REVIEW OF LITERATURE
Asphyxia is an insult to the foetus or newborn due to lack of oxygen (hypoxia) and or lack of perfusion (Ischemia) to various organs. The effect of hypoxia and ischemia may not be identical, but they can be difficult to separate clinically. Both factors probably contribute to asphyxial injury.

Asphyxia is a major contributory factor for still birth and perinatal deaths. Studies in human to assess the long term effect of asphyxia has been inconclusive, largely because of the difficulty of separating asphyxia from other adverse influences which may operate during labour and affect subsequent outcome.

Boyle (1970) established that the ability of animal to survive in an environment free of oxygen varies with age, younger and more immature the infants is, greater is the tolerance to total deprivation of oxygen. This increased resistance of the foetus to anoxia has been related to the adequacy of cardiac glycogen stores and possibly to additional source of energy to foetal tissue.

Adaptive mechanisms to withstand anoxia possessed by foetus may be overcome if the hypoxic insult is sufficiently severe. In foetal monkey it is known that neurological damage occurs after about 15 minutes of asphyxia, in humans the critical period can only be
surmised, as hypoxia at birth is so often continuation of intrauterine hypoxia of unknown duration.

The general consensus is that the redistribution and preferential routing of oxygenated blood to the upper body via foramen ovale are two mechanisms which place foetal heart and brain in a privileged position with respect to the arterial supply of oxygen (Born et al., 1954). However, the quantitative question concerning the effectiveness and limitations of the mechanisms remain to be answered. The cardiac output redistribution which has been observed experimentally has not been compared with theoretic requirement of preventing a decrease in the supply of oxygen to heart and brain. Therefore, it is not clear whether the foetal circulation response to hypoxia is an effective defence process and at what level of oxygenation it may become adequate. The difference of oxygen content between the blood that perfuses the upper and lower body has not been measured in chronic animal preparations or related to oxygen availability.

Asphyxia at birth may result from or be associated with many conditions. The mechanism of intrauterine or birth asphyxia common to these may be appreciated from a consideration of placental transfer of oxygen from mother to foetus and this initiation and maintenance of respiration at birth. The human placenta is haemochorial in type. Foetal capillaries come into direct relationship with a pool of maternal blood thereby creating a large interface
for exchange of oxygen and carbon dioxide.

The duration of foetal hypoxia is equally important. Studies in foetal monkey have demonstrated that total neuropathologic state (Ranck, 1959). However, partial hypoxia with metabolic acidosis must be present at least 2 hours before neuropathologic damage can be anticipated. A precise measure of the duration of foetal asphyxia in the human foetus is generally not available because of the periodic nature of foetal blood gas and acid base assessment and the intervention that abnormal blood gas and acid base measurements now require. However, the importance of duration of foetal asphyxia was implied in a study of 60 children with biochemical evidence of intrapartum foetal asphyxia at delivery. Children with deficits had an episode of asphyxia that was more severe and prolonged than the children with normal motor and cognitive development.

Bartels et al (1962) have shown schematic representation of foetal and maternal circulation within the uterus. They demonstrated that oxygen tension in foetal blood is very much lower than that of maternal or uterine venous blood. Formerly it was postulated that resistance to the diffusion of oxygen in the placenta was responsible for this large discrepancy. Later experimental work suggests, however, that there is little barrier to diffusion in the placenta and that the large fall in oxygen tension from 90-100 mm Hg in maternal arterial
blood to around 28 mm Hg in umbilical venous blood is explained by the level that the placenta itself consumes a great deal of oxygen. Uneven distribution of maternal and foetal placental blood flow to the site of gaseous exchange may also be important. The oxygen tension of umbilical venous blood led to the suggestion that the foetus lives under condition of oxygen deficiency comparable to a climber at altitudes around 18000 to 21000 feet. The apparent disadvantage of a low PO₂ is partially offset, however, by the high oxygen capacity of foetal blood and the Bohr Effect, thereby incompletely saturated hemoglobin binds less oxygen in an acid environment than in a basic one. The latter effect facilitates oxygen transfer from maternal to foetal blood and increases the delivery of oxygen to foetal tissues. The difference in oxygen affinity between maternal and foetal blood in later pregnancy is a relatively less important factor favouring oxygen transport from mother to foetus in utero. Although the precise oxygen requirements of foetus in utero are uncertain it seems that under normal circumstances foetal oxygen supply is far from precarious and the foetus can withstand stresses such as severe anaemia in erythroblastosis fetalis. Intrauterine hypoxia could result from a decrease in amount of oxygen reaching the site of gaseous exchange (low maternal arterial PO₂ or O₂ content, impaired uterine blood flow) limitation of the area available for gaseous exchange, imbalance between maternal and umbilical blood flow within the placenta,
reduced oxygen carrying capacity of foetal blood or decreased tissue utilization of oxygen. Several of these factors may act concurrently.

