REVIEW OF LITERATURE
Malnutrition has been prevalent in the most parts of the world for centuries. Proctor (1926–27) first described the appearance of children without bringing nutrition into picture.

Cicily Williams gave the name 'Kwashiorkar' to a tropical syndrome and maintained that it was nutritional in origin. The term Kwashiorkar owes its origin to 'GA' language (Kwashi-first, orkar-second) and means disease or disorder of displaced child i.e. the child has been displaced from mother's breast by another pregnancy or birth.

Before Williams' description (1933), German workers described (quoted by Jelliffe, 1959) another syndrome 'marasmus' and thought it to be due to starvation in younger children. Water low suggested that the two syndromes might not be rigidly distinct but one could transform into another by modification in calorie intake.

FAO/WHO joint expert committee on nutrition in its 6th report (1962) proposed the broad term protein-caloric malnutrition (PCM) to embrace all such conditions as marasmus, malignant nutrition, kwashiorkar, famine oedema, nutritional dystrophy etc..
Now the term PCM has been replaced by 'Protein Energy Malnutrition' (PEM) as proposed in 8th report of the joint FAO/WHO expert committee on nutrition.

**INCIDENCE**

PEM has been a major nutritional problem of most countries. It has been estimated that more than 350 million children in the world are suffering from various degrees of PEM (Banga, 1970) mortality being higher in developing countries.

Rao et al (1959) have recorded an incidence of kwashiorkar at 0.87% and that of marasmus at 1.6% in survey involving South-Indian population.

Rao, Singh and Swaminathan (1969) reported from their study at Hyderabad that 40 percent of children surveyed had evidence of one or more signs of nutrition deficiency. In most of the cases they observed significant growth retardation. The major deficiencies observed were protein caloric malnutrition, hypervitaminosis A, anaemia and deficiency of B-complex vitamins. They reported that the prevalence of advanced states of PCM with oedema feet was found to be 0.6% and that of marasmus was 0.9%.

In the same year (1969 and 1970) Reddy reported mortality rate of kwashiorkar and marasmus in a hospital at Hyderabad. Total number of admissions during years
1969 and 1970 were 19,090, case admitted for kwashiorkar were 720 (3.8%), number of deaths among them were 82 (11.5%), cases admitted for marasmus were 442 (2.3%) and number of deaths among them were 55 (12.4%).

In 1970, after conducting a survey on rural preschool children in Delhi, Udani et al reported that about 18% of all cases were under nourished and out of these 1.7% had frank marasmus while 0.9% suffered from kwashiorkar.

Bangoa (1974) reported on a data drawn from 77 nutrition surveys in 46 countries totalling nearly 2 lacs children, mostly under 5 years of age. He pointed out that about 100 million children throughout the world were suffering from moderate to severe PCM at any one time.

In the same year, Gopalan computed that nearly 65% toddlers in poor communities in India, suffered from moderate and 18% from severe malnutrition.

Ghai (1975) analysed cases of severe PEM in hospitals and reported 6.6% deaths in children suffering from marasmus and a total of 33.3% deaths due to kwashiorkar or marasmic kwashiorkar. Then again in 1977 he reported that 40% deaths in children could be attributed to malnutrition, even though it was often not listed as a primary cause of death in most of the studies.

Rao (1978) reported 1-2% incidence of marasmus and kwashiorkor in preschool children and observed that 60-70% of children suffered from mild to moderate
degree of PEM.

In 1981, Gosh estimated that there were 100 million preschool children in India. Out of 100 million, about 3-4 million suffered from severe type of malnutrition and out of which probably 1 million of them died every year.

In 1986, Steinhoff et al studied prevalence of malnutrition in Indian preschool children and reported that about 45% suffered from varying degrees of PEM.

Kapil and Bali (1989) assessed nutritional status of 486 preschool children of urban slum communities in Delhi. They reported that overall prevalence of PEM was found to be 81.8%. Maximum (44%) had moderate degree malnutrition (Grade II, classified according to Indian Academy of Pediatrics classification), while 31.8% had grade I, 5.7% had grade III and 0.2% had grade IV PEM.

MALNUTRITION VERSUS IMMUNITY

Throughout a large part of the world, the two most important factors determining the health of young children are infection and malnutrition. The mechanisms by which PEM could predispose to infections are less well understood.

The primary host resistance is of three types, humoral in which resistance to micro-organisms is mediated by circulating immunoglobulins, secondly the immune cellular response of thymic dependent lymphocytes, and
thirdly polymorphonuclear activity.

The cells of the body that respond to antigens are variously categorized as belonging to the hematopoietic, the reticuloendothelial, the phagocytic, or the lymphoid system.

HEMATOPOIETIC SYSTEM

Cells of the immune response systems are formed, maturate and are dispersed from the bone marrow. They are then reclassified as cells of the phagocytic, lymphoid, or other system according to the new functions, they acquire or express outside the bone marrow. These arise from a primitive, undifferentiated stem cell, the reticulum cell, which differentiates into a precursor for each cell line. Of these cell series, only those of granulocytic, monocytic and lymphocytic series are effector cells of the immune system.

