REVIEW OF LITERATURE
REVIEW OF LITERATURE

Septicemia in the neonatal infants refers to the generalised infection documented by a positive blood culture in the first 30 days of life.

The term 'sepsis' and 'septicemia' used synonymously, are not well defined. In contrast to bacteremia (bacteria in blood), septicemia usually consist of bacteria plus a constellation of signs and symptoms caused by micro-organism or their toxic products in the circulation.

Septicemia, inspite of the general impression to the contrary, is an important and relatively frequent cause of morbidity and mortality in the newborn (Dunkum, 1933). Many cases of septicemia are over-looked or are diagnosed only when localized lesions appear, unless blood cultures are made in all cases of obscure illness in the neonatal period.

During the past 50 years there has been a dramatic shift in the pattern of micro-organisms responsible for bacterial infection (Freedman, 1981). In 1930s and 1940s, group A beta hemolyticus streptococcus
was the commonest cause of sepsis. With the advent of antimicrobial agents, they were steadily replaced by the phage group I staphylococcus aureus and by the coliform organisms. Currently group B hemolytic streptococci and Escherichia coli account for the majority of cases of neonatal sepsis and meningitis. Other bacteria that have been increasingly observed in the past few years include - Listeria monocytogenes, Klebsiella, Enterobacteria, Staphylococcus aureus, Pseudomonas aerogenosa, Hemophilus influenzae and enterococci (Pyati, 1987).

Bacteria may invade the newborn via a number of routes. Apparent or inapparent maternal bacteria can produce fetal infection by the transplacental route. Infected amniotic fluid is a major source of neonatal septicemia. Premature rupture of the fetal membranes, prolonged labour and excessive manipulation during labour increase the risk of contamination of the amniotic fluid. Following birth, bacterial organisms may be acquired in the delivery room or in the newborn nursery. The main pathways are via the respiratory and gastro-intestinal tract. After birth, the skin and umbilical cord become important alternative routes for the entrance of bacteria into the systemic circulation (Gottoff and Behrman, 1970).

The mortality rate of septicemia in neonates prior to 1937 was about 90 percent. The figure has fallen since the advent of antibiotics and has ranged from 13 to 45 percent in recent years (Gottoff, 1970).
Abdominal distension, apnea and jaundice may be some of the earliest signs. In contrast, progressive abdominal distension, jaundice and an abdominal respiratory pattern in association with lethargy and weight loss may be relatively late presenting symptoms of sepsis. Hepatosplenomegally tachypnea, dyspnea, hypothermia, hyperthermia, and cyanosis also frequently occur as features of a fully developed syndrome of septicemia (Gotoff and Behrman, 1970).

**BAND NEUTROPHIL**

The 'band stage' is characterised by condensation of nuclear chromatin and transformation of nucleus into sausage or band shaped configuration which posses approximately uniform diameter throughout its length. Subsequently one or more constrictions begin to develop and progress until the nucleus is divided into two or more lobes connected by filamentous strands of heterochromatin - the polymorphonuclear stage (Wintrobe, 1981). The nucleus of neutrophil is of two types - non-segmented and segmented. According to the absence of lobulation segmented neutrophils which normally number 60-65% of white blood cells are mature cells in which the nucleus consist of 2 or 5 lobes connected by a thin strand of chromatin. The non-segmented cells number 4-5% of the total number of white cells and are variously designated as 'staff' or 'stab' cells. They
are slightly smaller than the metamylocytes in which the nucleus fails to segment presumably due to toxic or other influences (Smith, 1972).

"LEFT AND RIGHT SHIFT" (ARNETH COUNT, COOKE AND SCHILLING COUNT):

According to Arneth's theory (1904) the nucleus of polymorphonuclear cell becomes more segmented with age. The round or oval nucleus of the myelocyte becomes more indented as the cell matures, with increasing segmentation in older cells. As modified by Cooke and Schilling and in accordance with the present usage 'a shift to the left' implies the presence of immature forms consisting of large numbers of band forms in the blood.

An increase in younger forms (band cells, metamyelocyte and myelocytes), i.e. shift to the left suggests increased release of young neutrophils from the bone marrow. This is seen in association with acute infections (Marsh, 1943).