Whenever, arterial oxygen content decreases, the oxygen supply to every organ to the body tend to decrease also. Guyon et al. (1964) have emphasized the concept that the circulatory system can compensate for this effect of hypoxia by increasing cardiac output. An optimal compensation would require that the product of blood flow arterial oxygen content be kept virtually constant in each region of the body.

An increase in cardiac output concomitant with hypoxia has been described in adult animals and under certain experimental conditions. According to Guyton et al (1964) this increase in cardiac output has not been a consistent finding and its magnitude has been less than that required to hold constant O₂ supply to the entire system. There is general agreement that an increase in cardiac output does not play a significant role in the response of the ovine foetal hypoxia, probably because normal foetal cardiac output is already at a relatively high level. During hypoxia foetus attempts to preserve the arterial supply of oxygen to three regions of the body only namely heart, CNS, and adrenal. Of these adrenal requirement is small and can be neglected. However, as the arterial oxygen content decreases, the blood flow necessary to maintain the supply of oxygen to the heart and CNS
increases hyperbolically and become a large fraction of cardiac output.

During vaginal delivery there is diminished gaseous exchange across the placenta (Kubli and Berg, 1965). They observed acid base data during labour and at the time of delivery of vigorous healthy babies and asphyxiated depressed babies. Oxygen saturation was remarkably low in both normal and depressed infants. They further demonstrated that pH was the main indicator of severity of asphyxia and the low pH in severely depressed infants represented both respiratory and metabolic acidosis.

The percent of umbilical blood flow going through the ductus venosus increased with foetal distress at a time when the umbilical blood flow was decreasing. A sphincter at the junction of the umbilical vein with the ductus venosus has been described in sheep and humans. Although there is conflicting evidence about the role of such a sphincter in modifying blood flow through the ductus venosus (Peltonon and co-workers, 1965 and Lind et al, 1966). More recently, nerve fibres from the anterior and posterior vagal trunks have been described passing to a thickening of muscular wall in the region of the junction of umbilical vein with the ductus venosus and to the proximal portion of umbilical vein. No nerve fibres were traced to the wall of the ductus venosus itself. If the thickening is a sphincter like mechanism involving part of the proximal
end of the umbilical vein innervated by vagal and celiac plexes fibres as the evidence would seem to indicate, afferent and autonomic fibres of both sympathetic and parasympathetic function are probably also involved. According to Rudolf et al (1967), the blood flow to the gastrointestinal tract, kidney, spleen, liver (hepatic artery) in the primate in general, is slightly lower than those reported in sheep. They observed no significant change in the blood flow to these organs with foetal distress.

Successful respiratory adaptation in the transition period between foetus and newly born is crucial to extraterine survival. As gestation progresses, movements of foetal thorax are increasingly difficult to elicit, presumably because of mechanisms which limit the effectiveness in stimulating respiration by sensory and chemical changes in utero. At birth, medullary respiratory neurons are flooded by new sensory impulses, exteroceptive (pain, touch, temperature), proprioceptive (muscle tension, joint) and afferent baroreceptive following clamping of umbilical cord. The activities of respiratory neurons result in rhythmic phrenic and intercostal discharge impulses and increases sympathetic activity. It has been proposed by Purves (1964) that increased sympathetic activity activates the peripheral chemoreceptors which in turn become involved in the regulation of respiration. Successful adaptation presupposes that the lungs can expand and become
functionally competent soon after birth in the absence of gross neurological or cardiovascular defects.

