INTRODUCTION

It has been long realized that when a person catches an infection, recovery is often accompanied by an acquired resistance against that particular infection. Therefore, the convalescent person is unlikely to suffer from the same disease again. Greek historian Thucydides (464-404B.C.) noticed that during war time, those suffering from plague, were not given much attention if they had already suffered the infection earlier. Possibly such attitude of the physicians of that time was due to their awareness about the process how body fights and protects against the germs and all those particles which are recognized foreign by the body. Edward Jenner in 1796 performed a heroic experiment by exposing the small healthy boy James Phipps by inoculating him with material from cow pox pustule from a milk maid and then exposing him to small pox virus six week later. To the surprise of physicians the boy did not develop small pox. His method of inoculation was further improved and then adopted by WHO, ultimately eradicating small pox in 1980.
Later, in 1880 a French chemist Louis Pasteur observed that animals who had been exposed to weak germs of chicken cholera did not develop disease when exposed to the virulent strains of same virus. He experimented on his observations on human subjects and the findings were the same. The same was observed in case of rabies.

Many other scientists such as William Osler, James Salk, etc. worked on the principle of body’s mechanisms to fight against diseases which is broadly now termed as immunology. Immunology is precisely the discipline of medical science involved in study of body’s defense mechanisms against diseases and their applications in the treatment. The immune response i.e. the processes involved in body’s fight against disease is governed by a complex organ system in the body called immune system which bidirectionally communicates with other body systems and environment too. In the past few decades there has been tremendous research in the field of immunology and its interaction with brain helping to understand its implications in the genesis and treatment of various diseases. This interaction is so complex that it is now recognized as Psychoneuroimmunology (PNI)- a speciality of immunology (Ader, 2000, Sternberg, 2001).

Robert Koch discovered the aetiological agent of tuberculosis and its immunological treatment with tuberculin. Later, William Osler recognized emotional factors and whatever is going on in the patients’ mind do predict the outcome of pulmonary tuberculosis. George Day (1951) a British psychologist, noted life adjustment difficulties prior to the onset of tuberculosis.

The healthy relatives of patients with autoimmune (vide infra) disease who had antibodies against their own collagen tissue in skeleton (rheumatoid arthritis) had better psychological adjustment than those without this factor (Solomon and Moos, 1964). This finding again suggests that emotions have a complex interaction
with immune system, possibly through brain. More direct evidence about the role of emotions, brain and behaviour came from the animal experiments of Korneva and Khai (Solomon 2000) who demonstrated prolonged retention of antigen (the molecules that are capable of initiating an immune response) in the blood and due to suppression of complement fixing antibodies in the rabbits who had lesions in dorsal hypothalamus. Many workers consider this discovery as the time marker of beginning of era of psychoneuroimmunology as it showed beyond any doubt the involvement of brain in the immunomodulation. Later, Ader and his team mates (1991) demonstrated that the immune system can be conditioned to respond to many antigenic stimuli according to the principles of classical conditioning of the behaviour. They are also accredited for coining the term psychoneuroimmunology (PNI) which has many synonyms such as psychoimmunology, psychoneuroendocrinology, immunopsychology, etc. Irrespective of the term used, these all highlight the complex interplay of various body systems like nervous system, endocrine system, emotions and behaviours and immune response towards genesis and defense against the diseases.

PHYSIOLOGY OF IMMUNE SYSTEM

The Immune Response

The human body protects itself in many ways. The first line of defense is provided by physical barriers, such as skin, epithelial lining of the respiratory and digestive tracts, conjunctiva, etc. Whenever, a pathogen succeeds in breaching the surface barriers and enters the body, it encounters panoply of other factors that guard the inner tissues. Broadly, these inner defenses have been grouped into two categories - innate and adaptive.

The innate immune component is the body’s first line of defense. It initiates an immediate, generalized, and rapid but short-
lived response against intruders, whether they are bacteria, viruses, parasites, or fungi. Among the major types of innate immune cells are *macrophages*, particularly good at recognizing bacteria; *granulocytes* that recognize bacteria and parasites; *dendritic cells*, which are particularly good at recognizing viruses; *natural killer cells*, which play a role in recognizing viruses and tumour cells; and *mast cells*, which are involved in allergic responses. In inflammation, for instance, innate macrophages that encounter bacteria release chemicals called *cytokines* and *chemokines*, which help granulocytes migrate to the site of infection and attack, causing the redness, swelling, heat, and pain associated with infections. The macrophages also call for help from the body’s second line of defense, the adaptive immune cells.

In fact, a major role of the innate immune system’s macrophages and dendritic cells is to patrol the body for intruders and, when they are sighted, activate the body’s second line of defense, the *adaptive immune cells* that are called “lymphocytes”.

In *Adaptive Immune Response* there are two types of lymphocytes, “B” and “T” cells. These adaptive immune cells mount an exquisitely targeted and precise attack against a specific invader. In general, each invader that is found on the outside of the body’s cells is a target for a specific B cell, while each invader that enters the body’s cells is a target for a specific T cell. B cells act by secreting molecules called antibodies that circulate through the bloodstream to the intruder’s sites and attack it. In contrast, there are two major types of T cells, and they have different functions. One type is called “cytotoxic T cells.” These cells directly attack an intruder. The other type of T cells helps to stimulate B cells and macrophages to attack. That is why they are called “helper T cells.” Once a specific intruder is vanquished, either by B cells or T cells, some of the remaining B or T cells will remember what the intruder looked like and would
be able to mount a faster response whenever that intruder again attacks the body.

The innate and adaptive immune systems are each made up of numerous components that can carry out particular type of protective function. Some are specialized cells that have the capability to recognize, sequester, and eliminate various types of organisms or harmful substances; the defenses provided by such cells are collectively known as \textit{cell-mediated immunity}. The remainder are soluble macromolecules (usually proteins, immunoglobulins, Igs) that circulate in the blood and extracellular fluid, making these liquids inhospitable to foreign invaders even when all cells have been removed; cell-free defenses of this type are called \textit{humoral immunity}.

The innate and adaptive immune systems each play critical roles in host defense. Both systems are essential for health; they usually act in concert and often depend on each other to produce maximum effects. The action of one system frequently influences the other, and certain individual cell types or humoral proteins are pivotal to the workings of both systems.