RETICULOENDOTHELIAL AND MONONUCLEAR PHAGOCYTIC SYSTEMS

The reticuloendothelial system is a collection of cells of diverse morphology and tissue residence united by the sole property of a very active phagocytic behaviour.

The reticuloendothelial system has been divided into the tissue and blood phagocytes of large size - the macrophages - and those of lesser size - the microphages.
**Macrophages**: (Mononuclear phagocytic system)

These arise from the monocyctic series of the hematopoietic system and are represented in blood by circulating monocytes. The peripheral blood monocytes serve as the source of the free and fixed tissue macrophages.

**Microphages**

These are present in three forms: the neutrophil leukocytes, the basophils and the eosinophils. About 60% of all blood leukocytes are neutrophils and only 1% are basophils and 1% eosinophils.

**Neutrophils**: Of the granulocytes, the neutrophils are most phagocytic.

Granules of the neutrophils do not differ from the lysosomal granules of tissue macrophages, but the granules of eosinophils and basophils are not lysosomal. There are two types of granules in neutrophils; the primary granules are fewer in number than secondary granules in mature leukocytes. The primary granules contain peroxidase and several digestive enzymes. The secondary granules contain the microbiocidal protein lactoferrin.

**Eosinophils**

These acidophilic leukocytes contain granules, which are stained intensely by the acid dye-eosin.
This is attributed to an arginine rich protein in the granules, which are crystalline and do not contain the hydrolases found in neutrophilic granules.

**Basophils**

Their cytoplasmic granules stain easily with basic dyes.

**Lymphoid System**

The lymphocyte is the dominant cell of the lymphoid system.

The lymphoid system has central and peripheral lymphoid tissues.

The central lymphoid tissues are bone marrow and thymus. The peripheral lymphoid tissues are lymph nodes, spleen, tonsil, intestinal lymphoid tissue (Peyer's patches and appendix) and other collections of lymphocytes.

**Lymphocytes**

According to their life span, lymphocytes can be divided into two - those with a short span (mostly large lymphocytes) of 5 to 7 days and the small lymphocytes with a life span of months or even years. The former are B cells and the latter are T cells.

**T Lymphocytes**

T lymphocytes are formed in the thymus from lymphoblasts that leave the bone marrow and mature in the thymus. This maturation is expressed morphologically as
a reduction in size to about 7 μm in diameter.

Maturation is accompanied by the acquisition of a new and specific antigen for T lymphocytes, the Θ antigen.

Sixty five to 85 percent of all lymphocytes in the blood are of the T type. Lymphocytes of thoracic duct fluid are 90% to 95% of the T variety and those in Peyer's patches are 50 to 65% T cells. The T cell population of lymph nodes, particularly in the medullary region, is high, but is low in tonsil and appendix.

Function

When the T lymphocyte contacts antigen, it passes through a phase of growth and cell division known as lymphocyte transformation to produce a large population of its own kind. These growth or germinal centres usually contain macrophages, reticulum cells, and lymphocytes.

When antigen responses are induced in T lymphocytes, the cells grow, divide and excrete lymphokines. Among these lymphokines are a chemotaxin for monocytes, a macrophage migration inhibiting factor, a blastogenic factor, a lymphotoxin and interferon.

The chemotaxin attracts monocytes to the T cells and the migration inhibitory factor (MIF) holds them at that place. It has also functions of activation and clumping or agglutination of macrophages.
The blastogenic factor recruits additional T cells by forcing them into a growth phase.

Interferon, which may be produced by cells other than T lymphocytes, protects surrounding cells from invasion by intracellular parasites, including viruses, rickettsial, malarial and other parasites.

B Lymphocytes

B lymphocytes also have their origin from bone marrow, in form of lymphoblasts, which then mature to B lymphocytes outside the bone marrow, where they are imprinted with the characteristics of the B cells - the synthesis of the B antigen on the B cell surface.

The B cell population is high in spleen, tonsil and a few other tissues. It is low in circulating blood, which contains upto about 35% of B lymphocytes.

The sum of T and B cells in the blood does not always reach 100%. The remainder are known as null cells, and these may be immature T cells.

When the B cell contacts the specific antigen to which it has been programmed to respond, lymphocyte transformation follows. Thus this cell undergoes clonal proliferation and blast transformation, becoming converted into plasma cells which are end cells that synthesise and secrete antibodies. A small proportion of them develop into 'memory cells' which have a long life span and serve to recognize the same antigen when introduced subsequently.
B lymphocytes are the cells responsible for antibody production, but for humoral response to certain antigens (thymus-dependent antigens), the cooperation of T lymphocytes is necessary. These antigens include erythrocytes, serum proteins and a variety of protein hapten conjugates. Such antigens initially interact with T cells, which concentrate then on the cell surface and present them in the form of repeating surface units (epitopes) to B cells for antibody formation.

