REVIEW OF LITERATURE
Nomenclature:

The word measles probably has originated from the Latin term 'miscellus' or miscella itself a diminutive of the Latin 'miser' meaning miserable. The word miser was used for lepers. The term was used for the sufferer from various skin eruptions and sores by Langland in the 14th century in his poem "The vision of piers the Ploughman". Shakespear also used it in coriolanus, indicating, however, that the sores were infectious. John Gaddesden, however, identified unjustifiably, the non-specific leprous sore with the disease called in Latin morbilli. This term was a diminutive of morbus which referred to the major disease, bubonic plague, morbilli being a minor disease. In the anglicized form of miscellus, namely mesels, the word henceforward became applied not to sufferer of ill defined skin lesions but to the specific disease morbilli (G.S. Wilson, 1962).

History of Measles:

No accurate information is available on the early history of measles. The disease was confused with smallpox. Rhazes (A.D. 850), an Arabian Physician is generally credited with having drawn a distinction between the two diseases.
But he and Arabian school generally regarded them as intimately associated with each other. The demarcation became clearer by the beginning of 17th century and in annual bills of mortality drawn up by the Parish clerks of London in 1629, smallpox and measles were listed separately. Thomas Sydenham, a great physician and epidemiologist finally cleared up any obscurity which was left. Subsequently, confusion when it has existed, has been between measles and scarlet fever and between measles and rubella. Koplik in 1896 was able to establish a definite clinical basis for differentiating measles from rubella and other exanthems. Measles encephalitis for the first time was described by Lucas (1790) from England who described it as "an account of unknown symptoms following measles".

Measles has been recognised as a disease for almost 2000 years, however, exact etiological agent could not be identified till 1954. Hektoen (1905) showed that measles developed in susceptible volunteers after inoculation of blood free of bacteria that was taken from cases in acute stages.

Plotz (1938) published an account of the successful propagation of the agent in Chick embryo cultures. Enders & Peebles (1954) isolated the measles virus using tissue cultures of primary human renal cells. This still remains the most sensitive system to propagate wild measles virus.
Magnitude of problem:

Measles is a serious disease. Few other diseases cause as much morbidity and mortality as measles does among young children in India and other developing countries (John & Devrajan, 1973).

Terry (1962) said "measles is not as innocuous as it is popularly believed and with certain combination of causes it becomes so epidemic that it causes a very great slaughter of the human race". The depth of above statement can be judged by the fact that 6% of deaths in those less than 5 years of age in U.S.A. are caused by measles (Puffer & Serrano, 1973). The same observation has been made by Chen et al (1980) in India and Bangladesh. The deaths in rural Guatemalan in Central America was 153 per 1,00,000 population per year (Gordon, 1965).

However, in India, Taneja et al (1962) compared mortality pattern of measles and diphtheria in Madras. They observed that mortality due to measles was equal or even more than that of diphtheria and one out of every 800 children under five in the state, died of measles or its effect.

John et al (1980) state that almost every child gets measles. Serological evidence of measles virus infection even in children who escaped overt measles
infection confirms the earlier assertion that subclinical infection is not very uncommon.

Some popular beliefs about the causation and treatment of measles:

The delay in recognizing the severity of measles in many countries has been to some extent due to strong believes about the disease held universally by the villagers and poor city dwellers. In Europe, for more than 1000 years, measles was believed to be failure of the mother to menstruate during pregnancy. The retained "bad blood" was believed to enter the fetus and appear later as a rash of measles (Willis, 1695).

In Africa, measles is generally believed to be due to sorcery, though eating certain foods such as snails or beniseed are still thought in some areas to be responsible for the disease. All medicines, both traditional and scientific are avoided and infections which may prevent the rash from coming out, are feared. Two dangerous customs followed are the restriction of fluid during the course of the disease in many areas and in Zambesi valley, the application of astringent fluid from roots of Herbs to the eyes (Morley, 1969).

In Asia, it is often considered to be due to the curse by a malignant Goddess. The parents hide their child suffering from measles from neighbours and avoid bringing
him to hospital. If a child in hospital for some other condition develops measles, he is likely to be promptly removed by his parents.

Measles virus:

Measles virus is a member of Paramyxovirus group (Cornell and Norby, 1974). Its internal component of ribonucleic acid (RNA) within a helicole protein capsid is enclosed by an outer membrane of a lipid and protein. Electron photomicrograph demonstrate virons that are roughly circular or oval and average 1,200 to 1,400 Å in diameter. Anders and Peebles (1954) indicated that the virus was quite slow growing and moderately thermolabile. Girardi et al (1958) have reported on the inactivation of measles virus by heat at 56°C, by formaldehyde and by ultraviolet light.