MICRO ERYTHROCYTIC SEDIMENTATION RATE:

In 1918 Fahraus, while seeking an early test for pregnancy, discovered that suspension stability of blood was altered in pregnancy. He also found that the
speed of sedimentation of red cells is accelerated in many diseases. A test was thus discovered which, because of its simplicity and its wide applicability, soon became popular.

The rate of Erythrocytic sedimentation depends upon the interaction between opposing physical forces; settling occurs because the density of the red blood corpuscles is greater than the density of medium. The fall of red corpuscles causes an upward displacement of medium. Thus producing an upward current and a retarding force (Wintrobe, 1981).

Sedimentation can be observed to take place in three stages: a preliminary stage of at least a few minutes during which time rouleaux form, then a period in which the sinking of the rouleaux takes place, more or less, at a constant speed and finally a phase during which the rate of sedimentation slows as the rouleaux pack at the bottom of the tube (Dasie, 1977).

Landau et al in 1933 used LINZENMEIER RAHMERT MICROMETHOD of Erythrocytic sedimentation with some modification requiring only a few drops of capillary blood. They suggested that micro sedimentation be carried out under uniform environmental condition viz., the temperature. Slight variation in temperature was of little importance. Authors observed that if there was
partial coagulation of blood that could be the source of error. They observed that there was no particular difference in micro Erythrocytic sedimentation rate (mESR) of blood obtained from vein or capillary. Normal value of mESR observed was 1-3 mm in the 1st hour. Authors recommended that Linzenmien micro-method was reliable.

In 1933 Dunhum published his study of 39 cases of septicemia. He wrote that there was striking predominance among boys. General symptoms and signs observed were: fever, enlargement of spleen, jaundice, bleeding tendency. Total leukocyte count varied from leukopenia (4000 - 5000 cell/cu mm) to leukocytosis (30,000 to 50,000 c/cu mm). All the infants with leukopenia died. Commonest organism found were: the streptococcus, staphyloccocus, E.coli.

Smith et al (1936) studied the micro-sedimentation of erythrocytes by using apparatus of cutler with a little modification, keeping in view the practical difficulties of doing venipuncture in infants especially when repeated test were to be done within short intervals. Authors found that there was a close relationship between values obtained from blood drawn by heel prick method and by venipuncture. On using 5% sodium citrate as an anti-coagulant the average rate of settling in normal infants was 4.2 mm for 1/2 hour and 9.1 mm for one hour, whereas the average reading for the 1/2 hour period was 15.1 mm in pathologic group.
In 1949 Silverman et al described the clinical and laboratory manifestations in a group of 25 newborn infants with septicaemia. The responsible agents found were: enteric micro-organism, streptococcus, staphylococcus. Fever, jaundice, gastrointestinal symptoms, respiratory distress and hepatomegaly were the most frequently observed clinical manifestations.

Smith et al in 1956 published his study on fifteen cases, suffering from generalised infection. Authors observed that neonatal septicaemia was more often caused by enteric group of micro-organism particularly E.coli. Clinical manifestations of neonatal septicaemia were most variable and often misleading. Leukocytosis and fever, the hallmark of infection could be entirely absent. They observed that ESR was elevated in most cases.

Bustlow et al in 1965 published a report observing that in spite of recent decline in neonatal mortality rate to less than 20/1000 live births and premature live births to less than 10/1000 live births, infection remained the significant cause of neonatal deaths. He studied 2,906 infants in a span of 4 years weighing between 1001 gram to 2500 gram. A total of 188 infants had bacterial growth in blood culture. Susceptibility of septicaemia was more in lower birth weight and male infants. The incidence for male infant
was 65% whereas for females it was 45%. Presenting features in 158 cases were: jaundice in 59 cases, lethargy in 49, Cyanosis in 14, apnea in 33, poor feeding in 31, skin infection in 29, retraction in 28, vomiting in 23, distension in 21 and diarrhoea in 17 cases. Differential count showed 'Shift to the left' with half of the infants exhibiting 50% or more segmented neutrophils.