\textbf{CELLS INVOLVED IN IMMUNITY}

\textbf{Lymphocytes and lymphoid organs}

The normal adult human body contains in the order of trillion (10\textsuperscript{12}) lymphocytes. The typical lymphocyte is a small, round, or club-shaped cell, 5-12 µm in diameter with a spherical nucleus. The most fundamental distinction is the division of these cells into two major lineages known as \textit{T (thymus-derived) cells} and \textit{B (bone-marrow-derived) cells} (Figure 2.1). T and B cells account for about 75\% and 10\% of all lymphocytes, respectively. The remaining 15\% of peripheral blood lymphocytes belong to a separate and rather enigmatic lineage known as \textit{natural killer (NK) cells}. 

\textit{Physiology and Psychoimmunology}
FIGURE 1
"Development and differentiation of T and B lymphocytes with T cell subsets

T- and B-lineage cells arise from a subset of haemopoietic cells in the bone marrow or foetal liver that become committed to the lymphoid pathway of development. They are descendents of a committed marrow progenitor, called the lymphoid stem cell, that serves as a common precursor for both T and B cells, as well as for NK cells and some dendritic cells. Human B-lymphocyte development takes place entirely within the bone marrow. T lymphocytes, on the other hand, develop from immature precursors that leave the marrow and travel through the blood stream to the
thymus, where they proliferate and differentiate into mature T lymphocytes.

The thymus and bone marrow are sometimes referred to as primary lymphoid organs because they provide unique microenvironments that are essential for lymphopoiesis - the initial production of lymphocytes from uncommitted progenitor cells.

Mature lymphocytes that emerge from the thymus or bone marrow are in a quiescent or resting stage: they are mitotically inactive, and are yet not stimulated to either undergo cell division or carry out immunologic functions. When dispersed into the blood stream, these so-called naive lymphocytes migrate efficiently into various secondary (or peripheral) lymphoid organs, such as spleen, lymph nodes, tonsils, lymphatic tissue in the intestine (peyer’s patches), and the in the respiratory and genitor-urinary tracts (collectively known as mucosa-associated lymphoid tissue, MALT). The function of secondary lymphoid organs is to maximize encounters between lymphocytes and foreign substances, and it is from these sites that most immune responses are launched.

Lymphocytes are classified on the basis of surface markers using two important characteristics: Cluster determinants (CDs) and antigen recognition receptors.

Cluster determinants: CDs represent families of surface glycoprotein antigens that can be recognized by specific antibodies produced against them. Each class of leucocyte displays a diagnostic pattern of CDs. For example: CD3 is expressed only by T cells, CD19 is expressed only by B cells.

Antigen recognition receptors: These include membrane-bound immunoglobulins (Igs) on B cells and T-cell receptors (TCRs) on T cells.

B lymphocytes: The cells of the B-cell lineage have the ability to synthesize proteins called immunoglobulins. No other cell expresses these proteins. Mature B-cells express immunoglobulins
in two different forms. In resting B lymphocytes, immunoglobulins are expressed only on the cell surface, where they serve as membrane-bound receptors for specific antigens. Secondly, when the B-lymphocytes are exposed to the antigen, they divide and proliferate into the effector cells (called the plasma cells) which are uniquely specialized to secrete large amounts of immunoglobulin proteins. Secreted immunoglobulins retain the ability to recognize and bind their specific ligands on the antigens and are often referred to as antibodies.

The B-cells are the principal cell type involved in humoral immunity. B cells also play two additional roles in the immune system. First, they can function as antigen presenting cells by processing and displaying foreign substances in a manner that can be recognized by T cells. Second, activated B cells can secrete certain lymphokines and other factors that influence the growth and activities of other immunologically important cells.

T lymphocytes: T lymphocytes do not express immunoglobulins but, instead, detect the presence of foreign substances by way of surface proteins called T-cell receptors. T-cell receptors are closely related to immunoglobulins on B-cells in evolution and share with them a number of structural and functional properties, including the ability to detect specific small molecular ligands called antigens. Unlike, immunoglobulins, T-cell receptor proteins are never secreted, and, as a result, they lack the ability to strike their targets at long distance. Instead, they exert their protective effects either through direct contact with the target or by influencing the activity of other immune cells. Together with macrophages (acting as the antigen presenting cell), T cells are the primary cell type involved in cell-mediated immunity.

Other Cells and Mediators Involved in Immunity

Antigen presenting cells: T lymphocytes can detect foreign protein only if it is first cleaved into small peptides and are then
displayed on the surface of a second host cell, called *antigen presenting cell*. Although, all types of host cells can present antigen on the surface, but certain cell types are specially adapted for this purpose and are particularly important in controlling T-cell activity. These include *macrophages*, *B-lymphocytes*, and a family of bone-marrow derived cells known as *dendritic cells.*

*Neutrophils:* These are short lived, white blood cells with multilobulated nucleus which one produced in the bone marrow. These cells usually make the first line of defense in the body. Upon entry of bacteria/antigen into the body via injury or infection, the neutrophils migrate, phagocytose and kill the bacteria/antigen. Their action is more prompt when these bacterial cells are coated with antigens or antibodies.

*Macrophages:* These are delivered from bone marrow. In the blood, they mature to monocytes and stay in tissues as mononuclear phagocytes. Like neutrophils, they are capable of phagocytosis and killing bacteria. They act as one of the principal antigen presenting cells. They secrete a number of immune mediators -the cytokines which serve as the messengers of immune process to the T lymphocytes and other participating cells.

*Natural Killer (NK) cells:* These are large granular cells structurally similar to lymphocytes. They offer resistance against carcinogenesis and oral infections. These cells bear the receptors which recognise high molecular weight glycoprotein receptors on the foreign cells and kill them before these cells with antigens have a chance to reproduce. These cells also have receptors for antibody, therefore, can also act synergistically with B lymphocytes and more promptly in killing the cells coated with antibodies. The NK cells are usually activated by release of interferons produced by virus infected cells.

*Eosinophils:* These are granulated WBCs having toxic proteins in their granules. During allergic conditions and parasitic infections the number of eosinophils may increase dramatically.
Basophils and Mast cells: These are also granulated cells with many chemical mediators of inflammation and chemotactic activity. The granules contain pharmacological mediators of type I hypersensitivity. They have receptors for IgE antibodies, therefore, these cells are primarily involved in IgE-mediated allergic reactions.