Black et al (1959) studied the growth of measles virus in Hep-2-cell cultures. They observed that maturation of first new virus occurred 15 - 18 hours after inoculation, but no virus was released into the fluid phase for 27 - 30 hours. They further observed that even after this time major part of the active virus remained within the cells. At 37°C, the virus had a half life of about 2 hours. Thus they found that there was little accumulation of live virus in tissue culture but during the active virus production there was an equilibrium between release and decay. The virus was relatively stable when suspended in media at 0°C of pH 6 to 9, but titre was rapidly lost at 4.5 and lower pH.
No antigenic strain difference of measles virus have been identified (Ruckle, 1965). The virus envelope is associated with the antigen responsible for haemagglutination and haemolysis while complement fixing antibodies are mainly associated with nucleocapsid (Waterson, 1965).

Age incidence of measles:

Since the virus neutralizing antibodies are among those immunoglobulins that cross the placenta readily infants born to mother immune to measles are protected against infection during their first 6 or 7 months after birth. With the catabolism of maternal antibodies infants become increasingly susceptible in the second half of their first year and many on exposure develop disease of varying severity. Those with modified or occult illness are thought to be examples of partial protection by residual transplacentally acquired antibody. The infant of rare mother who has never had measles or vaccine is susceptible at birth and may acquire the infection at any time postnatally (John et al., 1980; Mehta et al., 1972).

Essentially all children will get measles unless protected by immunization. The age groups in which measles occurs are usually different in developed and in developing countries. The peak incidence of the measles in developing countries is between one to three years while in United Kingdom and Europe it is 5 years and older. In United States, it is 10 - 14 years (Morley, 1969).
In another study, Morley et al (1962) in Nigeria observed that three times as many children had measles before the age of one as those in an English town. Gordon et al (1965) while conducting the study of measles in rural Guatemala, found that the incidence was greatest in the second year of life in contrast to the peak seen in the first school year in United States.

Gupta & Singh (1975) observed maximum cases of measles in the second half of the first year of childhood in Tanzania.

In India, Sehar & Maur (1958) reported the peak incidence between 1 to 2 years. Children below the age of 4 years accounted for 80% of cases reported. Ghosh & Datt (1961) observed the highest incidence (32%) in children of 1 to 2 years. 15% of cases were under 1 year of age. The incidence above 5 years was low (5.4%). Desai & Shah (1967) observed maximum incidence in the age group 1 to 3 years. Nigam et al (1973) reported highest incidence between 2 – 6 years age group. Sinha (1977) reported that most of the cases occurred in children between 2 to 6 years (67%) and 91.5% were in children below 7 years of age. Krishnamurthy & Anantharaman (1974) found highest incidence between 1 – 2 years (21%).

Mehta et al (1972) while conducting the sero-epidemiology of measles in Bombay found 48% positivity by four years of age. Thus highest susceptibility and attack rate was seen in the pre-school and early school years.
Ramkrishnan et al (1978) observed maximum incidence in the age group of 0 - 1 years. Dorairajan et al (1979) reported that more than 80% of the children affected were below 3 years of age with a peak incidence between 1 - 2 years.

Bhau et al (1979) concluded that onset of measles infection occurs at pre-school age (2 to 4 years) with maximum rate of infection in school going age group 6 to 7 years (23%). The same has also been observed by Broor & co-workers (1976) in their work at Chandigarh.

Bhaskaran et al (1984) found maximum incidence in children between 1 and 3 years (45%), followed by less than one year (22%), 3 to 5 years (20%) and above 5 years (12%).

Sex incidence:

Measles is reported to be more common in boys (Nigam et al, 1973). Studies done by Shah et al (1972) also showed higher incidence in male. It was observed that when the infection was introduced into a school, the spread of measles was more frequent among boys as compared to girls (Wilson, 1962). Horwitz et al (1974) observed equal incidence among girls and boys upto the age of 6 years. After that age girls had higher incidence rates.

Seasonal variations:

Taneja et al (1962) while comparing the incidence of measles in India found that incidence increases during
March to June and most of the cases are seen during this periods.

In the equatorial countries of Uganda, Kenya, Tanzania, the peak month for measles is April. In Zambia, Rhodesia and Malawi, the peak months are November, December, January. In general, the farther a country is from the equator, the greater is the difference between maximum and minimum monthly incidence (Morley, 1969).

Nigam et al (1973) observed that the incidence of measles increased during March to June (94%). Shah et al (1972) on the contrary found the peak incidence during winter months.

The abrupt decline observed with the onset of monsoon indicates the probable effect of high humidity on survival of virus and its communicability (Ghosh & Datt, 1961; Dejong & Winkler, 1964; Morley, 1969).

Spread of measles:

Measles virus spreads by droplet infection. Although virus has been isolated from throat, conjunctival washing and urine during prodromal stage, the major source of virus is probably in secretions shed from respiratory tract during prodromal phase and early stages of rashes (Gresser & Chiny et al, 1963).