In the study of Herbert et al (1974), it was not possible to separate various factors which produce the vascular responses observed. The changes could be the result of direct local effects of hypoxemia and acidemia, increased autonomic nervous system activity and secretion of catecholamines and possibly the liberation of other vasoactive substances. Since maturation in the foetus of parasympathetic and alpha and beta sympathetic regulation is variable (Vapaavouri et al, 1973) it is possible that autonomic responses to hypoxemia may differ between species as well as with gestational development. There is also suggestive evidence that the adrenal gland secretes norepinephrine in the younger foetuses and a mixture of norepinephrine and epinephrine in later gestation.

Herbert et al (1974) showed that the foetal arterial blood pressure increased in response to maternal hypoxia, and this was particularly significant in the foetuses which developed hypoxemia and acidemia. Since combined ventricular output either did not change or fell, the hypertensive response was related to increased peripheral resistance. The vascular systems that participated in producing this increased resistance were those of the carcose, gut, kidney, spleen and to some extent the lung. Although the umbilical placental correlation has been
thought to be relatively unresponsive to the degree of hypoxemia produced in foetuses, the fact that the systemic arterial blood pressure increased consistently and umbilical flow did not change significantly suggests that there was some degree of umbilical placental vascular constriction. Although foetal central venous pressure did not increase during the hypoxemic period, the workers of the study did not know whether umbilical venous pressure increased or not as it was not measured. It is possible that the apparent increase in umbilical placental vascular resistance could be related to an increase in umbilical venous pressure, possibly associated with increased impidance in the ductus venosus or hepatic portal circulation.

Foetal adaptation to hypoxemia was accomplished predominantly by redistribution of combined ventricular output in order to maintain blood flow to vital organs such as placenta, heart, brain and adrenal glands, while flow to other organs, the skin, the musculoskeletal system, decreased. Further more the magnitude of the change of flow in the organs could have been influenced by the experimental manipulations such as anaesthesia and acute surgical stress. Thus it is apparent that the foetal circulatory responses to hypoxemia may be influenced not only by gestational maturation but also by mechanism of production of hypoxemia.

The same findings were observed by Cohn et al
(1974) who observed that the foetal response to hypoxemia is the key to the effect of the degree and duration of foetal asphyxia. Foetal hypoxemia results in an increase in arterial pressure due to increased vascular resistance. This is associated with redistribution of cardiac output characterised by reduced blood flow to the pulmonary, gastrointestinal circulation and the body with increased blood to the heart, brain and adrenal glands. However, the magnitude of the circulatory adjustment which is required by a certain level of oxygenation can be understood more clearly by focussing attention on arterial oxygen content.

The degree of asphyxia is relevant in regard to outcome. Neuropathologic findings in the foetal monkey in response to total anoxia were different from those after partial asphyxia (Myers, 1975). The human foetus in the clinical setting may develop a significant degree of metabolic acidosis because of severe hypoxemia acting over a short period or milder degree of asphyxia acting over a longer period.

According to Peeters and associates (1979) during moderate hypoxia, the blood flow to parts of the foetus like kidneys may also increase to some extent. Nevertheless the experimental points agree with the concept that the circulatory response of the foetus to hypoxia is centered on the requirement of maintaining a constant flow of oxygen to the heart and CNS without any
marked increase of cardiac output.

Each cardiac output is subdivided into four main sections. 1. Placental flow, 2. Lung flow, 3. Flow to CNS, and 4. Flow to the remainder of the body. These sections correspond closely to the four groups of tissues that respond differently to oxygen variability (Peeters et al, 1979). They found that the most consistent change of cardiac output distribution was the reciprocal relationship between oxygen content in ascending aorta and percentage of cardiac output directed to heart and CNS. They found lack of sufficient association between cardiac output and oxygen and suggested that there should be a reciprocal relationship between blood flow to other parts of body.

In agreement with this suggestion there will be a significant negative correlation between blood flow to the CNS and heart and blood flow to the rest of foetal body.

Umbilical placental blood flow is maintained when foetal hypoxia is a result of maternal hypoxemia or reduced maternal uteroplacental blood flow (Parer, 1980).

Foetal hypoxia due to cord occlusion is associated with decreased umbilical placental blood flow. However, blood flow to the central circulation is maintained through the ductus venosus with a marked reduction of blood flow through the liver (Isskowitz and co-workers, 1982).
The autonomic nervous system is principally responsible for the increased vascular resistance and redistribution of cardiac output. There is evidence to indicate that the response is initiated through arterial chemoreceptors and may be influenced by circulating endogenous opiates (La Gamma, 1982). Other factors may include increased angiotensin activity and release of vasopressive (Start et al, 1982).