Evans et al in 1970 studied the micro Erythrocytic sedimentation rate (mESR) in 9 infants with infection and compared its value with 21 infants having respiratory distress syndrome. mESR was determined according to the method of Landau et al employing clay Adams micro sedimentation rate pipettes. Authors observed that there was no correlation between mESR and gestational age, birth weight, or haematocrit in low birth weight or full term babies. In 8 out of 9 infected infants mESR was raised. These levels exceeded the ninety fifth percentile of the corresponding group of normal infants. Out of the 21 infants with respiratory distress syndrome, only one had an mESR value greater than the ninety-ninth percentile for the normal group (20 mm per hour). Authors had the impression that mESR was simple, inexpensive test, requiring only capillary blood and hence ideally suited for the newborn infant. Moreover, it had a potential usefulness in evaluating the small neonate with sepsis and was helpful in differentiating idiopathic respiratory
distress syndrome from infectious entity, having similar clinical manifestations. Authors recommended that in view of high mortality rate in neonatal septicaemia and the associated difficulty in establishing an early diagnosis, application of this test could be encouraged.

In 1970 Gotoff & Behrman wrote in their review that incidence of neonatal septicaemia was fairly constant over the past 40 years and varied from 1 per 500 to 1 per 1000 live births. The mortality rate ranged from 13 to 45 percent in recent years. Routes of invasion by bacteria were many. Transplacental route was particularly associated with Listeria monocytogenes. Infected amniotic fluid, premature rupture of the fetal membranes, prolonged labour and excessive manipulation during labour increased the risk of contamination of amniotic fluid. The ratio of infected amniotic fluid to systemic infection in the neonate was estimated to be somewhere between 30 to 1 and 100 to 1.

Authors found that in the amniotic fluid and vagina the most common organism were Escherichia coli, streptococcus faecalis, staphylococcus aureus and Beta hemolytic streptococci. The earliest indications of septicaemia were lethargy, poor feeding and vasomotor instability. The above mentioned features could as well be the manifestations of non-infectious disease process.
such as anaemia, hypovolumia, shock metabolic disturbance, viz., hypoglycaemia, acidosis, hypernatremia.

Regarding the laboratory findings authors found that diagnosis of neonatal septicaemia was ultimately based on positive blood culture. Leukopaenia (≤4000 WBC/cubic mm) or leukocytes (≥25000 WBC/cu mm) supported the diagnosis of septicaemia. A depression in platelet count (≤1.5 lac/cu mm) also, supported the diagnosis.

Davies et al (1971) from their study on bacterial infection in the fetus and newborn observed that increase in immature forms (band forms) and total neutrophil counts suggest bacterial infection. Authors also found that very ill and dying infants frequently had marked neutropenia.

Xanthau et al in 1972 studied the leukocyte picture in ill newborn babies. Authors did serial blood leukocyte counts in 35 ill preterm and term infants. They observed that there was an increase in absolute count of polymorphonuclear neutrophil in proven or suspected bacterial infection cases. Absolute count of immature neutrophils also increased significantly but in very ill patient there was a significant fall in polymorphonuclear neutrophils (below 1000/mm³). Authors found that there was an increase in the ratio of band
forms to neutrophils in all cases and in some the proportion of band forms was as high as 90%.

Authors opined that increase in number of band cells in sepsis as presumably due to increased bone marrow activity and possibly also due to the displacement of granulocytes from marginal layer of vessels. The abrupt disappearance of neutrophils from the blood in overwhelming infections was explained by the fact that leukocytes have a short half life of only 6-7 hours, because of massive removal of injured cells, presumably by lungs. They concluded that detection of band forms was an important evidence of neonatal sepsicaemia.

Gregory et al in 1972 decided to challenge the assumption that white cell count lacked diagnostic value. Authors did serial white blood cell counts and observed severe neutropaenia in 3 cases who died of overwhelming infection. However, a significant early rise was observed in absolute polymorphonuclear neutrophil count in 9 out of 11 cases of sepsicaemia. In more than 90% of healthy babies the neutrophil count was within the range, 1350 to 8840 cell/cu mm. Counts outside this range almost always occurred during serious bacterial infection.