In children the incubation period of natural measles averages 10 to 11 days while in adults it may be slightly
prolonged (Krujman et al., 1977). It may be shortened if the virus is introduced intravenously or subcutaneously or lengthened by administration of specific antibody (Morbins et al., 1962).

Clinical features:

The prodromal period usually lasts for 2 - 6 days (Ribbins, 1962; Nigam et al., 1973). It is characterized by fever, sore throat, watery nasal discharge, dry barking cough and non-purulent conjunctivitis. During early stages of disease, diagnosis of measles can be made with certainty by observance of Koplik spots which are bright red spots with blue white central speck (Koplik, 1896). They are present in 90 - 96% of cases in prodromal stage (Wagner, 1966; Nigam et al., 1973).

A morbilliform rash, which appear on 4th day of the illness, usually begins on head and neck and moves down to cover the entire body. The rash is generally last symptom of measles to develop and after it has spread to all areas of the skin lesions tend to develop sequelae to measles (Morley, 1969). The Arabian Physician Rhazes also wrote "The measles which are a deep red and violet colour, are of a bad and fatal kind".

Pathogenesis:

The classic investigations of Fenner (1950) on the pathogenesis of measles in mousepox, provide an experimental model with general applicability.
The sequence of events based on the Penner scheme and making the proper adaptations for measles would be as follows (Robbins, 1962):

Day 0  (1) invasion of respiratory epithelial cells and multiplication.

Day 1 + (2) Extension to regional lymph nodes.

Day 2 – (3) Primary viremia – this has not been conclusively demonstrated for measles.

Day 3 to 5  (4) Multiplication in lymphoid tissue and respiratory epithelium with formation of giant cells; infection of respiratory tract probably mediated through the blood.

Day 5 + (5) Secondary viremia.

Day 7 + (6) Establishment of infection in skin, this is yet to be shown by direct evidence; involvement of brain may result from virus reaching it through the blood.

Day 11 + (7) Onset of prodromata.

Day 14 + (8) Development of rash.

Day 15 + (9) Antibody appears, viremia ceases and viral content in organs diminishes.

Day 17 + (10) Symptoms ameliorate and rash begins to fade.
Incidence of complications:

Jiddiqui et al (1974) reported that the incidence of complications during 1969-1973 in the area they surveyed was 128 out of 1,222 cases of measles (10.47%), but whereas there were only 71 complications in 1,155 cases till 1972 (6.14%). There were 57 complications out of 67 cases in 1973 (85.07%). Although the incidence of measles was lower in the above 5 years age group, the percentage of complication was seen to be higher but the number in the two age groups are vastly different and so this may be a chance finding.

Out of 350 cases of measles, Silhar & Maru (1958) reported complication in 315 cases.

Ghosh et al (1961) reported 318 complications in 165 patients in their study, showing a high incidence of double and triple complications.

Taneja & Ghai (1962) reported that nearly half of the patients admitted to infectious disease hospital in Delhi with measles were below the age of 3 years. However, 76.3% children with complications were in this age group.

Sixty five patients got the complications out of 75 cases studied by Migam et al (1973).

Krishnamurthy et al (1974) noted that for every 1000 cases in Madurai, 3 to 4% of all admissions were for complication of measles with a mortality rate of over 20%.
Dorairajan et al (1979) recorded that in the urban block of integrated child development services, 1,353 children had measles in 1977. Fifty one of them were admitted with serious complications and 6 died. Among the others, 30 died for a case fatality rate of 2.7 percent.

Types of complications:

Measles per se is seldom fatal, it is the associated complications which make it one of the very dangerous illnesses.

Affection of central nervous system as a complication of measles was known in as early as 1872. Neal & Appelbaum (1927) and Musser & Hauser (1928) described measles encephalitis as a separate clinical entity.

Silhar & Maru (1958) found that the respiratory complications headed the list and were diagnosed in 50% cases; next in frequency was alimentary system 30%, followed by central nervous system complications 5.9%. Otitis media which is supposed to be quite a common complication was comparatively less frequent.

Ghosh et al (1961) reported pulmonary complication to be most frequently encountered complication in measles.

In another study, Desai & Charu Shah (1967) reported that respiratory complications were found to be highest i.e. 37% followed by the neurological 23%, gastrointestinal 12%
and combined in 34% cases. Other complications described were myocarditis, malnutrition, cancrum-oris and otitis media.

Bronchopulmonary complications have been reported to form 86.6% (Nigam et al., 1973), 78.2% (Sunderavalli et al., 1979), 59% (John et al., 1980), 25.4% (Biviji et al., 1972), 87.4% (Ghosh & Datt, 1961) of total measles complications.

