARY
The immune system is an extremely complicated one with a variety of roles in maintaining homeostasis and health. This function arises through the action of a number of subpopulation of the T and B cells and macrophages (Katz, 1982).

There are several defence mechanisms against infection. These include humoral mechanism which is concerned in production of immunoglobulins which combine with various antigens. The cell-mediated mechanism which result in production of lymphokines-from sensitized lymphocyte - which have different types of actions (Weir, 1983). The complement system passes through series of steps resulting in many factors which are important for opsonisation as well as lysis of the invading cells.

Rheumatic fever is multisystem disease of obscure aetiology. It occurs secondary to pharyngeal infection with group A beta-haemolytic streptococci. This disease manifests itself with polyarthritis, chorea erythema marginatum, subcutaneous nodules and carditis, these may occur singly or in combination (Markowitz et al., 1965). The worst sequelae of this disease is rheumatic heart
diseases which cause heart valves deformities.

Several studies showed that immunological process plays important role in the pathogenesis of rheumatic fever. It was found that certain types of immunoglobulins were elevated in the serum of rheumatic patients, especially in acute attack as compared to chronic state (Fahey, 1965). Also, many studies have suggested the presence of heart-reacting antibodies which react with the sarcolemmal and interfibrillar regions of mammalian heart tissue, these antibodies result from antigenic stimulation of streptococcal antigens (Zabriskie et al., 1970).

It has been suggested that complement components are decreased within the synovial fluid of the joints in patients who have polyarthritis, this may raise the possibility of the presence of complemental involvement in the developing rheumatic arthritis (Svartman et al., 1975).

The rheumatic patients also have high level of circulating immune complexes in their serum. This is due to presence of various antibodies against multiple cellular and extracellular streptococcal antigen (Yang et al., 1977).
The rheumatic patients exhibit exaggerated cellular reactivity to streptococcal membrane antigens. This heightened reactivity of lymphocyte is of particular interest, as this antigen cross-react with sarclemma of mammalian heart tissue and walls of blood vessels.

Many studies showed that cell-mediated immune response to cardiac antigen, present only in cases who have rheumatic carditis. This suggests that it is heart specific and produced only when the heart is involved (Agarwal et al., 1980).

These previous data suggest the role of immune system in the pathogenesis of rheumatic fever, but the precise nature of this process is still not fully clear.
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ARABIC SUMMARY
يُعتبر جهاز الطاعة من أجهزة الجسم المقدسة التي لها أدوار مختلفة هدفها
محافظة على صحة الجسم وذك عن طريق عدد من الخلايا مثل (أ) وخلايا (ب) وتوجد
طرق عديدة لحياه الجسم من الالتهاب عنها الأجسام المضادة والطاعة الخلية مثلاً
طريق الخلايا الليفافية الحساسة ونظام الكوبليست.

والحمى الروماتيزمية تصيب أجزاء عديدة من الجسم وهي تنتج من اصابة البلعوم
بالبكتيري السببي مجموعات (أ) ومن ضاغطها هذا المرض إصابة القلب (ب) وهكذا...
وهناك عدد من الأبحاث التي تؤكد دور المحيط المناعي في الألم والالتهابات المرضية
التي تسببها الحمى الروماتيزمية.

وجد أن مستوى الأجسام المضادة يزدهر في دم الأشخاص المصابين بالحمى الروماتيزمية
وبخاصة في الحالات الحادة. وهكذا من يقترح أن مركبات الكوبليست تحتوي دور في الاصابة
بالالتهاب المرضية في الحمى الروماتيزمية لأن هذه المركبات توجد أنها تنقل في السوائل
المثلية في المرضى المصابين بالالتهاب المرضي.

ويوجد في دم الأشخاص المصابين بالحمى الروماتيزمية مستوى مزود من المركبات
المضادة وذلك لوجود أجسام ضادة تتفاعل مع الأجسام الغريبة الناشئة من الميكوب السببي.
وتظهر معظم الأبحاث التي أن المادة الخلوية للأجسام الغريبة القلبية توجد فقط في حالات
الإصابة القلبية وهذا يدل على أنها خاصة بالقلب.

من الدلائل السابقة يقترح وجود دور للجهاز المناعي في العلامات المرضية
للحمى الروماتيزمية ولكن طبيعة هذا الدور لم تعرف بعد باحكام.
  Heart-reactive Antibodies associated with
  rheumatic fever, characterisation and Diagnostic

  Chemotaxis by polymorph nuclear leucocytes.
الصور المناعية في الحمى الروماتزمية في الأطفال

رسالة مقدمة من الطبيب / محمد بكر أمين بكر

توظيف للحصول على درجة الماجستير
في طب الأطفال

تحت إشراف

الدكتور / محمد كمال رزق
استاذ طب الأطفال المساعد
كلية طب بنيها

الأستاذ الدكتور / أحمد خشب
رئيس قسم الأطفال
كلية طب بنيها

كلية الطب
جامعة بنيها

1984