Haider et al in 1972 observed that in 80% of newborns, polymorphonuclear neutrophil count was below 7000/cu mm. The count in neonates with bacterial infection was found to be higher than the normal.
Franciosi et al in 1972 tried to evaluate the single blood culture strategy in a neonate to diagnose neonatal septicaemia. In a retrospective study of 366 neonates that they conducted, blood was cultured. The study revealed that 56 infants had positive blood culture, out of which 28 neonates were considered to have septicaemia. Eighteen out of 28 neonates with septicaemia were born prematurely and others had prolonged rupture of membranes necessitating endotracheal intubation etc. Staphylococci coagulase negative and gram positive rods of carnyp-bacterium species were the most common contaminants in blood culture.

Akensua et al in 1974 in their study assessed the value of neutrophils and band cells in the diagnosis of infection on the first day of life. Authors did serial total and differential leukocyte counts, estimated absolute number of neutrophils and band forms in the blood. They observed that neonates with confirmed infection had band cell count higher than the range for normal newborn infants. They found that absolute number of neutrophils was an unsatisfactory index of infection on the first day of life.

Wilson et al (1974) in their review article wrote that 'sepsis neonatorum' referred to a bacterial disease of infants occurring during the first 30 days of life which involved primarily the blood stream and
frequently the meninges. Prior to 1940, predominant organism causing neonatal sepsis was group A Beta hemolyticus streptococcus. But, during the past 3-5 years there had occurred a steady increase in the proportion of sepsis neonatorum caused by group B streptococcus haemolyticus. Group B streptococcus disease was present in two forms, 'early onset disease' and 'late onset disease'. The average annual rate of sepsis neonatorum in a modern North American hospital was found to be approximately 1 per 1000 live births, but the risk to premature infants was more i.e., 1 per 230 premature births.

In 1975 Adler et al modified the micro ESR tube and called it mini ESR tube. Author studied neonates with probable and proven sepsis and compared them with non-infected neonates. He used a standard 75 mm heparinized micro-hematocrit tube with an internal diameter of 1.1 and 1.2 mm. They observed that 3 after the every eight patients with suspected sepsis had elevated mini ESR's on the day the infection was first suspected. The mini ESR returned to within normal limits with clinical improvement in 5 out of 8 patients. Authors found that mini ESR test was a useful adjunct in the diagnosis of neonatal sepsis.

Some et al in 1976 in their study of 725 cases of sepsis revealed that progressive abdominal
distension, refusal of feeds, pallor, drowsiness, with
definite focus of sepsis almost formed the guideline
to diagnose neonatal septicaemia. Authors found that
ratio between Gram positive and Gram negative bacteria
causing septicaemia was roughly 1 : 2. Staphylococcus
aureus remained the most common among Gram positive
organisms. E. coli appeared to be the commonest among
Gram negative bacteria followed by others viz., coliform,
pseudomonas and proteus.

Murder et al in 1976 studied cases of necrotising
enterocolitis (NEC). They observed that about half of
the patients of NEC had absolute granulocyte count less
than 1500/mm$^3$ and mean absolute granulocyte count was
significantly lower in the group of infants who died in
the acute phase. About 80% of patients had platelet
count less than 1,50,000/cu mm. Authors concluded that
low absolute granulocyte count in severe NEC was associated
with poor prognosis.

Zipursky et al in 1976 studied a series of
premature infants for the presence of septicaemia on
the basis of clinical evidence and bacteriological
studies. He divided cases into three groups: definitely
septicemic, possibly septicemic, unlikely to have
septicemia. He observed that band neutrophil count
was elevated most frequently in 'sepsis proven' group
and the elevation occurred usually within 24 hours of
the onset of disease. Authors concluded that the elevation of 'band cell count' above the normal range was a valuable laboratory sign in premature infants in whom sepsis was suspected.

Manroe et al in 1977 studied the usefulness of differential white counts in distinguishing early onset group B streptococcal disease from other causes of neonatal respiratory distress. It was found that absolute immature (band) neutrophils was elevated in 42% of cases and 91% had an abnormal immature neutrophil versus total neutrophil ratio. Moreover, authors opined that differential white cell count appeared to be useful tool for screening infants presenting with respiratory distress, in the first 48 hour of life and for separating early onset Group B streptococcal disease from other causes of neonatal respiratory distress.