Respiratory complications included tracheobronchitis, pneumonia, bronchopneumonia and bronchiolitis (Silhar & Maru, 1958; Taneja et al., 1956; Wilson, 1962).

Pneumonia encountered during measles is usually divided into two types - (1) giant cell pneumonia caused by measles virus and it begins early in the course of the disease before the rash fades, and (2) other more frequent type appears after the initial symptoms of measles have subsides. Even this late onset type has frequently been shown to be caused by viruses e.g. adenovirus, measles virus and herpes virus. This may be the reason why early treatment with antibiotics may not prevent many deaths.

Diarrhoea is the second commonest symptom encountered during measles. Various workers have reported its incidence to be 76% (Morley, 1962), 45% (Sunderavalli et al., 1979), 52% (John et al., 1980) of total complications.

Koster et al. (1981) reported that diarrhoea was associated with variety of pathogens in both malnourished and
wellnourished children. Measles associated with prolonged diarrhoea significantly increased the risk of mortality.

Srivastava and Garg (1968) observed an overall incidence of post measles encephalitis in the range of 1 : 400 to 1 : 1000 cases with associated mortality of 23.5%.

Katiyar and Agarwal (1974) observed that acute encephalitis was very common in the age group 1 - 3 years. Males predominated over females in the ratio of 11 : 8. In the majority of their patients symptoms appeared on 4th day and the encephalitis was heralded by resurgence of fever, headache, seizures and coma. Cerebro-spinal fluid examination frequently revealed pleocytosis even without the symptoms of encephalitis. The majority of cells were Lymphocytes.

Some other complications such as stomatitis, cancrum oris, jaundice (Nigam et al, 1973) and pyogenic liver abscess (Madkur & Mittal, 1980) have been reported.

Morley (1969) reported involvement of the middle ear leading to a purulent discharge in 4.5% of children admitted to hospital.

Measles and Malnutrition:

The inter-relation between infection and nutrition is complex and their combined impact on child in developing countries, is responsible for a high mortality and morbidity (Morley, 1969).
Two separate phenomena must be distinguished. On the one hand measles makes the nutrition of the child worse and on the other hand it has been seen that measles is more severe in a malnourished child.

Measles leads to loss of weight more than any of the other acute infectious diseases in childhood. Creighton (1894) while writing an account of measles in England noted that a "number who recovered from measles were afterwards affected with debility, cough, emaciation and oedematous swelling of face and extremity, which proved very difficult to remove."

Morley et al (1962) observed that after an attack of measles in Nigeria about 2/3rd of cases lost 5% and under and 15% cases lost, 20% or more of their former weight. They also noted that 15% of children took more than 3 months to regain the previous weight.

Biviji et al (1972) studied the effect of measles on physical growth of 63 young children. At the time of contacting the disease 1% of these children were weighing about 80% of the 50th percentile of Harvard standard, 27.2% were weighing less than 70%, and 3.2% were below 60%. The subsequent weight gain was as expected in large number of children who had better nutrition. Those who had 71 to 80% and 61 to 70% of expected weight, the weight gain was delayed in 52% and 60% of the children, respectively as compared to well nourished children where it was delayed in only 38.1%.
95.2% of the cases did not lose weight, only 3.2% and 1.5% of children lost 5 to 10%, and 11% of the former weight respectively. Those who did not gain weight, it took about 0 to 2 weeks and 5 to 3 weeks for 67.9% and 28.6% of the children respectively to gain former weight. For those who lost weight, it took 6 to 7 months to regain their weight.

Nigam et al (1973) observed that children with malnutrition were more prone to get measles infection and liable to have much dreaded complications. Malnutrition in general and kwashiorkor in particular are common in children between 1 and 3 years of age. Measles being common and particularly severe in this age period, further debilitates the children (Taneja, 1962).

Ghosh and Datt (1961) tried to correlate the nutritional status with the incidence and complications and showed that 85.5% had vulnerable nutritional status.

According to Morley David (1973) malnourished children has a mortality 400 times higher than their well nourished counterparts.

Siddiqui et al (1974) documented that the most likely factors precipitating complications are socio-economically depressed condition resulting in malnourishment, over-crowding and strict adherence to rituals pertaining to measles.
Krishnamurthy and Anantharaman (1974) concluded that there was direct correlation between the incidence and severity of complication and malnutrition. Attack of measles in children invariably tipped the vulnerable nutritional balance to negative side and protein calorie malnutrition was precipitated in the border line cases and third degree malnutrition resulted in those who were already suffering from first and second degree malnutrition.

Gupta & Singh (1975) reported that death incidence increased with increasing severity of malnutrition. In their study they found that 36.8% had moderate malnutrition with weight for age of 60 - 80% of Harvard standard. There were 18 cases of frank marasmus (weight for age less than 60%). No child was having kwashiorkor. Highest mortality was seen in marasmic children (16.69%).