The target organs of perinatal asphyxia are the brain, heart, lung, kidney, liver, bowel and bone marrow. The most frequent abnormalities involved the kidney (50 percent), followed by the CNS (28 percent), cardiovascular (25 percent) and pulmonary (23 percent) systems. Often asphyxiated infants will succumb to dysfunctions of organs other than CNS (persistent foetal circulation) while showing minimal evidence of hypoxic ischemic brain injury. In such instances brain was spared at the expense of cardiac output to the affected organ (Brann, 1986). The degree of asphyxia required to cause permanent neurological impairment is just below that which is lethal from multi-system failure (Freeman et al, 1988).

The liver may be so damaged (shock liver) that it may not provide its basic functions. In such cases, liver function tests (transaminases SGOT, SGPT) clotting factors (PT, PTT, fibrinogen), albumin and bilirubin should be monitored. If total liver failure occurs it is a usually a bad prognostic sign. Otherwise, the cardiac, renal,
gastrointestinal, pulmonary, hepatic and haematological problems usually resolve if the infant survives.

In recent study of asphyxiated newborns by Perlman (1989), 24 percent had no evidence of organ injury, 23 percent had an abnormality confined to one organ, 34 percent involved two organs and 9 percent affected three organs.

Saili et al (1989) studied 46 full term neonates. Out of them, 31 neonates had suffered from severe birth asphyxia. They found in their study that liver was damaged as a result of perinatal asphyxia leading to increase in transaminase levels in serum. These levels were significantly higher in neonates who died due to asphyxia as compared to the one who survived.

**LIVER FUNCTIONS AND SERUM ENZYMES**

Clinician first became interested in serum enzymes more than 40 years ago when the role of alkaline phosphatase in the diagnosis of hepatobiliary disease was reported (Roberts, 1933).

Enzymes are found inside cell, where they catalyse numerous biochemical reactions. Normally they enter the blood in small amounts, as a result of natural cell turn over and perhaps also by diffusion through undamaged cell membranes (Baron, 1964).

Elevated serum activity are invariably found in clinical states in association with extensive tissue necrosis. Raised serum enzyme activity however, do not
always indicate widespread cell death, since marked
elevation are commonly present in reversibly inflammatory

SERUM GLUTAMIC OXALOTRANSAMINASE (SGOT) AND
SERUM GLUTAMIC PYRUVIC TRANSAMINASE (SGPT)

General Consideration

The determination of the activity of SGOT offers
a simple and rapid laboratory test for establishing the
presence of acute hepatocellular damage or dysfunction.
This enzyme had a wide spread distribution in animal and
human tissues and is also present in normal serum and
plasma (Cohn et al, 1941, Awapera et al, 1952).

The widespread use of enzyme tests followed the
observation of Karmen Wrobelwski et al (1953), that
transaminase activity was present in serum of normal
individual and that raised activity may reflect injury,
not only to liver but also to other organs.

SGOT exist in two intracellular forms, one in
the cytosol and the other in mitochondria. Only one form
of SGPT is known and liver is by far its richest source.
The two isoenzymes of SGOT have been separated electro-
phoretically. The ratio of cytosol to mitochondrial enzyme
is said to be correlated well with the severity of liver
damage (Franchis et al, 1972). Higher activity of SGOT is
recorded in early life than there after and Kattwinkel
et al (1973) found the SGOT, unlike SGPT, to be age related
between the years of 4 and 30.
According to Felix Wroblewski (1959) the mean SGOT activity of serum of normal persons determined by the calorimetric technics is $16 \pm 3.0$ units, with a normal range of 4 to 40 units. While that of SGPT is $22 \pm 12$ unit, with a normal range of 1 to 45 units. In all instances the activity of SGOT in any one tissue is greater than that of SGPT. In the case of SGOT the greatest activity is observed in extracts of skeletal, diaphragm and heart muscle and liver tissue.

The activity due to transaminase in serum of adults, both in physiologic and pathologic states, had been well documented, little information relative to the behaviour of the enzyme in the newborn infant is available (Abelson, 1956).