Some antigens, such as polymerised flagellin, ferritin and several polysaccharides have naturally repeating epitopes on their surface and hence do not require processing by T cells. These are known as 'thymus independent antigens' and can interact directly with B cells.

Macrophages

These cells are derived from the monocytes that are present in blood.

Among the important functions of macrophages one is phagocytosis. Macrophages can also imbibe soluble substances and these like the particulate substances are degraded within the phagocyte by hydrolytic enzymes present in the lysosomes. The macrophages spare the critical portions of the antigens known as the antigenic determinant sites.
The antigen determinant site is coupled to an RNA fragment and utilized as the antigenic message for subsequent cells in the immunocyte sequence, or antigen processing may terminate in the appearance of a messenger like RNA that holds the antigen secret even though antigen free. These RNA or RNA antigen fragments are considered as informational RNA, which in turn directs antibody formation by lymphoid cells innocent macrophages also receive RNA messages and express this in term of increased phagocytosis and intracellular destruction by activated macrophages.

Neutrophils

Neutrophils arise from a primitive undifferentiated stem cell, which differentiate into a precursor for each cell line and then to granulocytes (neutrophils, eosinophils, basophils).

Neutrophils are very active in phagocytosis. Besides being moved throughout the body by circulation of the blood, they have an active ameboid motion of their own by which they may migrate through blood vessels walls into tissues. Neutrophils engulf and degrade antigens, but the contribution of these cells to the total antigen processing function is minimal.

Eosinophils

Eosinophils also have a slow ameboid motion and some phagocytic activity but are more often associated
with immunity 'gone wrong', the hypersensitive and allergic reactions, than with immunity itself.

**Basophils**

These cells are unimportant as phagocytic cells but are closely related to tissue mast cells.

**Immunoglobulins**

Plasma cells are the source of the immunoglobulins. Each of the several classes of B cells give rise to a class of plasma cell responsible for the synthesis of one class of immunoglobulin.

The major classes of immunoglobulins are designated IgG, IgM, IgA, IgD and IgE.

**Immunoglobulin G (Ig G)**

It is also known as $\gamma$-globulin and 7s $\gamma$ globulin. Gamma indicates its position in the serum electrophoretic profile.

IgG represents about 80% of the total antibody in an antiserum. This high serum level is a reflection of both the rate of synthesis and the rate of elimination of IgG. It is produced at a rate of about 28 mg/kg body-weight/day and has a half life of approximately a month. It has a molecular weight of approximately 150,000; 2.5% of which is in the form of carbohydrate.
**Function:**

It participates in most immunological reactions such as complement fixation, precipitation and neutralization of toxins and viruses. It binds to micro-organism and enhances their phagocytosis.

**Immunoglobulin A (Ig A)**

Immunoglobulin A of serum is known as γA and β2A because of its intermediate positioning between the true gamma and beta regions on electrophoresis.

It represents only 5% to 15% of all serum globulins. It has a half life of 7 days and is synthesized at a rate of about 8-10 mg/kg/day.

IgA and IgG possess several common features. Both are composed of peptide chains, two light chains and two heavy chains. The light chains of both molecules are identical, but heavy chains differ.

**Secretory IgA**

The ratio of IgG to IgA in serum is 6:1, this is true for synovial fluid, cerebrospinal fluid, aqueous humor, and other internal secretions.

In the external secretions i.e. in colostrum, and early milk, nasal and respiratory mucus, intestinal mucus, saliva etc. - IgA is present in a much higher concentration than either IgG or IgM.

Both serum and secretory IgA have separate cellular origin.
Functions

Secretory IgA is selectively concentrated in secretions and on mucous surfaces, forming an antibody paste, and is believed to play an important role in local immunity against respiratory and intestinal pathogens.

Serum IgA promotes phagocytosis and intracellular killing of micro-organism. Antibody activity against erythrocyte antigen and bacteria has been noted in the serum fractions containing IgA. The erythrocytes and bacteria are not lysed by IgA. Since this requires further activity of complement and IgA does not activate the complement pathway.

Immunoglobulin M (Ig M)

The electrophoretic positioning of IgM is in the zone between the clear-cut gamma and beta globulins. It has a molecular weight of about 950,000. It has a short half life of about 10 days and too low synthetic rate 5-8 mg/kg/day. The carbohydrate component of IgM is about 10 to 11%. It constitutes about 5% of total immunoglobulins. Each molecule of IgM is composed ten light and ten heavy chains.

Functions

IgM is believed to be responsible for protection against blood invasion by micro-organism. Being a heavy molecule it is 500-1000 times more effective than IgG in opsonisation, a 100 times more effective in bactericidal
action and about 20 times in bacterial agglutination. In neutralisation of toxins and viruses it is less active than IgG.