Cytokines: These are soluble mediators which are involved in many critical interactions among cells of immune system. These cytokines are a diverse group of intercellular signaling peptides and glycoproteins with molecular weights between 6000 and 60,000 daltons, and most of them are genetically and structurally unrelated to one another. Several hundred cytokines have been identified to date. Collectively, they regulate not only immune and inflammatory responses but also wound healing, haematopoesis, angiogenesis, and many other biologic processes. Various cytokines are interferons (IFNs), interleukins (ILs), colony stimulating factors (CSFs), chemokines (chemotactic cytokines) and others like tumour necrosis factor (TNF-α, TNF-β), transforming growth factor (TGF-β), and lymphotoxins (LT-α and LT-β). Major properties of human cytokines are given in Table 1.1

Major Histocompatibility Complex (MHC): MHC consists of antigens which recognize self and non-self antigens. MHC in humans is known as Human Leukocyte Antigen (HLA) complex. The genes that code for the HLA antigens are found on the short arm of sixth pair of chromosome. The MHC genes are contained within four HLA loci known as A, B, C and D. There are many different alleles at each of HLA-A, HLA-B, HLA-C and HLA-D. There are three classes of genes in these HLA loci: class I, class II and class III which code for corresponding antigens.

Class I antigens are the products of HLA-A, HLA-B and HLA-C loci. They are present on virtually all nucleated cells with probable exception of ova, sperm and amniotic cells, in man. The cytotoxic T cells recognize the antigen only if it is presented simultaneously with class I antigens.
Class II antigens are encoded by HLA-DP, HLA-DQ and HLA-DR loci. In man, they are normally found on immunologically reactive cells such as B lymphocytes, macrophages, monocytes and activated T lymphocytes.

Class III antigens are products of the genes coding for the complement components of the classical (C2 and C4) and the alternate pathway.

T cell subsets: Four distinct subsets of T cells are known. Two each of these are regulator and effector cells (Figures 2.1 & 2.2)

FIGURE 2
“Mechanism of immune response”
During maturation and differentiation in thymus T cells also learn to recognize self-major histocompatibility (MHC) antigens. CD4+ cells recognize class II MHC antigens and CD8+ cells recognize class MHC antigens.

**Regulator Cells**

*Helper T (Th) cells:* They possess CD2, CD3 and CD4 surface antigens. They help in antigen specific activation of B cells and effector T cells. Th cells are of two types, Th1 and Th2. Th1 cytokines include IFN-é, IFN-â and IL-2 and Th1 cells are involved in cell-mediated inflammatory reactions. Th2 cytokines include IL-4 to IL-6, IL-9, IL-10 and IL-13. Th2 cells encourage production of antibody especially IgE, and are associated with regulation of strong antibody and allergic reactions.

*Suppressor T (Ts) cells:* They possess CD2, CD3 and CD8 surface antigens. They suppress expression of immune response by other lymphocytes.

**Effector Cells**

*Delayed-hypersensitivity T (Td) cells:* They possess CD2, CD3 and CD4 surface antigens. They are involved in delayed hypersensitivity and cell-mediated immune responses.

*Cytotoxic T (Tc) cells:* They possess CD2, CD3 and CD8 surface antigens. They are involved in cell-mediated immune responses and lyse target cells by direct cell-cell contact.

Immune response is regulated by mutually opposing influence of Th and Ts cells. Overactivity of Th or decreased activity of Ts causes autoimmunity. Whereas, diminished activity of Th and increased activity of Ts leads to immunodeficiency.

*Complement system:* This is a system of sequentially acting proteins that react in a cascade fashion thereby amplifying the response of their predecessor molecule. The system consists of a
series of immunoproteins named C1 to C9 that do not act in the same sequence. The complement system can be activated through classical pathway in the presence of immune complexes or alternate pathway which finally merges in common pathway for membrane attack complex.

**TABLE 1**

**Major Properties of Important Human Cytokines**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Principal cell source</th>
<th>Major effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1α and β</td>
<td>Macrophages, other APCs, other somatic cells</td>
<td>Costimulation of APCs and T cells B-cell growth and Ig production Acute-phase response Phagocyte activation Inflammation and fever Promotes haematopoiesis</td>
</tr>
<tr>
<td>IL-2</td>
<td>Activated Th2 cells, Tc cells, NK cells</td>
<td>Proliferation of activated T cells Apoptosis of T cells after prolonged or repeated activation NK cell and Tc cell functions B cell proliferation and IgG2 expression</td>
</tr>
<tr>
<td>IL-3</td>
<td>T lymphocytes</td>
<td>Growth of early haematopoietic progenitors</td>
</tr>
<tr>
<td>IL-4</td>
<td>Th2 cells, mast cells</td>
<td>B-cell proliferation IgG expression and class II MHC expression Th2 cell and Tc cell proliferation and functions Eosinophil and mast cell growth and function</td>
</tr>
<tr>
<td>IL-5</td>
<td>Th2 cells, mast cells</td>
<td>Eosinophil growth and function</td>
</tr>
<tr>
<td>IL-6</td>
<td>Activated Th2 cells, APCs, other somatic cells</td>
<td>Synergistic effects with IL-1 or TNFα Fever Acute-phase response B-cell growth and Ig production Haematopoiesis</td>
</tr>
<tr>
<td>IL-7</td>
<td>Thymic and marrow stromal cells</td>
<td>T and B lymphopoiesis Tc cell functions</td>
</tr>
<tr>
<td>IL-8</td>
<td>Macrophages, other somatic cells</td>
<td>Chemoattracts neutrophils and T cells Angiogenic</td>
</tr>
</tbody>
</table>
## TABLE 1 Cont...