Guha et al in 1978 studied cases admitted with clinical diagnosis of neonatal septicaemia. It was observed that blood culture was positive in 10.89% of total cases admitted in the nursery, and 40% of cases had blood culture positive with suspicion of septicaemia. The incidence of meningitis associated with septicaemia was 14%. Gram negative septicaemia was more common (72.2%) as compared to Gram positive septicaemia (27.8%). The mortality in septicaemia increased with a decrease in birth weight. The overall mortality in their study was 24.3%.
Boyle et al in 1978 did a prospective study of babies suffering from respiratory distress. They observed subjects during the first 24 hours of life. The following significant differences between septic and non-septic groups were observed: leucocyte count 6370 ± 1140/cu mm in septic cases as compared to 16,020 ± 710 cell/cu mm in non-septic cases; absolute neutrophil count (band plus PMN cells) 2820 ± 1220/cu mm in septic infant as compared to 9100 ± 620/cu mm in non-septic infants. Elevated band forms/total neutrophil ratio was 0.30 ± 0.09 in septic infants as compared to 0.14 ± 0.01 in non-septic infants. Authors wrote that absolute leukopenia or neutropenia was a simple and reliable indicator to identify early cases of sepsis in infants who have respiratory distress in the first few hours of life.

In 1979 Monroe et al observed neonatal blood cell count in 585 normal neonates and 320 neonates who had perinatal complications. Authors developed reference ranges for absolute total neutrophils/cu mm, absolute immature neutrophil /cu mm and the fraction of immature to total neutrophils during the first 28 days of life. They observed that neutropenia with the presence of respiratory distress in first 72 hours had 86% likelihood of predicting bacterial disease, whereas neutropenia in the presence of asphyxia had only 68% likelihood of having the bacterial disease. An abnormal proportion
of absolute immature neutrophils/mm$^3$ and the fraction of immature to total neutrophils had an accuracy of 82% and 61% respectively, in the same clinical setting.

Christensen et al in 1979 reported that white blood cell counts from vigorously crying babies could show leukocytosis and a 'shift to left' which could erroneously suggest bacterial infection.

Squire et al in 1979 studied consecutively newborn autopsy cases divided into infected and non-infected groups on the basis of pathologic findings and cultures, and compared them to a concomitant and consecutive group of neonatal survivors with proven bacterial sepsis. Authors observed that neonates dying of overwhelming infection often demonstrated leukopenia, neutropenia and thrombocytopenia. Neonates with non-fatal sepsis frequently had neutrophilia with an increase in absolute band count. In sepsis proven neonates, 81% had one or more haematologic abnormalities like those in 43% of newborns dying without bacterial infection.

Philips et al in 1980 tried a group of tests to assess their usefulness either singly or in combination, for predicting early neonatal sepsis. The five most useful tests (with definitions of abnormality) were band/total neutrophils (≥ 0.2); leukocyte count (≥ 3000/cu mm); latex C-reactive protein (positive ≥ 0.9 mg/100 ml); WBC (≥ 15 mm for first hour);
latex hepatoglobulin (positive $\geq$ 25 mg/100 ml). On application of these tests, authors observed that 93% proven cases, as compared to 8% non-proven cases of septicaemia had two or more abnormal tests. They opined that combination of leukopenia and elevated band/total neutrophil ratio in particular, had a predictive value in sepsis, when it was less than two.

Parida et al in 1980 used standard haematocrit capillary tube to obtain normal values from neonates and to test the usefulness of micro ESR as an indicator of neonatal septicaemia. Authors divided the cases into two groups: definitely infected (Group I) having positive blood, CSF or urine culture; probably infected (Group II) having clinical signs of poor feeding, sluggish reflexes, distension, vomiting, pustules, diarrhoea, sclerema, bleeding tendency, respiratory distress. Authors observed that 71.4% of definitely infected cases and 24% of probably infected cases had elevated values of ESR ($\geq$ 8 mm in 1st hour).