**Phagocytosis**

Natural defence against invasion of blood and tissues by micro-organisms and other foreign particles is mediated to a large extent by phagocytic cells, which ingest and destroy them. The vital role of phagocytosis in preventing infections has been emphasised by the discovery of a congenital disorder of phagocytosis (chronic granulomatous disease) in which the patient succumbs to recurrent bacterial infections, even though T and B cell functions remain normal.

Among circulating phagocytes, neutrophils are actively phagocytic and form the predominant cell type in acute inflammation. The primary function of neutrophilic granulocytes is the localisation and destruction of microorganisms. Several integrated activities are necessary to achieve this goal.

I. Directed movement toward the microbial invader (chemotaxis).

II. Phagocytosis of the organism, and

III. Killing or inhibition of replication of the ingested microbe.

(i) Circulating phagocytes have the capacity for unidirectional movement towards attraction substance
(chemotaxis). Factors attracting phagocytes (cytotaxis) are components of complement sequence, bacterial leucocyte components, damaged tissues and antigen - antibody complexes. Defective granulocyte locomotion may result from intrinsic (cellular) abnormalities of the phagocytes or from extrinsic factors (complement deficiency etc.).

(ii) Once physical contact between the phagocyte and the victim particle is made, phagocytosis ensues. This is a more rapid process if phagocytosis occurs on a surface - a blood vessel wall, fibrin network or tissue cell wall.

Molecular factors that promote the attachment of phagocytic cells to the object they will engulf are called opsonins.

The primary opsonins are either antibodies or products of the complement system, and antibodies are far more potent than the complement components.

Among antibodies IgM is the most efficient of the opsonic immunoglobulins and IgG appears to be 500–1000 times less efficient than IgM.

Humoral antibodies which attach to bacteria and other particles encourage phagocytosis by neutralizing ionic changes on the bacterial cell surface, making them more approachable by phagocyte. The negative chemotactic force of encapsulated bacteria such as the pneumococcus,
klebsiella pneumonias, Hemophilus influenzae, and others is clearly related to their capsule; nonencapsulated variants are easy prey for phagocytic cells. But when the capsules of the pathogenic form of these bacteria are coated with antibodies, they are no longer able to repel phagocytes and are as easily engulfed as the non encapsulated forms.

C\textsubscript{3b} formed by the antigen-antibody reaction (by classical pathway) or by the complex polysaccharides in microbial capsules (by alternate pathway) adheres to the antigen. It also has receptors on the surface of phagocytic cells. This permits C\textsubscript{3b} to serve as a link between the phagocytic cell and its victim, holding them together and facilitating phagocytosis.

In addition to the specific effect of these opsonins a number of nonspecific forces may favour phagocytosis. These include natural antibody, normal heat-labile serum proteins not related to complement and tuftsin.

**CELL-MEDIATED IMMUNITY IN PROTEIN ENERGY MALNUTRITION**

There is evidence that in states of malnutrition the immune cellular response is deficient.

Vint (1937) reported that malnourished children invariably had evidence of thymic atrophy which could be responsible for the depression of immune response.

Trowell et al (1954) studied immunological status in kwashiorkor. Autopsy studies of children with kwashi-
orkor revealed shrunken thymus. These workers thereby inferred that malnutrition affected the immune status.

Children with kwashiorkor or marasmus often have acute bacterial infections. Campbell (1956) found microscopical evidence of pyaemic abscesses or bronchopneumonia in lungs of 31 out of 40 malnourished children at necropsy and another six children had evidence of renal failure.

Brown (1965) found a 45% incidence of bronchopneumonia among malnourished infants in a survey of all pediatric necropsies performed over a 12 year period in Mulago hospital, Kampala.

Ianphilips and Brian Wharton (1968) studied 75 children (63 with kwashiorkor and 12 with marasmus). Out of which 32 (43%) were found to be infected and 43(57%) were non infected. They also found a greater incidence of hypothermia and anaemia, and a greater severity of diarrhoea in children who had associated sugar intolerance and a systemic infection.

Mortality rate was 22% among infected children as compared to 5% among non infected.

McFarlane et al (1969) found the serum transferrin to be the most accurate index for assessing kwashiorkor. In 1970 they studied 40 children with kwashiorkor and serum albumin, transferrin and immunoglobulin levels were measured. They suggested that in children with severe kwashiorkor and low serum transferrin levels any increase in free circulating iron may result in overwhelming
infection and death. They found that immunoglobulin IgG, IgM, IgA levels were not generally affected by lack of protein intake.

In 1971 Geefhugsen et al studied cellular immunity in cases of kwashiorkor and they found it to be impaired in form of significantly less frequently positive candida and diphtheria toxoid skin tests and significantly low lymphocyte transformation index. They also found a correlation between the degree of impairment of tests of cellular immunity and the severity of kwashiorkor and an improvement after refeeding. They also suggested that the finding of a normal lymphocyte transformation index and positive reactions to the skin antigens in a group of well nourished but infected children indicates that in kwashiorkor the impaired lymphocyte function is related to protein deprivation rather than to the presence of infection.