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Principal cell source</th>
<th>Major effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-9</td>
<td>T cells</td>
<td>Some haematopoietic and thymopoietic effects</td>
</tr>
<tr>
<td>IL-10</td>
<td>Activated Th2, CD8+ T, and B lymphocytes, macrophages</td>
<td>Inhibits cytokine production by Th1 cells, NK cells, and APCs Promotes B-cell proliferation and antibody responses Suppresses cell-mediated immunity</td>
</tr>
<tr>
<td>IL-11</td>
<td>B cells, macrophages</td>
<td>Synergistic effects on haematopoiesis and thrombopoiesis</td>
</tr>
<tr>
<td>IL-12</td>
<td>B cells, macrophages</td>
<td>Proliferation and function of activated Tc cells and NK cells IFNg production Promotes Th1 cell induction; suppression of Th2 cell functions Promotes cell-mediated immunity</td>
</tr>
<tr>
<td>IL-13</td>
<td>Th2 cells</td>
<td>Similar, but additive, to IL-4 effects</td>
</tr>
<tr>
<td>IL-15</td>
<td>Epithelial cells and monocytes, nonlymphocytic cells</td>
<td>Mimics IL-2 T-cell effects Mast-cell and NK activation</td>
</tr>
<tr>
<td>IL-16</td>
<td>CD8+ and some CD4 T+ lymphocytes</td>
<td>Chemoattracts CD4+ T cells, eosinophils, and monocytes</td>
</tr>
<tr>
<td>IL-17</td>
<td>Activated memory T cells</td>
<td>Promotes T-cell proliferation, neutrophil development</td>
</tr>
<tr>
<td>IL-18</td>
<td>Macrophages, Keratinocytes</td>
<td>Coinduces IFNg production Coactivates Th1 and NK cell development</td>
</tr>
<tr>
<td>TNFα</td>
<td>Activated macrophages, other somatic cells</td>
<td>IL-1 like effects Vascular thrombosis and tumour necrosis</td>
</tr>
<tr>
<td>LTα</td>
<td>Activated Th1 cells</td>
<td>IL-1 like and TNFa like effects Development of peripheral (secondary) lymphoid organs</td>
</tr>
<tr>
<td>LTα-LTβ complex</td>
<td>Activated Th1 cells</td>
<td>IL-1 like and TNFa like effects Development of peripheral (secondary) lymphoid organs</td>
</tr>
<tr>
<td>Cytokine</td>
<td>Principal cell source</td>
<td>Major effects</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>IFN α and β</td>
<td>Macrophages, neutrophils, other somatic cells</td>
<td>Antiviral effects Induction of class I MHC on all somatic cells Activated of macrophages and NK cells</td>
</tr>
<tr>
<td>IFNγ</td>
<td>Activated Th1 and NK cells</td>
<td>Induction of class I MHC on all somatic cells Induction of class II MHC on APCs and somatic cells Activation of macrophages, neutrophils, and NK cells Promotion of cell-mediated immunity (inhibits Th2 cells) Antiviral effects</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Activated T lymphocytes, platelets, macrophages and other somatic cells</td>
<td>Antiinflammatory (suppression of cytokine production and class II MHC expression) Antiproliferative for stem cells, monomyelocytic cells and lymphocytes Promotion of fibroblast proliferation and wound healing</td>
</tr>
</tbody>
</table>

**The CNS-Immune System Interaction**

The immune system and the nervous system share three common features: (1) both have a high degree of complexity, (2) they have a memory *i.e.* the capability to store newly acquired information, and (3) the ability to recall that information in response to an appropriate external stimulus. But this is not the all new about commonalities between the two. What is functionally more important is that both these systems can interact with each other bilaterally (McKhann and Asbury 2004).

**Evidence from the Nervous System**

Immunologically important components were once kept out of the nervous system. We have known for about a century that nerve cells communicate with one another through connections called synapses. Now it is apparent that immune cells also
communicate with one another through synapse-like junctions that appear to share some common features with nerve cell synapses, including some molecules. And there is new evidence to suggest that brain cell synapses are influenced by immune reactions in the brain (Safire, Kendel, Weston, Rover, Albert and Andreasen, 2004). Recently and to the surprise of scientific community, the immune molecules have been shown to regulate the developmental process of the brain. The finding came from the studies that examined the development of synapse in the lateral geniculate nuclei in the visual pathway. It was remarkable that ‘Major histocompatibility complexes’ were the key factors for the neurons signaling and fine tuning the development of synaptic connections. Shatz and colleagues (Huh, Du, Boulanger, Riquelme, Brotz, and Shatz, 2000), further showed in their researches that in the other parts of the brain also the neurons are able to establish synaptic connections only on the basis of MHC compatibility of neuron.

Many other molecules have also been identified such as ‘semiphorins’ which guide the development of autonomic nervous system and the ‘neurophorins’ that regulate the MHC. Possibly this is the reason that the brain wiring is not random but highly structured which is guided by the immunological processes. (Huh et al., 2000).

Not only the immune mechanisms in the brain are capable of causing and preventing disease but, as shown by, brain-driven processes such as chronic stress, in turn, exert an aging effect on the immune system. (Kiecolt-Glaser, Preacher and MacCallum, 2003) thereby affecting all body organ systems.

As an outcome of this finding one can imagine that any immunological disturbance can affect the development and functioning of brain. Coincidental findings of the degenerative changes in the specific parts of the brain with systemic malignancy without any metastasis to CNS have also been reported. The
antibodies developed against the tumour cross reacted with the brain tissue having antigenic similarity with the tumour. This is a clear example where any alteration in the immune response would alter the brain functions too. Later as extension of this coincidental observation, many scientific studies showed that in ovarian and other cancers the antibodies against the tumour proteins target the CNS proteins too, especially produced by the Purkinje neurons. Even in the pathogenesis of mental disorders the immune response apparently has a role. Several lines of evidences suggest the role of immune dysfunction in the aetiology of schizophrenia. (Delisi, Goodman, Neckers, Wyatt 1982; Rabbin, Ganguly, Cunnick and Lysle, 1988; Ganguli, Brar, Chengappa, Yang, Nimgaonkar and Rabin 1993) It has been seen in many old studies that the schizophrenics are winter born i.e. born in a season much conducive to viral infections, have elder siblings at home - which might be possible source of infection, an increased incidence of schizophrenia in viral epidemics, particularly influenza have also been noticed Many serological investigations have also found that these patients have increased expression of IL-2 receptors with decreased IL-2 production. The findings have been interpreted differently - it may either be the result of immune system dysregulation due to schizophrenia or an autoimmune process against the brain tissue leading to the mental condition. In the postmortem findings, no virus could ever be demonstrated in the schizophrenic brain tissue, but a possibility of contracting infection in-utero leading to structural abnormalities in the synapse could not be ruled out. Autoantibodies against the brain tissue in the schizophrenia too have never been consistently demonstrated. The brain damage seen in many patients may be due to schizophrenic process itself. This process may release the brain antigen which may get exposed to the immune system setting in an autoimmune response. Thus the autoimmunity in schizophrenia may be the effect of mental disorder rather than the cause of it.
Thus, it is now high time that both systems should be considered in unison than the independent functional units of the living body (Huh et al, 2000).

**Neuronal Lesions and Immunity**

As pointed out earlier, the demonstration of CNS lesions accompanied with altered immune response as observed in 1960s marked the beginning of phase of brain-immunity interaction. Jancovic and Isacovic (1973) pointed out that lesion in the anterior hypothalamus leads to immunosuppression through direct increase in macrophage suppressor activity rather than through any hormone or any mediator. Hypothalamic nuclei especially the anterior nucleus appears to regulate the immune process directly. Lesion in this area protects the experimental animals against the anaphylactic reactions. This was also accompanied by a decrease in the splenic and thymic immune cells, decreased splenic mitogen responsiveness and reduced NK cell activity. Increased mitogen responsiveness was seen with bilateral amygdala and hippocampal lesions, whereas these lesions did not decrease the thymic or splenic cell numbers.