Christensen et al in 1980 in order to determine whether neutropenia signalled neutrophil supply exhaustion in infected infants, examined the marrow of nine living infants and six infants who had died from sepsis. Authors found that two infected neutropenic infants, who had normal neutrophil storage pool (ESP), survived. Seven other neonates who had diminished neutrophil storage (ESP)
and those with the most profound depletion of NSP died. Authors concluded that neutropenia in infected infants frequently reflect neutrophil storage pool depletion. Authors suggested that infants with neutrophil storage pool depletion could be prognosticated as poor.

Freedman et al in 1981 published their 50 years observational study regarding the changes in pattern of neonatal bacterial infection. They wrote that during the past 50 years their ability to diagnose and treat sepsis in the newborn had improved markedly. In the earliest series, organism responsible for neonatal septicaemia were predominantly Gram positive bacteria primarily B hemolyticus streptococci. Later Gram negative enteric bacilli emerged as the major neonatal pathogen. The overall mortality of infants with documented septicaemia during 50 years study was 26%.

Siegel et al (1981) in a review article wrote that in the 1970’s the group B streptococcus was the predominant pathogen in most North American nurseries. Approximately 60% cases of septicaemia were attributed to this organism and E.coli. Vertical transmission of group B streptococci from mother to infant during delivery was more common than the horizontal transmission. An infant born to a woman with infected amniotic fluid had 5% chances of becoming infected. The risk was greater if gestation was less than 34 weeks or if the membranes
had ruptured for more than 24 hours. Many indirect indicators of bacterial infections were evaluated. Authors opined that peripheral white cell count was most reliable of these tests. An absolute neutrophil count outside the normal range, as defined by Manroe et al (1979) in their study, and a ratio of immature to total neutrophils higher than 0.14 indicated bacterial infection.

Philips et al in 1981 evaluated the use of antibiotics in cases of suspected septicaemia, by using 'sepsis screen'. The principal risk factors were prolonged rupture of membranes (>24 hr.), evidence of maternal infection, and premature labour without adequate explanation. The principal clinical factors were lethargy, temperature instability, abdominal distension, unexplained apnea or cyanotic spells and irritability. Sepsis screen constituted five items, viz., (1) total leukocyte count less than 5000/mm\(^3\), (2) non-segmented (Bands) neutrophil to total neutrophils ratio (N/N ratio) of > 0.2, (3) latex C-Reactive protein, (4) latex hepatoglobulin, (5) mini ESR > 15 mm in 1st hr. When two of the five items were present, the screen was considered positive for septicaemia, whereas presence of one or no item was designated negative. Authors observed that 3 babies with proven sepsis and 5 babies with very probable infection were not detected by sepsis screen. But for the rest sepsis screen was significant.
Christensen et al (1981) examined blood and bone marrow samples in groups of non-infected and infected neonatal dogs and human beings in order to determine which screening method vis., absolute band count, band/segmented neutrophil ratio, band/total neutrophil ratio, and immature/total neutrophil ratio, most clearly reflected an increase call upon bone marrow neutrophil reserves and which correlates best with the presence and severity of infection. They found that the neutrophil ratio (B/N ratio) was more frequently abnormal during neonatal sepsis than was the absolute band cell count. All subjects in whom the immature (Band)/ total neutrophil ratio exceeded 0.8 were found to have depletion of the marrow neutrophil reserves and those with the most profound depletion, died. Their study supported the concept that an elevated immature to total neutrophil ratio could aid in the diagnosis of bacterial infection in newborn infants and suggested that the degree of elevation could serve as a method for detecting subjects at high risk for depletion of the marrow neutrophils reserves and death from septicaemia.

Farida et al in 1982 evaluated cases of suspected septicaemia and proven cases of septicaemia. They did total leukocyte count, calculated percentage neutrophils and Band cells. They found in their study that leukocytosis was present in 25% of both the groups and
percentage of neutrophils did not vary significantly (30% and 33%) in either group. Fifty percent of neonates with proven sepsis and 25% of neonates with suspected sepsis had elevated band counts respectively. The predictive value of elevated band count and simplicity of the test justified its routine use in early diagnosis of neonatal septicaemia.