Smythe et al (1971) also investigated cell mediated immunity and thymolympathic system in children with PCM. They found a decreased size of tonsils, significantly impaired capacity to respond to chemical sensitisation of the skin and the rate of transformation of lymphocytes stimulated with phytohaemagglutinin, frequent agglutination of infants' red cells by antisera to serum complement components, particularly C₄ and reduced hemolytic serum component. On necropsy they found a high proportion of chronic atrophy of thymus with wasting of peripheral lymphoid tissue, depletion of paracortical cells and less
of germinal centres. They suggested that profound deletion of thymolymphatic system and severe depression of cell-mediated immunity could contribute to the type of infection from which children with PCM die.

Chandra (1971) investigated pathophysiologic mechanisms of increased susceptibility and severity of infections in 90 malnourished children. He found that tonsils were small in 47 children and observed significant lymphopenia in 15 children. He also found a significant depression of serum siderophilin and complement component C₃.

Serum immunoglobulins were found to be raised tremendously in children with concurrent or recent history of infection, where as in children without such evidence, he found a very significant lowering of IgG and to a lesser extent of IgA. Antibody response to tetanus toxoid was found to be adequate, but response to S. typhi vaccine was significantly reduced. Cutaneous hypersensitivity was also found to be distinctly impaired, and the in vitro lymphocyte transformation response to phyto-haemagglutinin stimulation was reduced.

Mantoux conversion following BCG vaccination occurred in 22 percent of the study group compared to 72 percent of the healthy control subjects.

In 1972 Sellmeyer et al also studied lymphocyte transformation in malnourished children and reported sub-
normal transformation values of lymphocyte stimulation with phytohaemagglutination in children with protein calorie malnutrition. They suggested that impaired cell-mediated immunity may be one important mechanism for the susceptibility of malnourished children to infections. In their study lymphocyte transformation was found to be subnormal in children with measles and gastroenteritis also but tended to be increased in pneumonia. Cell mediated immunity is a bulwark against certain intracellular micro-organisms including viruses, fungi, protozoans and metazoans.

In 1975, Purtilo et al studied 25 children who had protein calorie malnutrition with thymolymphatic atrophy and died of fatal infections. They found that all subjects except for four were found at necropsy to have nutritional thymectomy and all except for 3 died of infectious diseases. The infectious agents in their study were reported to be chiefly intracellular micro-organisms including mycobacterium tuberculosis (causing miliary tuberculosis), herpes simplex virus, varicella virus, measles virus, pneumocystis carinii and plasmodium falciparum. Staphylococcal infections, salmonellosis, shigellosis, strongyloidiasis, and hookworm were reported to be other significant infectious agents. They suggested that nutritionally acquired defective immunity, especially cell-mediated immunity, probably permitted these infectious agents to multiply and to discriminate widely.
In the same year Chandra (1975) reported reduced secretory antibody response to live attenuated measles and poliovirus vaccines in malnourished children. He studied 20 malnourished and 20 matched healthy children and measured their total serum protein, albumin and serum and nasopharyngeal IgA antibody levels after immunization with a single dose of live attenuated measles or polio virus vaccine (10 children in each group). He found that seroconversion after polio virus vaccine was achieved in eight out of the malnourished children and in all the healthy controls. There was a slight difference in the serum antibody levels attained by the two groups, statistically insignificant. Only six out of the malnourished patients had detectable levels of specific IgA antibody in nasopharyngeal washings and the titres were significantly lower than those in the controls. The first appearance of the secretory antibody was delayed by one to three weeks compared with findings in the control group.

Measles neutralising antibodies were detected in the sera of all the malnourished and healthy children. There was a significant difference in the frequency of detection, time of first appearance and titre of nasopharyngeal IgA antibody to measles virus. Secretory antibody was found in samples of five out of ten undernourished patients and in seven out of eight controls.

Humoral and cellular immune function was assayed in 76 malnourished children and 41 controls by Neumann et al.
(1975). They found increased immunoglobulin levels in all three groups (severely nourished, moderately nourished and controls). Levels were somewhat higher in the malnourished groups. Antibody response to Keyhok limpet hemocyanin and polyvalent pneumococcal polysaccharide were found to be equal in all three groups. Cutaneous delayed hypersensitivity was found to be decreased in both of the malnourished groups as compared with controls.

Dossetor et al (1977) studied thirty malnourished and 25 well nourished children from six to thirtyone days after the onset of a measles rash. Evidence of the virus was found in 40% of the malnourished children but in none of the well nourished controls. They found giant cells in nasal secretions of five out of 17 malnourished children and measles antigen was detected in the lymphocytes of eight out of 28. The malnourished children showed depressed cell mediated immunity to measles and candida antigens and a low response to meningococcal vaccine. Fifteen children died from intercurrent infections. They suggested that malnutrition could have led to depressed immune response in these children, resulting in a severe and prolonged attack of measles; thus in turn led to further damage to the immune system and more severe malnutrition. Thus these children were made susceptible to intercurrent infections.
Reddy et al in the same year studied 160 preschool children and reported that both the cell mediated immune response and antibody response to bacterial antigens (typhoid antigen) were impaired in children with severe PCM. However, the immunological responses were not found to be altered in those with mild-moderate PCM. Antibody response to diphtheria and tetanus toxoids, however was not altered even in severe PCM.