The left sided brain lesions affected immune response more adversely in comparison with the right sided lesions. In contrast to this in human subjects the left handedness (i.e. the right brain dominance) is found to be associated with more immune disorders especially those of thyroid and gastrointestinal tract. Although these findings are not consistently replicated in experiments but it does suggest a possibility of a differential specialization of cerebral hemispheres in the regulation of immunity. Similarly, the studies conducted before and after hypophysectomy show altered immune response of the animals. Many other findings have suggested that hypothalamus, pituitary gland, and the other endocrine components of the brain regulate the immune response (Keller, Schliefer, Liotta, Bond, Farhoody and Stein 1998).
The CNS and immune system interaction though difficult to understand can be superficially postulated to have two different pathways. Firstly, most of the lymphoid tissues receive direct sympathetic innervations. The blood vessels as well as the lymphoid tissue cells too have receptors for catecholamines. Secondly, the nervous system itself controls the output in all endocrine hormones including corticosteroids, growth hormone, thyroxine, adrenaline, etc., which in turn can modulate the immune response, thus justifying the term *Psychoneuroendocrinology*.

**Evidence from the Immune System**

*Neuronal Receptors on Immune Cells*

As the nervous system regulates the other body organs, it works in perfect coordination with immune system too. The evidence is available from the studies of immune cells and organs. Different immune organs and the immune cells have receptors for many molecular modulators that have origin in the nervous system. These mediators as shown in the table are neurotransmitters, neuropeptides and many hormones too.

**TABLE 2**

Receptors of Nervous system mediators on immune cells

<table>
<thead>
<tr>
<th>Neurotransmitters</th>
<th>Neuropeptides</th>
<th>Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-adrenergic</td>
<td>Growth hormone</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>A-adrenergic</td>
<td>Prolactin</td>
<td>Mineralocorticoids</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Corticotrophin</td>
<td>Estrogens</td>
</tr>
<tr>
<td>Serotonin</td>
<td>CRH</td>
<td>Progestrone</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Substance P</td>
<td></td>
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<tr>
<td>Histamines</td>
<td></td>
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<tr>
<td>VIP</td>
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</tr>
<tr>
<td>Endorphins</td>
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<td></td>
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<tr>
<td>Vasopressins</td>
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</tbody>
</table>
The receptors for neurochemicals on the immune cells are generally located on the cell membrane and are usually coupled to the G proteins and therefore to the second messenger pathways. The presence of these receptors makes the immune cells functions susceptible to the changes in neurons and/or behaviour. The presence of these receptors is not just any random phenomenon. Through these receptors the immune system responds to the signals from the CNS to maintain homeostasis. (Besedovsky and Del Rey, 1996)

Further, the expression of the receptors on all immune cells is not uniform. The expression depends on their site of origin of the cells and many a times also on their functional specificity. The T-cells maturing in the thymus have receptors for the glucocorticoids, whereas the T-cells present in the spleen have receptors for the glucocorticoids as well as mineralocorticoids. Besides the heterogeneity for the type of receptors, there is heterogeneity for the receptor density also. Among the T cells, adrenergic receptors are maximum on the T-suppressor cells, followed by T-cytotoxic cells. Therefore due to the receptor heterogeneity, the specific stimulus from CNS would arose the specific immune cell response. This heterogeneity, both the type and the number present on the immune cells and tissues, determines the direction and intensity of modulatory effects in immune response in relations to the brain. It is well known that the adrenergic stimulation lowers the functional indices of the immunity. But stimulation of the B adrenergic receptors on the T-suppressor cells which are more susceptible to this hormone, may actually decrease their inhibition and thereby paradoxically enhance the immune response. The concentration of modulating biochemical in the circulation also determines the direction of immune modulation. This change may not be equally reflected in all the compartments of immune system. The stress related release of glucocorticoids from adrenal gland has more profound effect
on the thymus and in the peripheral blood in comparison with the spleen. The modulation of immunity also depends on the phase of immune response. During the proliferation phase high levels of norepinephrine in the blood diminish immune activity whereas the low levels may actually enhance the effect.

Clearly the heterogeneity in the distribution of receptor type and number influence the function depending on the type of cell and its receptors, density of receptors on the cells, on the site where the cell is localized, and also the phase of immune response (Dhabhar, Miller, McEwen & Spendeer, 1996). The presence of receptors for the neuronal products itself is a sufficient evidence that the nervous system and the immune system can communicate with each other.

**Lymphoid Tissue Innervation**

As stated earlier the lymphoid tissue is highly innervated by the autonomic nervous system (ANS). These innervations are important in the development and maturity of the lymphocytes. Other neurotransmitters such as substance P, calcitonin, vasoactive intestinal peptide (VIP) are also colonized in the immune tissues. But their functional importance is still obscure. There is marked heterogeneity in the pattern of innervation also and, therefore, in the pattern of lymphatic tissue stimulation by the ANS. The thymus gland receives high density of efferent nerves from the vagus, phrenic and recurrent laryngeal nerves, and from the stellate and other ganglia of thoracic sympathetic chain. Spleen receives autonomic inputs from the celiac ganglion. The bone marrow gets sympathetic innervation from the respective spinal segment of the spinal chord innervating that particular bone. The lymph nodes are innervated by the sympathetic nerves accompanying the arterioles supplying them. Since the arterioles in the nodes have smooth muscles also, their action is expected on these arterioles too, besides direct influence on the tissue of that lymph
node. The heterogeneity of innervations pattern undoubtedly would cause a heterogeneous immune response depending on the pattern and area of sympathetic stimulation. The catecholamines have differential action on immune response at different concentration. In many animal studies the chemical sympathectomy suppressed NK cell activity and antibody production against various kinds of antigens (Dhabhar et al. 1996; Goehler, Gaykema, Nguyen, Lee, Tilders Maier, Watkins, 1999; Stein, Miller & Trestman, 1991).