Placsek et al in 1983 in their four year study among 1000 cases of septicaemia found that 65 infants had positive blood cultures. Mortality was 70% among 17 infants who had septicaemia in the first 48 hours of life and for whom appropriate treatment had been given too late because of the difficulty in early diagnosis. In the remaining 48 infants mortality was 12%. Septicaemia occurred later, and was associated with staphylococcus epidermidis (56%) and with the presence of an intra-vascular catheter (50%).

Benuck et al in 1983 tried to test the sensitivity of already published neutrophil indexes in diagnosing neonatal septicaemia. The indexes (Absolute neutrophil count, immature neutrophil count and immature to total neutrophil ratio) were determined using automatic leukocyte counts and manual differential cell counts. The purpose of their report was to apply published criteria for leukocyte indexes, especially those of Monroe et al (1979) to determine the sensitivity of
these screening test when performed by a routine clinical laboratory. According to criteria of Manroe et al (1979) about 94% of cases were identified using three separate indexes. Majority of infected infants had two abnormal indexes. It was observed that pre-term infant, with abnormal leukocyte count, was more likely to have neutropenia as compared to term infant.

Harris et al in 1983 published in their review that over the past four decades there have been several shifts in the predominant organisms responsible for neonatal septicaemia and meningitis. "Group B streptococcal and gram-negative enteric bacteria were presently the most common etiologic agents", opined the authors. Anaerobic bacteria were also increasingly recognized as causative agents, as suggested by the authors.

Namdeo et al in 1985 studied the clinico-bacterio-hematological profile of neonates with septicaemia in order to evaluate the hematological indices for early diagnosis of neonatal septicaemia. Authors observed that 50% cases were bacteriologically positive and 50% cases were bacteriologically negative. Out of 50% positive cases, blood culture was positive in 96% cases and CSF culture was positive in 16% of cases. Haematological indices viz., leukopenia; Band/total neutrophil ratio "equal to or more than 0.3"; neutrophil with toxic granulations in more than 40%; mini ESR more than 8 mm
were found to be particularly predictive of septicaemia with a specificity of 98% and positive predictive accuracy of 89% as observed by authors. Authors opined that if more than one of the four tests were positive, they became more sensitive and sufficiently specific.

Mishra et al in 1985 worked on 120 cases of neonatal septicaemia and revealed that jaundice, refusal of feed, vomiting and lethargy were common manifestation of septicaemia. Whereas, sclerema, apnea and hypothermia and abdominal distension were associated with high mortality. Mortality was 71% in Gram negative infection in comparison to 49% seen in Gram positive infection. Incidence of Gram negative infection was higher in babies under 2000 gm of birth weight. Common bacteria isolated were E.coli, Pseudomonas and staph.pyogenes and mortality was highest (76%) in Pseudomonas infection.

Khatua et al in 1986 in their study of 92 consecutive cases of neonatal septicaemia found the incidence of clinical and bacteriological positive septicaemia in 10.97 and 6.55 per 1000 live births, respectively. Blood culture was positive in 59.6% cases, of which 76.3% showed Gram-negative organisms like Klebsiella, E.coli, Citro-bacter, P. aeruginosa and 23.7% Gram positive organisms, predominantly staphylococci and streptococci. As many as 68.5% cases had rupture of membranes more than 24 hours before the delivery and 70%
cases developed septicaemia within 5 days. Refusal of feeds, lethargy, diarrhoea, hypothermia, abdominal distension and jaundice were the major presenting features. Respiratory distress, apnoic spells, convulsions, sclerema were bad prognostic features. All cases were resistant to ampicillin. The overall mortality was 57.6%. Male sex, prematurity, low birth weight and Gram negative infection were associated with higher incidence and mortality.

Koshi et al in 1986 opined that for blood culture, proportion of blood to liquid medium should be 1 : 10. In infants and children, the volume should be about 1 to 5 ml. Adequate results could be obtained with 1 ml of venous blood. Blood should be collected at onset of fever, as the bacteremia preceded as much as 30 minutes to 1 hour before the onset of fever and chills. A single culture was usually adequate in neonates, as they have on average a higher blood concentration of organisms, when infected.