Simon Kove et al (1957) determined the normal activity of SGOT in the serum in the early neonatal period and compared it with that of adult values. They measured activity of SGOT in serum of cord blood of nine newborns, forty six newborns between the age of 1-5 days and eight newborns between the age of 6-11 days. Infants were chosen randomly. Infants with physiological jaundice were included. They observed a range of 13-105 units of SGOT in the newborn period (with the exception of one infant in whom the level was 160 units). This is considerably wider range than that of 5-45 units found in normal adults and a value more than 45 units in adults is considered abnormal.
and raises a strong suspicion of the presence of some pathologic state. According to them the activity of SGOT was not related to the age of infant within neonatal period studied and varied widely in different infants for each day of age, without any distinctive pattern. Variations of the activity of SGOT in specimens of cord blood studied ranged below the 59 units, which was lower than for any other day of neonatal period adequately investigated. No relation was found between the concentration of bilirubin and the activity of SGOT in the serum of normal neonates.

A rise in serum transaminase activity occurs in most hepatocellular disorders. These tests are most sensitive indicators for liver cell damage. By contrast rise in transaminase is much less constant in chronic hepatocellular disorders. Less than one third of adult patients with well compensated cirrhosis for example, have increased SGOT activity (Fouk, 1964). The cells of several organs contribute the SGOT activity, because the liver is the prime source of SGPT, measurement of this enzyme is more specific for liver damage. Hence during viral hepatitis there is a proportionately greater rise in SGPT activity. This increases by 20 to 100 folds in more than ninety percent of patients, while in eighty percent SGPT rises by only about 10 to 20 folds. The ratio of SGPT : SGOT therefore is about 1.2, which falls during infective hepatitis to about 0.2 (De Ritis et al, 1972). Finally
SGOT and SGPT provides no clue to prognosis, in either acute or chronic liver disease, since they do not measure the extent of hepatocellular damage. In acute hepatocellular disease, the electrophoretic separation of the SGOT isoenzyme affords an indication of the severity of liver damage. In massive necrosis for example, large amounts of mitochondrial enzyme are released into circulation. Conversely because this isoenzyme has a short half life, its disappearance from the serum heralds recovery (Wilkinson, 1970).

**SGOT AND SGPT IN BIRTH ASPHYXIA**

In the presence of liver cell necrosis both the cytoplasmic and mitochondrial enzymes are increased (Isselbacher et al, 1983).

Fits Simons et al (1984) in their study reported an increase in SGOT in asphyxiated neonates while no significant increase was observed in the values of alkaline phosphatase.

According to Vincenzo Zanardo et al (1985) the serum activity of SGOT and SGPT is one of the most specific parameter of liver cell injury in adults and infants. The release of these enzyme from damaged tissues into the blood stream is the principal factor responsible for increased serum transaminase activity in the presence of hepatic cellular injury due to both cellular necrosis and reversible injuries of permeability of cellular or intracellular membranes. They showed that during perinatal hypoxia which
causes a reversible increase in cellular membrane permeability, there is a release into the blood stream of cytoplasmic enzymes (SGOT and SGPT). In the presence of liver cell necrosis both the cytoplasmic and mitochondrial enzymes are increased. In their study they examined the behaviour of SGOT and SGPT activity in full term and preterm newborns. The mean value of SGOT activity was 50 units/l and seemed to decrease over the first 30 days of life.

During first 72 hours of life in full term asphyxiated newborns there was a significant increase in mean SGOT activity as compared to full term healthy newborns (Mean±S.D. - 100±68.9 and 52±12.9 respectively; p < 0.01). Moreover, in full term asphyxiated newborns the mean values of SGOT activity were significantly higher than in preterm asphyxiated newborns (100±68.9, 59.2±29.1 respectively, p < 0.005) whereas there were no statistical difference between healthy full term and preterm newborns (52±12.9, 50.1±13.4 respectively), nor between healthy and asphyxiated preterm newborns (50.1±13.4, 59.2±29.1 respectively). Between 5th and 10th day of life in full term asphyxiated newborns the mean value of enzymatic SGOT activity decreased.

In healthy full term and preterm newborn, the mean value of SGPT serum activity was 25 U/l and was lower than in asphyxiated full term newborns, which was 54.5 U/l. During first 72 hours of life, in full term asphyxiated newborns there was a significant increase in the mean SGPT activity in comparison with healthy full term newborns.
(mean +SD = 54.5±54.4, 18±6.6 respectively, p < 0.025).