Immunocytes: The Tools for Exploring the Neurobiology

Immune cells are readily available for investigations from the peripheral blood and express receptors for hormones and transmitters that are altered in a variety of psychiatric disorders. Therefore they also provide an easy pathway to investigate the brain functions. Immune cells may therefore provide useful receptor models for exploring the molecular and biochemical basis of altered neuroendocrine or neurotransmitter functions. Adrenal steroid receptors which are expressed in immune tissues along with brain and, after long-term exposure to glucocorticoids in rats, those receptors in immune tissue exhibit down-regulation in parallel with adrenal steroid receptors in multiple brain regions, including the hypothalamus and the hippocampus. During major depression, abnormalities in hypothalmic-pituitary-adrenal (HPA) axis activity, including hypercortisolemia and nonsuppression of the HPA axis by dexamethasone, are believed to be partly related to reduced glucocorticoid receptor responsiveness to feedback inhibition by glucocorticoids at the level of the hippocampus, the hypothalamus, and the pituitary. Nevertheless, results of studies conducted on depressed patients have been inconsistent regarding glucocorticoid receptor functions in lymphocytes. Fewer studies have investigated the functional sensitivity of cells to inhibitory effects of glucocorticoids, but they have been more consistent, showing an increased resistance of cells from depressed patients
to the inhibitory effects of glucocorticoids on immune function. Evidence of altered glucocorticoid receptor function in lymphocytes from depressed patients indicates that the glucocorticoid resistance in this disorder may be reflected in the readily accessible cells from the immune system (Miller, Bradley & Priante, 2000).

In contrast to patients with depression, patients with posttraumatic stress disorder exhibit significantly higher number of glucocorticoid receptors than in controls; these findings are accompanied by significantly lower concentrations of plasma corticoster in posttraumatic stress disorder patients. Thereby altered immune lymphocytic functions in both cases. Immune cells may therefore provide a useful receptor model both for identifying persons with HPA axis alterations and exploring the molecular mechanisms involved (Watson, Mulles and Jones, 1993).

β-adrenergic receptors of peripheral immune cells from depressed patients have exhibited evidence of diminished β-adrenergic responsiveness. The decreased responsiveness may be the result of desensitization (diminished function, normal number) or down-regulation (diminished number) of leukocyte β-receptors. Because postmortem brain β-receptors from depressed patients (death by suicide) have been shown to be up-regulated (increased receptor binding), brain and lymphocyte β-receptors appear to have an inverse relationship in the depressive disorders. However, whether the decreased responsiveness of immune cell β-receptors is caused by an increase in plasma catecholamines or a decrease in peripheral sensitivity to catecholamines, or whether a decrease in peripheral sensitivity to catecholamines leads to an increase in brain catecholamine production is unknown. Nevertheless, as with glucocorticoid receptors, immune cells may be an important tool for identifying and evaluating β-receptor alterations in the depressive disorders (Miller Bradley and Priante, 2000).
Therefore as mentioned in above earlier, evidence is beyond any doubt that central nervous system and immune system communicate with each other.

**Psychoimmunology: The Brain-Behaviour-Immune System Link**

*Behavioural Conditioning of Immune Response*

The immune response can also be conditioned to respond in a specific learnt way on the classical Pavlovian paradigm (Ader & Cohen, 1983). In the taste aversion paradigm studies, the healthy rats were simultaneously exposed to the sweet taste of oral saccharine (conditioned stimulus) and an unpleasant experience of intraperitoneal dose of cyclophosphamide (unconditioned stimulus) - which suppresses the immune response leading to death. After repeated exposures (conditioning) the mortality rates in those receiving conditioned and unconditioned stimuli separately were identical. In the subsequent experiments the animals conditioned to saccharine showed decreased production of antibodies against sheep RBCs.

Thereafter, the experiments were also replicated on mice with systemic lupus erythematosus (an immunocompromised state) who were conditioned to saccharine in classical paradigm as described above. Then the animals were divided in three groups which received either (1) only saccharine, (2) saccharine with cyclophosphamide, and (3) no intervention at all. The mortality in the first two groups was equal and lower than in the group receiving no treatment.

These results can best be explained by the Pavlovian conditioning confirming the hypothesis that immune system can be trained to respond in a specific way both in immunocompetent and immuno-compromised states. Similar results were also seen with the other immune responses such as NK cell activity, T-cell mediated immunity.
However, only few such studies are available on human subjects. The proliferative response to T cell mitogens in the patients with ovarian cancer showed a suppressive response after hospitalisations as compared to several days before at home, even after controlling for increased anxiety levels (Bovbjerg, Redd, Maier, Holland, Lesko and Niedzwiecki, 1990). The results about conditioning of immune response in human subjects are not consistent and further controlled studies are required (Locke, Bernard, Zachariae, Francine, Tollins, Covino, and Danforth, 1994). Possibly, such variability is due to the reason that not all immune functions are susceptible to behavioural or other therapeutic interventions. Functional indices of lymphocytes are more sensitive to changes than the peripheral blood cell counts (Locke, Ader, Besedovsky, Hall, Solomon and Storm, 1985). Further the selection of subjects may also bias the response e.g. it would be difficult to improve immunity of a person having already optimal level of immune response. Therefore, it is evident that behaviour and immune response have close interaction with each other. However the understanding of the exact pathways of this interaction is not very robust due the its intricate mechanisms and methodological problems in carrying out studies on human subjects. Clearly, there is a need of methodologically robust studies using a battery of immuno-assays.

**Stress and Immune Response**

In the laboratory conditions, transient immune changes have been seen under physically stressful circumstances. The experiment conducted in 1950-60 (Locke, Ader, Besedovsky, Hall, Solomon and Storm 1985) on animals who were subjected to various stress such as exposures to predator, crowding and forced rotation had more morbidity and mortality due to infections and tumours than among the unexposed animals. Morbidity and mortality rates were more if the animals were exposed to the antigens during or soon after the stress. The animals in acute
stressful conditions demonstrated decrease in mitogen induced proliferation of lymphocytes, decreased NK cell activity. Even mild stressors also lead to changes in immune functions. Glaser, Keicolt-Glaser, Bonneau, Malrkey, Kennedy and Hughes (1992) observed that medical students who were stressed failed in seroconversion to series of hepatitis vaccine. The interleukin-1 levels have also been found to be low during stress which also leads to delay in wound healing by about 40% of time (Marchua, 1998).

Taken together, the findings of different studies are consistent with the findings that acute stress may mediate and impair the immune functions and that too through autonomic or brain mechanisms. This is also likely, as immune system perhaps does not get acclimatize to acute stress changes. Keicolt-Glaser, McGuire, Robeles and Glaser (2002) pointed that students (who are assumed experts in taking tests) can not get adapted to immune changes due to the examination. Psychologically they may not feel the stress of examination but they do have reduced immune function indices. The stress that is unpredictable and uncontrollable may continue to be related to elevated stress hormones even after repeated exposure (Baum, Cohen, and Hall, 1993). Ability to cope with stressor and the psychological state of mind might mitigate the results (Herbert, & Cohen, 1993).