Monga et al in 1986 observed that incidence of neonatal septicaemia was 26.3%. Gram negative organisms were isolated in the majority of blood cultures (43.3%) in their study. Authors opined that Klebsiella though showing a fall in the incidence, still remained the commonest Gram-negative organism isolated.
Sinha et al in 1986 studied cases of septicaemia in neonatal and early infancy period. He conducted detailed clinico-pathological study in 82 bacteriologically confirmed cases of septicaemia. There were 55 neonates and 27 cases of early infancy. Male babies with low birth weight were predominant (64.9%). The bacteriological study of blood revealed pure Gram-negative bacilli causing septicaemia in 86.6% of the cases. P. aerogenosa was the most common infecting organism followed by Klebsiella and E. coli.

Singh et al in 1987 evaluated 'sepsis screen' in the diagnosis of neonatal septicaemia. Sepsis screen consisted of micro ESR, gastric aspirate for polymorph, absolute neutrophil count, Band neutrophil to absolute neutrophil ratio, C-Reactive protein (CRP). Authors observed that CRP was the most sensitive (80%) and specific (91%) test. The combination of any two or more positive tests was found sensitive in 88% of cases and specific in 89.6% cases. Even if CRP was excluded from the sepsis screen the sensitivity of two or more positive test in the diagnosis of septicaemia was 83%.

Chandha et al in 1989 studied 50 clinically suspected cases of septicaemia. Blood culture was positive in 45% cases among whom Gram negative bacilli predominated (71%). C-Reactive protein test, total leukocyte count, ratio of Band cells to total poly-
morphonuclear cells, buffy coat smear examination for organisms and gastric aspirate cytology for polymorph percentage were the rapid diagnostic tests performed by authors. They revealed that CRP was the most useful single test with a high degree of sensitivity (83%) and specificity (42%) with a positive predictive accuracy of 57%. The best combination of tests were CRP and gastric aspirate cytology with a sensitivity of 83%, specificity 76% and positive predictive accuracy of 48%.

Mishra et al in 1989 conducted simple haematological tests: TLC, DLC, mESR, platelet count in 128 neonates of which 50 were controls and 78 were cases of suspected septicaemia. Thirty three had positive blood cultures and were taken as 'proved' and the remaining as 'probable sepsis'. A Band cell neutrophil (B/N) ratio of > 0.2 was most sensitive index (92%), followed by raised mESR of > 78 mm for 1st hour, whereas Leukopenia of < 75 x 10³/mm³ was the most specific index for the diagnosis of sepsis. Thrombocytopenia of < 1.5 x 10³ cells/cu mm was taken as positive test for sepsis. A combination of three positive tests had the highest positive predictive accuracy (94%) for early diagnosis of sepsis, when compared to single test or two positive test combinations. The best combination of tests was B/N ratio, leukopenia and mESR which could be done easily in a side laboratory.
Anand et al (1991) studied coagulase negative staphylococcus (C-NS) positive blood culture cases. Authors observed that out of 2177 cases 34% neonates yielded C-NS in blood cultures. Of these, 27% infants had clinical and haematological features compatible with the diagnosis of septicaemia, remaining cases with positive blood culture had no evidence of sepsis. These cases were designated as "C-NS bacteremia". They found that more than two thirds cases were premature and of low birth weight. Prominent clinical features included lethargy, poor feeding and fever. Apneic spells were seen in babies weighing less than 1.5 kg. Overall mortality in C-NS sepsis was 17.24%, distinctly higher in neonates with RDS and those requiring mechanical ventilation.

Singh et al in 1992, in order to find out incidence of bacteremia and serious bacterial infections in febrile children without an apparent focus of infection, studied prospectively 100 febrile children with rectal temperature $> 39^\circ$C. Authors found that 10 children were blood culture positive, 9 cases had serology positive for bacteremia, 6 had urinary tract infection, 5 otitis media and 8 meningitis. A diagnosis of non-bacterial illness was made in 62 patients. Staphylococcus aureus was the most common bacteriologic isolate on blood culture. TLC $> 15,000$/cu mm, mESR $> 25$ mm and temperature $> 39^\circ$C had high specificity (95-100%) but low sensitivity for the diagnosis of bacteremia.