The effect of radiation on the liver is not well understood. Without much conclusive evidence, it was assumed by earlier workers that liver was radioresistant. However, some earlier and most of the recent workers have reported a definite radiosensitive nature of this organ to low and moderate doses of radiation. According to Ellinger (1945), "perhaps there is no field in radiation biology where the opinions are so divergent as in assessing the effect of radiation on liver".

It was Seldin (1904), who studied the effect of radiation on liver for the first time. He did not observe any change
in the liver of guinea pig exposed to X-rays and in the normal liver of the guinea pigs. Further, morphological studies led to the assumption that the liver is relatively radioresistant, although minor cytological changes were observed (Heineke, 1904; Lepine and Boulud, 1904; Krause and Ziegler, 1906; Hudeillette, 1907; Triboncdo and Hudeillette, 1907; Aubertin and Beaulard, 1909; Hall and Whipple, 1919; Smyth and Whipple, 1924; Kohle and Bunting, 1932; Ely et al., 1947; Khoades, 1948; Agrawal and Mehrotra, 1964a,b, 1966).

This may be attributed either to the low oxygen tension of the tissue (Fatt and Eru, 1954) or to the exceedingly large regenerative capacity of liver. Kohle and Bunting (1932) exposed the liver of adult rats to doses of 600-2500 r of X-irradiation. They did not observe liver necrosis, although, minute cytoplasmic changes were observed by them. These changes quickly disappeared and the liver became normal. Temporary atrophy of hepatic cells was, however, noticed.

The result of an extensive study reported by Khoades (1948), in which livers of rabbits, mice, rats and guinea pigs were examined after total body X-irradiation with dosages of 25-1200 r confirmed the radioresistance of liver. The changes that occur may not be due to the primary effects of
irradiation on liver but rather secondary to general toxicity. She did not find any significant change in liver of mice, rats, guinea pigs when Pu$^{239}$ or Y$^{90}$ was administered. Grad and Stevens (1950) while studying the histological changes produced by a single, large injection of radiophosphorus ($^{32}$P) in albino rats and C$_{3}$H mice found little or no damage in liver. Similarly, Koletsky and Christie (1951) found liver to be radioreistant organ when rats in their experimental studies were injected with radioactive phosphorus ($^{32}$P).

Gross studies to prove the disturbances in liver function following irradiation have repeatedly been made and the result are negative (Borak and Kriser, 1923). Many works followed in which an attempt was made to study the effects of radiation on liver using X-rays (whole-body exposure or direct exposure of the organ) but no significant alterations were observed either histologically or functionally (Warren and Whipple, 1922; Ludin, 1925; Gabriel, 1926; Tsuzuki, 1926; Keller, 1927; Brans and Darnbacher, 1929; Desjardins, 1931; Barrow and Tulia, 1952; Agrawal and Mehrotra, 1964a,b, 1966).

Experimental studies of the pioneer era did not reveal any change in adult animals (Seldin, 1904; Hall and Whipple, 1919), however, alterations were observed in the young
animals. Later studies have been helpful to reconcile the controversial opinions concerning the response of the liver to ionizing radiations. Factors have been brought to light, which explain why in some cases liver effects have been observed and in other cases no changes were noticed. Responsible for this controversy are cyclic changes in the hepatic cells and the enormous repair power of this organ (Fohle and Bunting, 1932; Fischel, 1941; Mignard et al., 1965; Reed and Cox, 1966).

Theis (1905) was the first observer to note special changes like hyperaemia, haemorrhage, necrosis, karyolysis and granular degeneration in the liver of guinea pigs following radium irradiation on the liver of rabbits. He observed localized congestion and leukocyte infiltration on the second day, swelling and degranulation of cytoplasm, vacuolation and eventually loss of nuclei on fourth day, both in the adult and young rabbits. In another experiment, he observed marked histological alterations in the form of atrophy and fatty degeneration of the hepatic cells.

On the basis of clinical experience, most of the workers consider liver as very radiosensitive (Case and Warthin, 1924; Bromeis, 1926; Germer and Møllengaard, 1934; Pack and Livingston, 1940) while others take the opposite view (Jungling, 1929; Wintz, 1931). Bianchi (1938) recorded the
functional disturbance of liver in man after irradiating the liver by using different doses of roentgen rays and came to the conclusion that liver is radioresistant anatomically but is very sensitive physiologically. According to him, the functional state of the liver at the time of irradiation has an effect on the radiosensitivity. Ingold et al. (1965) did not regard human liver as a radioresistant organ on the basis of clinical features. Histologically, the acute effects of radiation are those of centrolobular haemorrhage and sinusoidal congestion with adjacent atrophy of the hepatic cells. Therapeutic irradiation of adult human liver with doses of 3000-5900 rads was followed by intense hyperaemia and hepatic cell loss, most pronounced near the lobule centres (Reed and Cox, 1966).

Experimental studies by some earlier and most of the recent workers on different animals employing both external as well as internal source of irradiation have confirmed the radiosensitivity of liver (Wetzel, 1921; Beutel, 1932; Ariel, 1951; Koletsky and Gustafson, 1952; Kelly and Hirsch, 1955; Horst and Rubinicki, 1962; Bhartiya, 1970; Gupta, 1970; Sengupta, 1972; Gupta, 1977; Khan, 1980).

Kolodny (1925) studying tissue changes after deep roentgen irradiation in rabbits found necrosis of liver. This necrosis
was not only confined to liver cells but also to biliary epithelium. Changes in the form of atrophy and vacuolation of liver parenchyma as a result of intravenous injection of thorium dioxide (ThO₂) has also been reported in the liver of rabbits by Fohle and Ritchie (1934).