Such experimental studies are few in human beings due to the ethical issues involved. The naturalistic studies among the medical students taking exam have demonstrated decrease in NK cell activity, T cell count, mitogen response to T cell proliferation, and interferon production.

Stressor, whether brief or chronic, generally leads to decrease in the functional measures of immunity. One possible mechanism proposed by Rabin (1999) is that acute secretion of stress responsive hormones can alter immune function. Even when the
cardiovascular indices are taken as autonomic measure of stress, they appear directly related to magnitude in the immunological changes.

Short term changes in immune response are very much like responses to epinephrine injections as seen in many studies (Schedlowski, Falk, Rohne, Wagner, Jacobs, Tewes, and Schmidt, 1993). The changes in the lymphocytic migration may either be mediated through catecholamine receptors on the lymphocytes or this may also be the impact of sympathetic innervations of the organs like spleen (Ackerman, Bellinger, Felten, & Felten, 1991). Therefore as concluded by Glaser et al. (Glaser, Sheridan, Malarkey, MacCallum & Kiecolt-Glaser, 2000) the change in the lymphocyte number observed during stress might not be a true change but a relative one only.

Many studies have found immune dysregulation, arterial response to vaccine and wound healing in the chronically stressed caregivers of patients with Alzheimer’s disease (Vedhara, Cox, Wilcock, Perks, Hunt, Anderson et al. 1999) and the changes may even persist after the stress ceases (Glaser, Keicolt-Glaser, Markley, Sheridan, 1998). The caregivers of the Alzheimer’s disease patients showed decreased antibody titre to herpes simplex virus and lesser proliferative response to the mitogens (Vedhara et al. 1999; Mills, Zeigler, Patterson & Grant 1999). Similarly the loss of spouse has also been shown to lower the immune response. The husbands loosing their spouses due to cancer breast were found to have decreased lymphocyte stimulation to various antigenic stimuli and lower peripheral blood cell count. One year post bereavement, these indices returned to the base level showing the effect of coping with the loss. (Schleifer, Keller, Camerino, Thornton & Sterin, 1993; Coe Rosenberg, Fischer Levine, 1987) The methodology about immune functions assessment with behavioural treatment in stressed subjects is highly variable. But
the results show a consistent trend. The studies using psychotherapeutic modes of treatment consistently showed a positive outcome of disease and impact on immune system. In a series of studies (Antoni, 1997; Schneiderman, Antoni, Ironson, Klimas, LaPerriere, Kumar, et al. 1994) on HIV positive subjects, cognitive behavioural stress management technique and aerobic exercise training programme had a good recovery in mood. Their immune function also showed a trend of improvement. The neuroendocrine factors may be responsible for the impairment in the immunofunctions. The disclosure about traumatic events and emotions also improved the mood state and immunological state (Lutgendorf, Antoni, Kumar, & Schneiderman, 1994).

**Emotions and Immunity**

Negative affects though transient or persistent, or depressive episodes lower the levels of secretory antibodies (Herbert, & Cohen, 1993; Stone, Mezzacappa, Donatone, & Gonder 1999; Stone, Neale, Cox, Napoli, Valdimarsdottir, & Kennedy-Moore, 1994). Negative emotions have also been associated with reduced NK cell-mediated lysis. It is quite possible that such immunomodulation is due to hemispheric asymmetry of brain (Lutgendorf, Vitaliano, Tripp-Reimer, Harvey & Lubarooff, 1999; Davidson, Coe, Dolski, and Donzella, 1999). Negative emotions have been seen associated with greater activity of right pre-frontal cortex and lower level of NK cell lysis (Davidson, Jackson, and Kalin, 2000). High cynical hostility followed by self disclosure also has been associated with decrease in NK cell cytotoxicity as the self disclosure by cynical hostile persons is felt more threatening, whereas no difference was seen in non-disclosure situation (Christensen, Edwards, Wiebe, Benotsch, McKelvey, Andrews, & Lubarooff, 1996; Kiecolt-Glaser, & Glaser, 1992).

Depressive disorder has a multifactorial aetiology, in which the possibility of immune mechanisms is difficult to rule out
Connor and Leonard 1998; McEwen, 1998). There have been many studies demonstrating presence of the proinflammatory cytokines - IL-1 and IL-6, and increased acute phase proteins - haptoglobins in depressed patients. The cellular markers of immune activation in depressive disorder have also been demonstrated. It is quite possible that corticotrophic release hormone (CRH) might induce proinflammatory cytokines in absence of any frank immune threat. Experiments have proved that exposure to various cytokines can produce depressive symptoms. It is hypothesized that acute phase immune response may cause relative or absolute deficiency of L-tryptophan, therefore reduces production of serotonin and, hence, the depressive symptoms. The social stressors may also release cytokines leading to the cascade of changes with depressive symptoms as outcome. The recent interest in the immune aetiology of depression is also due the observation that Borna disease virus which can infect humans also, does lead to inflammatory changes and dysfunction of T and B cells. The human infection with this virus has been seen accompanied with behavioral changes too (Grop and Cummings, 1995). However, studies are needed to confirm the findings to establish or refute the viral/immune hypothesis for aetiology of depression.

**Social Factors and Immunity**

Social factors too influence the immune response. Individuals with lower levels of socialites have been found more susceptible to the respiratory infections (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997). Spousal care givers who felt less social relations were noticed to have poor NK cell augmentation (Esterling, Antoni, Fletcher, Margulies, and Schneiderman, 1994). Even the discordant marital relationship had a persistent immunodysregulation of various parameters. Close relationship having a chronic stressful interactions show a persistent immune

As expected, contrary to the above findings, optimism was positively associated with better immune functions (Segerstrom, Taylor, Kemeny, & Fahey, 1998) but the negative affect, poor perceived social support, inadequate coping leading to repression, rejection sensitivity, all associated with altered cell count and dysregulated cellular immune function (Segerstrom, 2000).

**Stress and Immune Response—What is the Path Way**

There appears to be a complex interplay of brain-behaviour, endocrine regulatory hormones and immune functions. The pathway is not that simple as it appears. With the evidence as till now the endocrine system appears to be the central common pathway for influencing the immune response by the behaviour of a person. The endocrine hormones have both positive as well as negative influences on the immune response, growth hormone that is normally secreted by pituitary during sleep has a positive influence on the immune response. However, even the minor stress that interferes with normal sleep architecture may not only deprive the person of growth hormone influence, additionally, the release of cortisol and other stress hormones would worsen the immune functioning (Rabin, 1999; Lutgendorf, Antoni, Ironson, Klimas., McCabe, Cleven, *et al.* 1997; Veldhuis & Iranmanesch, 1996).