Sundaravalli et al (1979) observed that post measles complication were very common in undernourished patients. In their study 96% of them were undernourished, only 4% were from well nourished group. So there were definite interaction of infection in malnutrition.

Chen et al (1980) reported that the children who were hospitalised for measles, 89% of those poorly nourished had more than one complication as compared to only 20% of the well nourished children.
Koster *et al* (1981) observed that greatest weight loss was seen in children with measles complicated by prolonged diarrhoea and children under 4 years of age in this group failed to achieve "catch-up" growth. Thus measles and diarrhoea appeared to interact synergistically to increase mortality and the irreversible effects of nutritional deprivation.

However, Shah *et al* (1972), John & Devrajan (1973), Sinha (1977) and Bhaskaran *et al* (1986) do not agree that malnutrition contributes to serious complications and death due to measles.

Bhaskaran (1984) observed in their study that 7 children with measles developed corneal changes during the acute stages. Serum Vit. A levels were significantly low in their cases. They concluded that the fact that all children with corneal lesions responded to Vit. A confirms that Vit. A deficiency is the major cause of blindness.

More than half of the incidence of blindness may be attributable to measles in areas where Vit. A deficiency is common (Sauter, 1976).

**Measles and age interaction:**

Black *et al* (1976) observed that the other host factor which was of primary importance and contributing to the high mortality associated with measles, was involvement of younger children. In general, infants and toddlers were
more likely to experience complications and to die from measles than the older children. The death to case ratio for infants was many times greater than it is for the older children in their study.

Gordon et al (1965) reported a fatality rate of 11.5% in infants while fatality rate in older children was 4.5%.

Gupta & Singh (1975) noted that diarrhoea occurred in 2/3rd of children younger than four years of age but in less than 28% of those older than five years.

In Zambia, McGregor (1964) reported a mortality rate of 24% in children below 5 years and 11% in those cases who were above 5 years.

**Discovery of Immunoglobulins**

The relation of serum proteins to immune bodies have been a subject of investigations for a long time. The earlier research published on the relation of serum proteins to antibody was that of Widal & Sicard (1897) who demonstrated that agglutinins in immune sera precipitated along with globulins, when treated with magnesium sulphate.

In 1899, Wintenberg while investigating the action of various protein precipitants observed that animal membranes are impermeable to agglutinins and dialysis over a month seldom shows a loss of more than ten percent.
The name immunoglobulin was first proposed by Heremans (1959). By that time only 3 classes of immunoglobulins namely IgG, IgM & IgA were known. IgD was first described by Rowe & Fahey (1965) and Ishizaka et al (1966) provided evidence for a fifth class of immunoglobulin, having all the characteristics of homocytotrophic and reaginic antibodies.

To avoid confusion in the nomenclature and classifications, W.H.O. constituted a committee in 1964 to define and recommend standard nomenclature for immunoglobulins. This Committee recommended that the group of these proteins should be termed as immunoglobulin and symbolised as Ig or rg. It recommended the following nomenclature for immunoglobulin classes.

IgG or rg $\rightarrow$ r 7Sr, 6.6 Sr, 2, r ss
IgA or rA $\rightarrow$ B₂, A, r1A
IgM or rm $\rightarrow$ r1, M, B₂M, 19 Sr, r-macroglobal.

The presence of IgE & IgD was recognised later on.

**Structure and functions of Immunoglobulins:**

Immunoglobulins are a family of structurally related proteins which mediate circulating antibody responses. There are 5 major classes of proteins in most mammals namely IgG, IgA, IgM, IgD & IgE. Each of them are composed of polypeptide chains: two light chains (L chains) and two heavy chains (H chains) (Rowe & Fahey, 1965). The light chains are common
to all immunoglobulins whereas the heavy chains are distinctive in structure (Pahey, 1963; Carbonora & Haremans, 1968).

**Human Immunoglobulin G:**

IgG is the major immunoglobulin in normal human serum accounting for 70 - 75% of total immunoglobulin pool. It has got a sedimentation coefficient of 6.6 and a molecular weight of 1,46,000. At least half of total IgG immunoglobulin is in interstitial fluids and remainder in plasma. The rate of synthesis is approximately 28 mg/kg/day (Cohen & Freeman, 1960) and in healthy adult about 2 gms of IgG are synthesized and catabolised each day (Cohen, 1963). Half life of IgG ranges from 23 - 35 days (Solomon et al, 1963).

The IgG globulins contain the majority of antibacterial and antitoxic antibodies. Additional antibodies e.g. anti-insulin (Yagi et al, 1963), antinuclear factor (Barnette et al, 1964) etc. also have been demonstrated.