Moreover, in full term asphyxiated newborns the mean values of SGPT activity were significantly higher than in preterm asphyxiated newborn (54.5±54.4, 11.8±8.2 respectively, p < 0.0001), as well as in full term healthy newborn when compared with preterm healthy newborns (18±6.6, 11.1±5.8 respectively, p < 0.005). There was no significant difference between healthy and asphyxiated preterm newborns (11.1±5.8, 11.8±8.2 respectively).

Between 5th and the 10th day of life in full term asphyxiated newborns the mean values of SGPT remained significantly higher than in full term newborn, as well as in full term asphyxiated newborn in comparison with preterm asphyxiated newborns.

Saili et al (1988) studied liver function tests in 46 full term neonates. Out of this 31 infants had suffered severe birth asphyxia, while 15 normal babies formed the control group. They showed that liver function tests (SGOT and SGPT) were deranged in asphyxiated babies. According to them deranged levels of SGOT and SGPT were noted in 64.52% of asphyxiated babies. There was 60% mortality in asphyxiated babies with deranged liver function. The serum levels of transaminases in non survivors were significantly higher than those of survivors. The SGOT level among controls was in the range of 54.83±48.86 IU/l while in asphyxiated babies 97.84±119.42 IU/l. The SGPT level among controls was in the range of 22.4±32.96 IU/l while in asphyxiated babies in the range of
44.09±61.94 IU/l.

Therefore knowledge of behaviour of SGOT and SGPT activity may have important implication in the diagnosis and early treatment of perinatal asphyxia.

**ALKALINE PHOSPHATASE**

The name alkaline phosphatase applied to a group of enzymes which, acting optimally at alkaline pH, catalyse the hydrolysis of several organic phosphate ester with liberation of inorganic phosphate. The total serum alkaline phosphatase activity is the sum of various distinct tissue components which may be separated by electrophoresis. In the fasting individual both hepatic and intestinal isoenzymes are present, the latter enzyme is enhanced following ingestion of a lipid meal and is greater in individuals who are secretors of blood group B and O (Langman et al, 1966). A third fraction, of osseous origin, is present in the serum of children particularly. The relative proportion of this fraction in total alkaline phosphatase activity at different ages is important. Less significant amount of alkaline phosphatase activity is also present in kidney, leucocytes and neoplastic tissues.

Unlike the total alkaline phosphatase activity in adults, that recorded during childhood and adolescence is principally of osteoblastic activity and is, therefore, closely related to age. During periods of rapid skeletal growth relatively high activity is usual. Thus from birth
to 12 months of age. Clarke and Beck (1950) reported values up to 50 percent higher than the mean in the middle years of childhood.

Alkaline phosphatase activity closely mirrored the growth velocity. Round (1973) showed a significant alkaline phosphatase rise in boys of 10 to 14 years (p < 0.0005) which paralleled the adolescent growth spurt, a less obvious rise occurred in girls between 8 and 12 years (0.005 < p < 0.0001).

Within liver itself more than one form of alkaline phosphatase exists. In the rat for example, two iso-enzymes have been identified, one in the cytosol, the other bound to nuclear or microsomal membranes (Simons and Sutherland, 1973).

Total alkaline phosphatase is a nonspecific determination whose major contribution is derived from bone and liver. Therefore, its value in the differential diagnosis of infantile liver diseases is very limited (Mowat et al., 1976). Biliary obstruction, particularly if protracted, tend to be associated with high values, while in less prolonged biliary obstruction or in hepatocellular jaundice, only mild raised alkaline phosphatase activities are recorded (Backer and Stauffer, 1962).

**ALKALINE PHOSPHATASE IN BIRTH ANOXIA**

In clinical practice, total alkaline phosphatase lacks the sensitivity of a good screening test for liver
disease. In a group of children known to have hepatobiliary dysfunction, Belfield and Goldberg (1971) found that 27 percent had normal activity.

Clinically the increase in alkaline phosphatase activity is clearly not related to hepatocellular damage, since even total hepatic necrosis accounts for only about two folds rise (Ritt et al, 1969).

According to Sall et al (1989) there is rise in alkaline phosphatase in severely asphyxiated newborns. According to them serum alkaline phosphatase in asphyxiated group was $17.64\pm12.30$ KAU/dl as compared to $14.36\pm9.06$ KAU/dl in controls.