Another possible pathway where psychosocial factors may interfere with the immune functions is the autonomic nervous system. All the lymph nodes in body are highly innervated with the autonomic neurons. Under the effect of acute stress, autonomic nervous system may modulate both functioning of lymphoid organs as well as sensitivity of the different immune cells
The cumulative long term effects of physiological response to stress, the allostatic load, is also modulated by ANS along with the neuroendocrine system (McEwen, 1998). However, such long term mediation of these effects have not been consistently demonstrated (Keicolt-Glaser 2002; Bauer, Vedhara, Perks, Wilcock, Lightman & Shanks, 2000). More recently, cytokines have also been implicated in immunodysregulation in response to stress. Cytokines play central coordinating role in immune processes. Any physical or psychological stress can alter the role of cytokines, especially the release of proinflammatory cytokines, particularly IL-6. It has been postulated that chronic and repeated overproduction of these cytokines inhibit the beneficial effects of immune response such as suppression of IL-2 leading to immunodepression (Catania, Airaghi, Motta, Manfredi, Annoni, Pettenati, et al. 1997; Cohen, 2000).

Any stress can influence the immune system in two different ways - 1) the stress can lead to the distribution of immune cells in any part of body and 2) it can also alter the responsiveness of the immunological tissues. A decrease in the peripheral cell counts have been seen in the animal as well as human studies during stressful situations and subsequently the counts returning to the normal level after the stress is removed. An interesting finding during dermatological experiments is noticed that during stress the cell often migrate to area of skin where they are more likely to find the pathogens (Dhabhar & McEwen 1999). Different mechanisms proposed for this phenomenon include decrease in functions of specific cells including impaired T cell mitogenesis in spleen and IL-2 gene receptor changes. Recent studies have also shown release of nitric oxide (NO) by macrophage which has a negative influence on the T cell proliferation in response to antigen (Dhabhar et al., 1996).
Brain - An Immunological Organ:

There is a vast amount of data that proves beyond doubt the role of stress and CNS in modulation of immune response. Two different mechanisms seem to be operational behind this modulation: (1) the neuroendocrine pathways - which have been dealt with in a separate chapter ‘Neuroendocrine System and Immune Functions’ in the book by Sethi et al., and (2) the autonomic outputs in response to stress and altered brain mechanisms. Indeed the brain plays a central role in modulating in both the pathways as reviewed in various studies. The recent findings also show that the neuroendocrine and autonomic systems interact in a complex way in making this modulation (Mair & Watkins 1998). The corticotrophic hormone release hormone appears to occupy the central controlling position in this whole process. The studies have shown suppression of T cell proliferation in response to the stress, both in splenic tissue as well in the peripheral blood. Administration of beta-blockers reverses the suppression in the spleen but not in the blood, whereas adrenalectomy leading to removal of endogenous steroids diminishes the suppression in blood but not in spleen. This clearly shows the differential involvement of the CNS in modulating the site-specific immune response. The spleen appears to be responding to the influence of pituitary whereas the peripheral blood response appears to be mediated through the adrenal hormones. The CRH modulates both the hypothalamic-pituitary-adrenal axis as well as the autonomic nervous system. Through its action on the adrenal gland it releases glucocorticoids which are closely related to suppression of B cell production, and through its influence on the autonomic nervous system it releases catecholamines suppressing the cell-mediated as well as humoral immunity. It also inhibits production of cytokines and ultimately decreased activity of NK cells in the spleen.
FIGURE 3
CNS Immune Interaction

Brain

HPA axis

Lymphoid organs

ANS

CR - Cytokine receptor
NR - Neurotransmitter receptor
HR - Hormone receptor
CONCLUSION

The immune system is an integral part of the body involved in protection of body from various diseases. Its presence and role in protection against disease was known since ancient times. Its anatomy and physiology has become more clear only in the last fifty years or so. Broadly, its components can be divided into the cellular and humoral components. The cellular component i.e. the cell-mediated immunity is constituted by the T-lymphocytes which are derived from the thymus gland. The T-lymphocytes constitute about the 75% of all lymphocytes. The humoral component is constituted by the bone marrow derived B-lymphocytes which make about 10% of all lymphocytes. The rest 15% of cells belong to a heterogeneous group which primarily include natural killer cells. These cells are histologically and physiologically different and can be recognized by the presence of unique cluster determinant antigens (CD) present on their cell membrane. T-lymphocytes are further differentiated into various categories depending on their functions and presence of CD markers. The T-helper (Th) cells and the T-suppressor (Ts) cells are the main two categories of T lymphocytes which act to increase and decrease the immune response, therefore they work in coordination with each other to maintain homeostasis. They also play an important role in cancer immunity and various autoimmune diseases. The B-lymphocytes act by synthesis of antibodies - a specialized form of protein molecules active against the particles like bacteria, viruses, etc. which are pathogenic and/or foreign to the organism. The recognition of self and non-self molecules is again determined by a complex system of molecules in which the Major Histocompatibility Complex (MHC) is the most important. Both cell-mediated and humoral-mediated immunity also work in coordinated way through secretion of cytokines and interleukins from lymphocytes which guide their interaction.

Although the immune system is perfectly specialized system of the body involved in defense against foreign and pathogenic
particles, it also interacts bilaterally with the other body systems including the CNS. This interaction attracted the researchers all over so much that it acquired a separate meaning and status as psychoneuroimmunology. The immune molecules particularly the MHC also regulate the development of nervous system. Like other body responses, the response of immune system can also be conditioned. The neurons have receptors for interleukins and the immune cell respond to the neurotransmitters through these receptors. Under the stressful situation whether physical or psychological the CNS release stress biochemicals such as cortisol through HPA activation; activates ANS to prepare the body for fight and flight response. However, such activation paradoxically lowers the immune functions and makes the organism susceptible to infections and other pathologic processes as the requirement at such times is a “strong defense”. The evidence to this conclusion has come from various animal and human studies. In the depressive and anxiety disorders the indices of immune functioning have been consistently seen to be lower than the normal. Under social isolation and ambiguous situations the immune response is consistently seen inadequate in various studies. The CNS -Immune System interaction is quite intricate one (Fig:1.3). Despite plethora of studies the exact mechanism of this interaction is still beyond a reasonable level of understanding. Clearly more studies are required to elucidate this complex mechanism.

REFERENCES


Physiology and Psychoimmunology