**Human Immunoglobulin IgA:**

IgA accounts for 15 - 20% of total immunoglobulin pool. The body distribution of IgA is similar to IgG. Secretory IgA is the principal secretory form of antibody (Tomasi et al, 1965) and it is present in many body fluids and secretion including tracheobronchial secretions. It possibly provides a protective actions against microorganism (Bellanti et al, 1965). The rate of synthesis of
IgA globulin is approximately 8 - 10 mg/kg/day with a half life of 6 - 8 days.

The IgA globulin has been shown to possess a variety of antibody functions such as antitoxins (Haremans et al., 1963), antibacterial agglutinins (Row & Turner, 1964), isoagglutinations, cold agglutinin, antinuclear and incomplete Rh antibodies. The secretory IgA contains antibodies of certain viruses (Smith et al., 1967) and intrinsic factor (Goldberger et al., 1968).

**Human Immunoglobulin M:**

IgM predominately occurs in man as a pentamer with a molecular weight of 9,50,000 - 1,000,000. It is predominately intravascular (Cohen & Freeman, 1960). The average synthesis of IgM is 5 to 8 mg/kg/day with biological half life ranging from 5 - 11 days (Gitlin, 1966).

The IgM fraction contains most natural antibodies, especially those against gram negative organism (Robbins et al., 1965).

The role of IgD & IgE is not well established and is not discussed here.

**Immunoglobulins in children in state of health and disease:**

Immunoglobulins level in state of health are influenced by several factors. Of these, age and environment related differences are much more clearly defined than others.
A new born and an infant differ greatly in immunological status from adult. The difference is both in qualitative i.e. the type of immune-mechanism activated and quantitative i.e. in the level of immunity achieved.

Immunoglobulin synthesis starts in _in vitro_ after 20 weeks of gestation (Van Furth _et al_, 1965). Apparently the quantity and quality of stimulation are such that only IgG and IgM responses are evoked.

Fundenberg & Fundenberg (1964) found that in the cord blood IgM is routinely present and evidence indicates that IgG synthesized by the baby is also probably present though in low amounts.

Similarly the infant _in utero_ is capable of producing IgA also but usually does not. To do so an unusually strong stimulus such as maternal infection with pneumococcus, rubella virus or the agent of syphilis is required (Steihm _et al_, 1966).

At birth new born is born with considerable amount of IgG levels similar to maternal sera or even higher have been shown by various workers (Allensmith _et al_, 1968, Steihm & Fundenberg, 1966, Chandra, 1972).

The only exception to this was a study by Prasad _et al_ (1971) who found cord sera IgG levels to be about 50% of adult levels. The explanation given was the possibility of a correspondingly lower levels of IgG in those mothers.
IgA immunoglobulin levels are the last to mature to adult levels. It is either absent or present in trace amount in cord sera (Steinh et al., 1966). Its appearance in the sera in IgA negative infants after birth has been reported at different ages.

Allensmith et al. (1968) noted its presence as early as on 5th postnatal day while most of the other workers found it to be present by 4 weeks (Chandra & Ghai, 1972; Prasad et al., 1971).

Once it appears it starts rising till adult levels are reached by 2-16 years of age (Steinh et al., 1966).

In the developing countries, the immunoglobulin levels usually reached adult levels earlier than in the developed countries. This is largely related to frequent infections with a varied variety of pathogens (Chandra & Ghai, 1972). But the ultimate adult levels in Indians do not differ from those reported in western countries (Chandra & Ghai, 1972; Maheshwari & Singh, 1982).

**Malnutrition:**

The results of studies showing effect of malnutrition on humoral immunity are conflicting. High levels of immunoglobulin have been reported by various workers (Prasad et al., 1971). But Chandra et al. (1972) showed that in malnourished children without evidence of concurrent infection or recent history of it, there was significant lowering of serum
immunoglobulin G levels which may be responsible for predisposition to infections.

Rapid rise in IgM, IgG & IgA levels during the first year of life are reported in studies of communities where malnutrition is frequent. IgM & IgG frequently approach adult levels by 12 months of age (Nayyar et al., 1969). In direct contrast to this finding, children in Egypt with severe kwashiorkor have been reported to have very low levels of IgM & IgA during the first year of life and partial defect persisted even after special feeding (Aref et al., 1970).

Measles and Immunity:

Long before the discovery of Immunoglobulin, Panum in 1847 published a famous account of measles in the Faroe Island in which the disease had been absent for 60 years. When the epidemic had been through the Island everyone was infected except those who had been children exposed to the previous epidemic 60 years before. This rather clearly makes the two points -

1. that immunity against measles is life long and specific.

2. that once a person has recovered from measles he never sheds virus into the environment.