**SERUM BILIRUBIN**

Bilirubin in the blood is produced from the ferroporphyrin, haem, after removal of its iron component. Eighty percent is derived from haemoglobin breakdown by Kupffer cells in the liver and other macrophages in the spleen and liver.

Within the hepatic cell, bilirubin is conjugated to bilirubin glucuronide, Schmid (1956) and Billing et al (1957).

\[
\begin{align*}
2 \text{ UDP glucose } + 2 \text{ NAD } & \overset{\text{UDP glucose dehydrogenase}}{\rightarrow} 2 \text{ UDP glucoronic acid } + 2 \text{ NADH } + 2 \text{ H. } \\
2 \text{ UDP Glucoronic acid } + \text{ Bilirubin } & \overset{\text{UDP glucuronyl transferase}}{\rightarrow} \text{ Bilirubin diglucuronide } + 2 \text{ UDP. }
\end{align*}
\]
The serum bilirubin tends to be low in the fetal circulation and rises sharply in the newborn infant shortly after birth (Davidson et al, 1941). Since both UDP glucose dehydrogenase and UDP glucuronyl transferase are very low in fetal liver (Brown and Zuelzer, 1958) conjugation of bilirubin to its glucuronide cannot occur in the fetus at a normal rate. Therefore, the bilirubin must be removed from the fetal circulation by transfer across the placenta to the maternal circulation and eventually must be conjugated by the maternal liver and excreted in her bile.

In 1959, Schmid et al carried out preliminary investigations on the placental transfer of bilirubin in pregnant guinea pigs during last weeks of gestation. On the maternal side, a uterine vein was cannulated which permitted continuous sampling of venous blood from an individual placenta. On the fetal side, an umbilical artery was cannulated while the umbilical vein was served and the cord clamped proximal to the fetus.

As soon as the cord is cut, the fetus loses the placental mechanism for the removal of bilirubin through the maternal liver and bile. As a result there is a moderate accumulation of unconjugated bilirubin in the plasma.

Brown and Zuelzer (1958) reported a marked decrease of UDP glucose dehydrogenase and UDP glucuronyl transferase activity in the fetal and newborn guinea pig.
In older children and adults the concentration of serum bilirubin is 0.2 to 0.8 mg/dl, although in normal adults, values as high as 1.5 mg/dl may be found (Zieve and Still, 1955). In the mature newborns, however, levels up to 6 mg/dl are recorded on the 2nd to 4th days of life, while the preterm baby 5 to 7 days after birth, often shows values of 12-14 mg/dl.

The total bilirubin concentration is rarely of value in differentiating the cause of jaundice. Although much overlap occurs between values found in various types of jaundice. Outside the newborn period it is generally agreed that simple haemolysis rarely results in levels greater than 5 mg/dl. Similarly the bilirubin level does not correlate with the severity of liver disease.

An elevated direct reacting bilirubin is a more sensitive indicator of mild or early liver injury than an increase in the total serum bilirubin. In neonatal period, however, this finding is less specific since a rise in conjugated bilirubin is found in serious, pyogenic non hepatic infection (Hamilton et al, 1963).

Serum concentration of bilirubin represents a balance between its production and metabolism. Hyperbilirubinemia therefore, may be the result of over production of bile pigment or impaired hepatic uptake, conjugation or excretion (Arios, 1974, Maisels, 1975).

A raised bilirubin level lacks liver specificity, since an increase may occurs in haemolysis. In the newborns
the physiological rise of bilirubin, may be exaggerated by several abnormalities not caused by primary hepatic dysfunction; these include hyperthyroidism, a large haematoma, or a high bowel obstruction, in each of which the bilirubin is unconjugated (Johnson, 1975).

A study carried out by Simon Kove et al (1957) illustrated that hyperbilirubinemia, which is normally present in the neonatal period is not associated with increased activity of SGOT. He demonstrated a case where the activity of SGOT was only 28 units, despite marked clinical icterus and the concentration of bilirubin in the serum was 33 mg/dl. In contrast to this infant, others with low concentration of bilirubin often displayed increased activity of SGOT in the serum.

SERUM BILIRUBIN IN BIRTH ASPHYXIA

Saili et al (1989); in their study compared serum bilirubin in severe asphyxiated newborns with normal newborns. According to them mean serum bilirubin level in control and asphyxiated newborns was 4.50±6.12 and 4.78±6.62 mg/dl respectively. But due to multifactorial etiology of serum bilirubin, they were not able to conclude that this rise in serum bilirubin was due to asphyxiated damage of liver.