Serum levels of immunoglobulins were found to be normal in all the groups. All the mildly malnourished children who were immunized against smallpox showed a normal reaction.

As immunological responses were not found to be altered in children with mild-moderate PCM. Thus they suggested that even in poor undernourished communities a great majority of children would respond satisfactorily to active immunization procedures.

Keeping in view the doubts regarding the efficacy of the vaccines in the malnourished subjects, Puri et al (1979) studied immune response in 80 children following routine D.P.T. immunization, 80 percent of whom were malnourished. All the subjects were protected against diphtheria, pertussis and tetanus. Half of them (40) followed schedule B, 36.9% and 43.2% of subjects were protected against tetanus following schedule A and B respectively. There were significantly low levels of antibody to diphtheria and tetanus in the malnourished group. The low
levels of tetanus antitoxin titre following immunization were probably due to the low levels of tetanus toxoid in the vaccine used, because Chandra had shown good response to tetanus toxoid by both normal and malnourished children following 2 doses of tetanus toxoid but his vaccine contained 10^4Lf/ml of tetanus toxoid. Thus they suggested the possibility of inadequate response of the malnourished to low antigenic strength, but they respond well when strong antigenic stimulus is given repeatedly, which they proved by the observation that following 2 doses of DPT the diphtheria antitoxin titre varied widely between normal and malnourished children (p<0.01), the difference was narrowed down following 3 doses.

Kalra et al (1980) studied impact of malnutrition on intelligence in 100 cases of various grades malnutrition and an equal number of healthy controls - all drawn from the low socio-economic group of families. The age range was 1-12 years. The mean I.Q./S.Q. of controls was 92.57 and mean I.Q./S.Q. of malnourished cases was 61.22. The difference in the mean I.Qs. (31.35 points) was statistically significant. In the malnourished group, there was no case with normal intelligence (I.Q. above 90) and 57% had mental subnormality (I.Q. below 70). In the control group, the number of cases with I.Q. above 90 was 64% and of these 2% had intelligence above the average range. With increasing severity of malnutrition, there was a significant fall in
the performance on the intelligence scale and this decline was more significant in younger children. Thirty five cases of the malnourished group were reassessed six months after nutritional rehabilitation, it was found that their intelligence had improved.

Vashi et al (1980) studied growth hormone secretion in 20 malnourished children of 8 months to 12 years, 5 with frank kwashiorkor, 13 with protein calorie malnutrition and 2 with marasmus, 10 normal children were taken as controls. The growth hormone level was found to be within the normal limits. On the basis of which they suggested that growth retardation in malnutrition has no relation to the hormonal control but is due essentially to the lack of amino acids and calories necessary for growth.

In the same year Puri et al studied immune status in thirty cases of PCM and thirteen control children. They also reported that all the parameters of cellular immune response studied were found to be significantly depressed in severe PCM group. They reported that humoral immunity was not altered in PCM except in the presence of infection, when there was some increase in IgG levels.

Rai et al (1981) studied CMI in 170 malnourished and 30 normal children using DNCB skin sensitization test, Mantoux test (in those malnourished and control group children who were previously immunized with BCG), lymphocyte count and by assessing tonsillar size. Their study
revealed that malnourished children developed impaired reaction to DNCB reaction, it was positive only in 54% of malnourished children compared to 86% in control group, Mantoux test was positive only in 8.8% in malnourished children as compared to 80% in control group, tonsillar size was decreased in 75% of malnourished children compared to only 10% control group, lymphocyte count showed lymphopenia in 50.5% as compared to 13.3% in control group.

Kumar et al (1984) studied complement activity in 32 malnourished and 12 healthy preschool children along with hemoglobin and serum albumin level measurement. They observed a significant decrease of complement (C₃) in malnourished subjects as compared to those obtained in healthy control subjects. However, total hemolytic complement (CH₅₀) activity or alternate pathway activity (AP₅₀) did not show significant depression in either of the groups. Both serum albumin and blood hemoglobin levels showed significant and positive correlation with complement C₃ values.

HUMORAL IMMUNITY IN PROTEIN ENERGY MALNUTRITION

Anderson and Altmann (1951) found that the total gamma-globulin fraction of the serum proteins tended to be high in kwashiorkor, whereas Brown and Katz (1965) reported a significant reduction (p < 0.05) in the serum IgG concentrations of 20 kwashiorkor patients compared with 5 controls, with no difference between IgA and IgM levels in the two groups.
Keet and Thom (1969) reported that there was no significant difference between the serum levels of IgG and IgM of kwashiorkor cases they studied, but serum IgA levels were much higher in the kwashiorkor group.