Antibodies appear in the serum after 12 to 15 days following infection of man and experimental animals.
They specially neutralize viral infectivity, fix complement with viral antigen and inhibit viral haemagglutination and haemolysis. No evidence has been found of significant variation among measles strains isolated during the past couple of decades. This homogenesity correlates with the extreme rarity of second attacks of the disease (Mehta, 1961).

The whole process of eruptive stage of measles and subsequent immunity is mediated by the thymus dependent system. A few days after the exanthem has appeared, antibodies become detectable in the circulating blood, and concurrently virus is no longer demonstrable and the patient becomes non-infectious. Antibodies rise to high level some time after the attack and after the moderate fall persist in demonstrable amount for many years perhaps for life and therefore it seems clear enough that antibody is what protect the measles convalescent against reinfection.

Coovadia et al (1978) showed that function of measles antigen sensitive cells is probably impaired during severe measles infection. All the children who died, failed to produce an adequate or sustained measles antibody response. The muted antibody response in children who did badly was probably clinically important as patients with secondary immuno-deficiency who develop fatal Mecht's giant cell pneumonia also failed to produce adequate antibodies (Nitus et al, 1959; Dosettar, 1977).
Bhaskaran et al (1983) reported that antibody response to measles was found to be satisfactory even in undernourished children with measles.

Measles is a serious disease with consequences to the immunological mechanism. It is probably the most common of secondary immunological deficiency syndrome (Gatti & Good, 1970).

Prolonged morbidity due to secondary infection is frequent in malnourished children and this has been attributed to immuno-suppression (Coovadia et al, 1977).

As early as 1908 Von Pinquet reported that tuberculin reaction became negative during an attack of measles who had previously been positive to this test. This observation has been confirmed in natural measles (Starr & Berkomin, 1964). Subsequently it has been reported that infection with other myxoviruses can have a similar immuno-depressive effect (Peuhale & Pow, 1970).

Tuberculosis and moniliasis infections normally controlled by cell mediated immune responses, are known to follow measles (Bech, 1962; Smyth et al, 1971). Pyogenic infections, which are usually limited by humoral immune responses, are also frequent and severe in children with measles (Taneja et al, 1962; Morley, 1969).

Starr & Berkovisch (1964) reported that immuno-suppression following measles is a transient phenomenon and recovery occurs within six weeks following measles.
But Kipps et al (1966) observed that in at least 43rd of children abnormal cutaneous response persisted for more than one year. They also showed that it takes more than six months for these immune mechanisms to restore to normal. This prolonged immunosuppression can explain increased infective morbidity in children with measles.

Burnet (1968) reported that in the course of the generalised delayed hyper-sensitivity reaction which we see as the measles rash, there is discharge and exhaustion of all those local cells probably including mast cells, which can contribute pharmacologically to the local reaction. He further added that it could also be assumed that regions from which large number of thymus dependant cells are liberated have been temporarily exhausted. Taken together, these are responsible for the failure of the classical Mantoux reaction against tuberculin to be elicited in the weeks following measles. He stated that the phenomenon is a clear indication of the fact that the measles rash is itself a diffuse delayed hyper-sensitivity reaction. The whole pattern of measles pathogenesis and immunity is clearly based on thymus dependant immunocytes, measles is in fact a complex and severe delayed hyper-sensitivity reaction. The gut dependant (G.D.) system and its antibody are side effects, epiphenomena of minimal or no importance.

They documented the following facts in favour for confirmation of their theory -
(a) In agammaglobulinemia the measles runs a normal course and gives rise to normal subsequent immunity.

(b) In cortisone treated acute leukemia where the cell mediated immunity is eliminated, measles takes on the form of a fatal giant cell pneumonia without rash.

(c) Presence of normal levels of humoral immunity in subacute sclerosing panencephalitis (SSPE).

Since then various workers (Bhaskaran et al., 1983; Usha et al., 1975; Rackdeshel & Graziano, 1975; Whittle et al., 1975; Coradio, 1978) have confirmed that there is transient suppression of cell mediated immunity lasting for 6 weeks to 6 months of measles infection.

An absolute lymphopenia is found early in measles infection (Coovadia et al., 1978). There appears to be an important link between lymphocytes number and immediate and late complications of certain neoplastic and infectious disease (Coovadia et al., 1977; Jackson et al., 1977).

Coovadia et al. (1977) observed that estimation of lymphocyte number in peripheral blood has been shown to be a reliable index of outcome in measles. Profound lymphopenia (\( \leq \)2000 cm) during the exanthem in measles generally distinguishes children who will die or develop a chronic chest disease from those who will recover. Smyth et al. (1971) demonstrated lymphopenia in 26.8% of children who died and in 1.59% of those who survived, emphasizing the importance of lymphopenia in recovery.
Exact cause of this lymphopenia is not known. Another paramyxovirus interferes the migration pattern of rat lymphocytes, but no such study has yet been reported with measles virus.