APGAR SCORE

The Apgar score devised in 1952 by Dr. Virginia Apgar, is a quick method of assessing the state of newborn
(Curr Res Anaesthesia Analg, 1953). Although Apgar score continues to provide a convenient shorthand for reporting the state of the baby and the effectiveness of resuscitation. The purpose of this statement is to place the APGAR score in its proper perspective as a tool for assessing asphyxia and for prognostication. The Apgar score was developed to identify quickly the newborn in need of resuscitation (Apgar, 1953).

The Apgar score is comprised of five components: heart rate, respiratory effort, tone, irritability and colour. Each of which can be given a score of 0, 1 and 2.

<table>
<thead>
<tr>
<th>Component</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
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<tbody>
<tr>
<td>1. Heart rate</td>
<td>Absent</td>
<td>Slow ($\leq 100$ beats/min.)</td>
<td>$\geq 100$ beats/min.</td>
</tr>
<tr>
<td>2. Respiration</td>
<td>Absent</td>
<td>Weak cry, hypoventilation</td>
<td>Good strong cry</td>
</tr>
<tr>
<td>3. Muscle tone</td>
<td>Limp</td>
<td>Some flexion</td>
<td>Active motion</td>
</tr>
<tr>
<td>4. Reflex</td>
<td>No response</td>
<td>Grimeace</td>
<td>Cough or sneezing</td>
</tr>
<tr>
<td>5. Colour</td>
<td>Blue or pale</td>
<td>Body pink extremities blue</td>
<td>Completely pink</td>
</tr>
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</table>

It is important to recognise that elements of the score such as tone, colour and reflex irritability are partially dependent on the physiologic maturity of the infant. The normal premature infant may thus receive a low score purely because of immaturity with no evidence of anoxic insult or cerebral depression.
One minute Apgar score: A low one minute Apgar score indicates an infant who may need resuscitation. Although a score of less than 6 is listed in the international classification of diseases, revision 9, codes as asphyxia, a low score at one minute neither indicates that substantial hypoxia or ischemia has occurred nor has much prognostic significance.

In the collaborative perinatal project 4.8 percent of surviving infants has a one minute Apgar score of 3 or less (Nelson et al, 1979). The one minute Apgar score should not itself be used as indication of prior asphyxia or as a predictor of future deficit.

Five minute Apgar score: The Apgar score at five minutes indicates the infant who needs continued resuscitative efforts. The score is affected by all the conditions noted to affect the one minute Apgar score.

Ten Minute Apgar score: An Apgar score that continues to be 3 or less at 10 minutes indicates that the infant has remained hypoxic or hypoperfused despite resuscitative efforts. Only a small fraction of one percent of all full term infants in the collaborative perinatal project had such a score. Of these 34 percent died during the first year. However, if they survived most of these infants did well.

Fifteen and Twenty minute Apgar score: A score of 3 or less at fifteen or twenty minutes after delivery despite resuscitative efforts indicates that the full term
infant has suffered a severe antecedent injury with the possibility of additional postnatal effect. Often but not always this may be a result of intrauterine hypoxia. The mortality rate of these infants is 53 percent and 59 percent respectively. Failure of low scores to increase at 5, 10 or 20 minutes indicates an ongoing insult that could affect, or further affect outcome. Continued low scores at 10, 15 and 20 minutes are associated with increasing mortality and long term morbidity. However, only a small fraction of 1 percent of infants had a score of less than 3 at 20 minutes and survived. Rapid improvements of scores by five to ten minutes indicate that the prior insult was unlikely to have been sufficiently severe to result in permanent deficit (Nelson, Elbenberg, 1981).

In an infant with a low Apgar score, umbilical cord acidemia in the absence of maternal acidemia, large base deficit, and presence of nucleated RBC, in the peripheral blood provide supporting evidence of asphyxia. Liver, renal and cardiac dysfunction may also provide evidence of asphyxia.

It should be noted that Apgar score partially depends upon the maturity of the newborn (Catlin et al., 1986). Immature infants are more likely to be hypotonic to have cyanotic extremities, and to have decreased responsiveness. Therefore a score of 7 may be "Maximum" for a normal premature infant.