In 1970 Ghulmy et al studied seventeen cases of marasmus to compare their serum immunoglobulin levels with that of the controls. They found that IgG simulated more or less the normal pattern, IgA levels also simulated normal pattern but IgM levels were found to be much higher than that of normal cases.

Alvarado and Luthringer (1971) also studied edematous protein calorie malnourished children. The parameters used to assess their protein nutrition were the level of total serum proteins, creatinine/height index and serum immunoglobulins. They divided the subjects into three groups - malnourished, recovered, control. The total serum protein was found to be definitely depressed in the "malnourished group" and normal in the other two groups. Creatinine/height index (CHI) in everyone of malnourished children was below 0.70 with an average value of 0.54. Normal values of CHI are always above 0.85 (Vitri and Alvarado). No direct relation was found between the CHI and the serum levels of immunoglobulin fractions IgG, IgA and IgM. No significant difference was found among the three groups - malnourished, recovered, control with respect to IgG and IgM values. Serum IgA values were significantly statistically higher in malnourished group
(p ≤ 0.001) when the children with PCM were divided into two groups according to their age below or above 36 months, the mean serum immunoglobulin fractions of the two groups did not differ significantly.

In a study by Chandra in the same year (1971) the serum immunoglobulin were found to be raised tremendously in children with concurrent or recent history of infection (in comparison with values in healthy control subjects), where as in children without such evidence he found a very significant lowering of IgG and to a lesser extent of IgM. Thus he suggested that the capacity of these children to respond to bacterial challenge seems to be intact.

In 1975 Neumann et al studied immunoglobulins levels, along with other immunologic responses in malnourished children. Almost all the children in their study had infections except for some patients in control group. The three major immunoglobulins (IgG, IgM and IgA) and IgE were found to be elevated. Significantly higher levels were found in severely malnourished group as compared to moderately malnourished or control group. Immunoglobulins of moderately malnourished children were not found to differ significantly from those of control children. They suggested that marked elevations of IgE levels, particularly in the severely malnourished group, might be due to disordered T cell function.
As secretory antibodies of the IgA class play an important role in the protection of mucosal surfaces against certain infectious agents and evidence by Tomasi (1972) suggested that this local immunity in independent of systemic immunity. Thus Reddy et al (1976) investigated secretory IgA levels and other serum immunoglobulins in 38 children with PCM between one and 6 years. These children were classified into 3 groups based on deficit in weight for age. Serum albumin concentration was significantly low in children with severe PCM but there was no significant difference between normal children and those with mild - moderate PCM. Serum levels of IgG, IgM and IgA were similar in all 3 groups. At admission children with severe PCM had significantly lower IgA concentrations in duodenal fluid, saliva, nasal washings and tears as compared with normals. This difference was significant. There were no differences between kwashiorkor and marasmus. Four weeks after treatment there was a significant increase in the IgA levels in all 9 malnourished children studied. There was no difference in levels of IgA in the secretions of children with mild-moderate PCM and normal subjects.

In another study by Puri et al (1980) the humoral immunity was not found to be altered in PCM except in the presence of infections, when they found some increase in IgG levels, which was statistically significant.
In 1985 Seth et al studied immune parameters in children with malnutrition, without infection. They found that besides mild to moderate malnutrition as shown by Reddy et al (1976), even severe malnutrition does not alter the immune status and suggested that PEM without infection has only a quantitative decrease in the immune parameters which is compensated by normal qualitative function of specific T and B cells. The percentage of T cells was found to be significantly low in severe malnutrition in the presence of normal total lymphocytes and absolute T cell counts. Humoral response was measured by the percentage of B-cells and was found to be significantly low in the severely malnourished group in comparison to the normally nourished group. However, the value of absolute counts of B-cells were found to be comparable in the three groups. They suggested that the normal number of absolute B-cells could possibly be due to the increase in the total lymphocyte counts as a compensatory mechanism. The study of immunoglobulin profile revealed that only IgA levels were increased in the severely malnourished group whereas the values of IgG, IgM were comparable to healthy children. They explained this on the same basis as Chandra (1977) who attributed this rise in IgA levels in blood to respiratory and gastro-intestinal infections. However, it has not been worked out as yet for how long IgA levels remain elevated after an episode of infection.
POLYMORPHONUCLEAR LEUKOCYTIC ACTIVITY
IN PROTEIN ENERGY MALNUTRITION

Bacterial infections are frequent and often fatal in patients suffering from kwashiorkor, or marasmus. In a study by Smythe and Campbell in 1956, staphylococci and enterobacteriaceae were found to account for 14 out of 16 positive cultures. A similar pattern of infecting organism was found by lung puncture-aspiration in the pneumonias of malnourished children by Axton. Resistance to these groups of organisms is dependent upon polymorphonuclear activity a process which has been shown to be defective in the genetically determined condition, chronic granulomatous disease (C.G.D.) (Good et al, 1968).