White & Boyd (1973) demonstrated the loss of all desirable cortex from thymus in case of measles. The cortex remained deficient for at least one month and recovery of cortex occurred in cases seen at 91 & 122 post measles days. These destructive changes in thymus may lead to decreased lymphocyte count in measles in peripheral blood. The resulting deficiency of thymus dependent lymphocytes may be sufficient to impair the specific immunological attack on measles virus and allow persistence of large amount of virus in thymus (Burnet, 1968) and brain (Conolly et al., 1967).

The profound immuno-suppression during the first few days of rash has been shown to affect chiefly T & B cell sub-populations with less severe effect on C3 & T cells function assessed by phytohaemagglutinin transformation of lymphocytes (Coovadia et al., 1977).

Coovadia (1978) reported that Fc cells were undetectable and null cells were higher for at least fifteen days after the rash in those who did not recover from attack of measles. Reduction of T, B, null lymphocyte subpopulation has been shown in acute measles resulting in absolute lymphopenia.
Immunoglobulin levels in measles have not been studied adequately. Coovadia et al. (1977) reported that immunoglobulin levels did not differ in patients who subsequently died from those who recovered. He also found that the children with acute measles have widespread immunodeficiency i.e. low IgA level. However, in another study they found that during acute measles serum IgA levels are low and the haemolytic function of complement (H$_{50}$) and C$_3$, i.e. a factor utilised in alternative pathway were also decreased (Coovadia et al., 1978).

Peltron et al. (1982) showed that immunoglobulin synthesis was depressed by measles virus but the extent of this suppression did not depend upon the time of infection in relation to antigen stimulation.

Aby et al. (1987) have extensively reviewed the literature about immunoglobulin therapy, measurement of antibody response and/or severe to fatal cases of measles, including all reports of 'giant cells pneumonia' and encephalitis since 1960. They classified severe cases of measles -

(a) as those with neurological complication excluding SSPE, and

(b) those with other symptoms, usually with extensive pulmonary involvement.
They found that in cases with non-neurological symptoms there was a strong correlation between fatal outcome and depression of H.I. for both normal individual and children with underlying disease. They reviewed 27 cases with a documented complement fixing antibody response that with one exception all had undetectable, low (≤ 10), or falling concentration of antibodies. In most cases time of measurement of antibodies in relation to appearance of rash is not indicated. However, 12 fatal cases had a delayed C.F. response more than two days after the rash, a time when recovering individuals usually have antibodies. In contrast, individuals surviving severe pneumonia had high or increasing C.F. antibody titres. In the some fatal cases where a neutralizing antibody response has been reported, the titre was low (≤ 10). Since there is usually a good correlation between C.F. and neut antibodies in measles infection, the neut antibody response may be depressed in most fatal cases of measles. The haemagglutination-inhibiting (HAI) antibody response was depressed in nine of ten cases where it was documented. There are five possible exceptions to this pattern of antibody response in fatal cases of measles. Three of these cases had no specific indication except the antibodies were present. One case had an antibody titre 7128 two weeks before death. In the remaining case, a high HAI titre was measured on the day of the rash, two days before death.
The antibody response in patients with neurological symptoms is more variable. Survival cases of encephalitis had low level of antibody in initial phase whereas they had higher than normal antibodies responses in convalescent phase. Individuals with SSPE have high antibody titres in CSF and serum. They hypothesised that inefficacy of measles antibodies in cases with neurological involvements is due to lack of another immunological components.

Greenberg et al collected all cases of encephalitis reported in New York city between 1949-1954 and claimed to have found that immunoglobulin had no effect. Since his research was not a control study, as demonstrated by the much higher percentage of severe cases among those treated with immunoglobulin, a definite conclusion on its therapeutic value was not warranted.

Gupta et al (1987) studied antibody titres and immunoglobulins levels (IgG, IgM, IgA) in sixty cases of measles, half of them with complications and rest of half without it. They did not find any significant difference in development of antibody titres in two groups. However, they found that IgG and IgM immunoglobulin levels were higher in those who had complication with measles. In contrast, the level of IgA immunoglobulin were found to be lower in individual having complications with measles. They opined that as most of complications of measles are surface infections, e.g. Bronchopneumonia, diarrhoea etc.
it may be possible that patients with complication may have been selected for susceptibility of the relatively severe form of the disease by a pre-existing IgA deficiency.

Anderson et al (1976) and Yetin & Altay (1980) studied polymorphonuclear (PNM) functions in cases of measles. They reported defective mortality of PNM in measles. They opined that measles virus causes some metabolic and morphological changes in cells causing defective bacteriocidal action of these cells. These changes in PNM further makes the children with measles prone to bacterial infection.