On comparing patients suffering from C.G.D. with those suffering from kwashiorkor, not only the similarities between the infecting organisms have been reported, but the pulmonary infections of patients with C.G.D. typified by their chronicity, tendency to encapsulation and enlargement of the hilar shadows (Wolfson et al, 1968) have been reported to be reminiscent of the pneumonias seen in severely malnourished children. These considerations suggest that PMN activity may be defective in malnutrition.

Studies of the way in which the PMN's destroy certain pathogenic bacteria have shown the two stages to be involved. The first is phagocytic ingestion, the second enzymatic killing and digestion of the intracellular bacteria.
Tejada et al (1964) studied phagocytic and alkaline phosphatase activity of leukocytes in kwashiorkor. Phagocytic activity was tested using staphylococcus albus as the test organism and was reported to be normal. Alkaline phosphatase activity was found to be high presumably due to concurrent infection, which also indicated that circulating leukocytes were mature and able to phagocytize bacteria.

Increased severity of bacterial infections in malnourished children may be the result of an inadequate leucocytosis or a defect in bactericidal capacity of the PMN's. In 1972 Kendall and Nolan studied polymorphonuclear leukocytic activity in malnourished children by using Nitroblue tetrazolium reduction test. The test showed a very significant difference between the PMN's of children below the third percentile by weight as compared with those above.

Sbarra et al (1959) reported from their study on biochemical basis of phagocytosis that glycolytic and oxidative metabolism of neutrophils increases during phagocytosis. Thus it has been shown that glycolytic activity of neutrophils provides the energy for particle uptake and the stimulated lysosomal enzymes and hexose monophosphate shunt (HMS) activities are involved in the bactericidal activity.

Selvaraj and Bhat (1972) studied metabolic and bactericidal activities of leukocytes in PCM and found low in vitro glycolytic activity and complete failure of
leukocytes to show an increase in lactate production in response to particle challenge. Further they also found these leukocytes to fail to show an adequate stimulation of HMS, which supplies $H_2O_2$ for bactericidal activity. Bactericidal activity as such was found to be significantly lower than those of controls. They carried out longitudinal study in four of these patients and found an improved bactericidal activity after treatment.

In the same year (1972) Seth and Chandra studied opsonic activity of plasma, phagocytosis and bactericidal capacity of polymorphs in fifteen undernourished children. The opsonic activity was found to be slightly increased and they found a significant decrease in bacterial killing by polymorphs of malnourished individuals compared with healthy controls. Phagocytosis was found to be comparable in the two groups.

Altay et al (1972) studied the capacity of leukocytes to reduce nitroblue tetrazolium dye during the phagocytosis of latex particles (in 25 patients with malnutrition and in 15 age-matched control subjects). No difference in this activity was found by them between children in the study and control groups.

In 1974, Douglas and Schopfer investigated 16 children with kwashiorkor type of protein-calorie malnutrition, to assess the functional activity of their peripheral blood phagocytes. They measured Hexose-monophosphate shunt
activity in the resting and phagocytizing state and bactericidal capacity with Escherischia Coli and Staphylococcus aureus. HMS stimulation, determined by CO₂ production during phagocytosis was found to be in the normal range. The bactericidal capacity of phagocytes from kwashiorkor patients was found to be normal in the early phase (first 30 minutes) and significantly reduced during the later phase (after 60 minutes) of the assay as compared with cells from healthy children.

In 1975, a study of leukocyte response to infection, polymorphonuclear leukocyte chemotaxis and bactericidal activity, and nitroblue tetrazolium (NBT) reduction in children with kwashiorkor was undertaken by Rosen et al and were compared with a control group. They found that total leukocyte counts, were depressed in children with kwashiorkor and lymphopenia was found to be not infrequent. NBT reduction was found to be normal. Polymorphonuclear leukocyte chemotaxis and bactericidal activity was found to be reduced in infected malnourished as well as control subjects. In uninfected children (malnourished and control) chemotaxis and bactericidal capacity were found to be normal.

In 1976 Schopfer and Douglas again studied forty six kwashiorkor patients to assess functions of their neutrophils. They excluded children with clinically overt infections. The NBT score was found to be significantly higher for cells from children with kwashiorkor than for controls, chemotactic response was found to be reduced at
early time intervals and was found to reach control values after 180 minutes. They also reported an impairment of candidacidal activity for the PMN's from kwashiorkor children. On electron microscopic study of candida phagocytosis by PMN's they found no major difference between PMN's from kwashiorkor children who had candidacidal defects and controls. No difference was found in enzymes activities and glycolysis of the two groups. No impairment of $T_4$ degradation by PMN's of kwashiorkor children was found by them.

In 1982 Bhaskaram and Reddy also studied macrophage function in kwashiorkor. The function of macrophage per se and the opsonic activity (mostly contributed by antibodies) was found to be unaltered in kwashiorkor in their study.