Warren et al. (1951) observed intranuclear vacuolation in the liver cells of rats following radiophosphorus (P³²) administration. They also observed eccentrical displacement of nucleoli. Graevskii (1955) observed extensive vacuolation of cytoplasm, enlarged nuclei and destruction of liver parenchyma in mice exposed to 700 r X-irradiation. Ingold et al. (1965) found typical histological changes in the centrolobular region consisting of severe sinusoidal congestion, atrophy of some hepatic cells and mild dilation of central vein with red blood corpuscles. Radioclesions in the form of vacuolation of cytoplasm, dislocation of nuclei, enucleated cells, pyknotic nuclei, hyperaemia, haemorrhage and lymphocytic infiltration have been described following internal irradiation (Bhartiya, 1970; Kumar and Mehta, 1973) and external irradiation (Mehta et al., 1975; Dixit et al., 1976).

Local irradiation of the liver of mice with doses of 5000-12,000 r (1000 r/minute) causes the cytoplasm to shrink and
the nucleus and nucleolus to enlarge 29 and 62 per cent respectively. The nucleus cytoplasm ratio shifts in the favour of nucleus, the later approximately doubles and the lipid content of the cytoplasm decreases from 33.4 per cent to 9.7 per cent (Wilson and Stowell, 1953). Weseloh et al. (1967) concluded that liver is a radiosensitive organ, which, however, by means of its functional and structural potentialities is capable of counteracting the damage.

Waller and Wordsworth (1974) studied the long-term liver radiation damage in rats following both internal and external irradiation. They observed some necrosis on 28th day post-irradiation and as the damage progressed, many cells were found to contain intranuclear inclusion bodies. At 60-90 days post-irradiation period, numerous small cystic cavities were observed. Apart from these changes, liver became granular.

Benjamin et al. (1975) injected intraperitoneally Ce144-Pr144 citrate, a β-γ-emitter, into Chinese hamsters (Cricetulus crisseus). They observed nodular hepatic lesions of varying size and appearance after a period of 700 days. Some cells were enlarged ten times of the normal cells. The hepatocyttoplasm became vacuolated and nuclei enlarged. The nuclei often occupied 50 per cent of the cell volume and were
with irregular, clumped chromatin and abnormal and multiple nucleoli.

Mehta et al. (1975) observed cytoplasmic vacuolation, pyknotic nuclei, widening of liver cords, perivascular infiltration, haemorrhage and cellular necrosis followed by early fibrosis in the liver of albino rats following whole-body X-irradiation to varying doses (250-1000 r). Severity of damage was directly related to the dose of exposure and the recovery varied inversely with the dose.

Continuous exposure of mice from one day after birth to six weeks of age with tritiated water (HTO) resulted in a distorted architecture of liver along with various histopathological lesions which included granular degeneration and vacuolation of cytoplasm, numerous enucleated cells, pyknotic nuclei, karyolysis and karyorrhexis (Gupta and Bhatia, 1979).

Reticuloendothelial changes as a result of radiation have been described by several workers in Kupffer cells. However, majority of the reports mentioning changes in the Kupffer cells have been correlated with their vital staining properties which either increases or decreases (Schmidt, 1921;
Tsuzuki (1926) described hypertrophy of Kupffer cells in animals soon after treatment with 20-150 per cent of erythema dose. Several changes like degeneration of Kupffer cells in rats after X-rays exposure (Schwenhorst, 1928); hyperplasia of Kupffer cells in mice (Callierio, 1931; Calo, 1933); vacuolation of Kupffer cells in guinea pigs (Windholz, 1937); rarefaction of these cells in rabbits (Tang, 1939); and enlargement and irregularity in shape and size after radioactive phosphorus P³² administration in patients with malignant lymphomas (Platt, 1947) have been observed.

There have been several studies on the changes in the function of Kupffer cells after exposure to radiation but most of them have had no histologic correlation. Diminished phagocytic activity and necrosis of these cells simultaneously with the necrosis of liver cells have been observed in a zone of liver adjacent to implanted gold radon seeds from 3 to 35 days after the implantation (Higgins and Rogers, 1932). Restorative activity was, however, manifested by these cells after some time.
Increase in the number of Kupffer cells has been reported following external irradiation (Tsuzuki, 1926; Calo, 1933) as well as following internal irradiation (Sengupta, 1972; Kumar and Mehta, 1973; Gupta, 1977).

The action of X-rays on hepatic glycogenesis was first shown by Lepine and Boulud (1904). They irradiated dog liver and observed decrease in the percentage of hepatic glycogen content and increase in the percentage of glucose. This led to Aubertin and Beaujard (1909) a possibility for the treatment of glycogenic hepatomegaly of saturnine origin. They intoxicated two guinea pigs with lead acetate and observed a glycogenic surcharge without liver cirrhosis. They then, subjected one of the guinea pigs to repeated doses of X-irradiation and observed the disappearance of glycogen in the liver.

The direct action of radiation on liver was suggested by Strauss and Rother (1924). They performed series of experiments. The groups of rabbits given whole-body X-irradiation induced diminution of glycogen in the liver and pronounced hyperglycemia. However, hyperglycemia was also observed when only the exteriorized right lobe was exposed to X-irradiation. Hyperglycemia reached to a maximum level after one hour but it became normal after 8 hours.
In the third experiment, it was found that irradiation of a part of the body other than the upper abdominal region had no effect on glucose level. Similar observations were made by Tsukamoto (1928) in the liver of rabbits exposed to X-irradiation under various conditions. He concluded that (i) there is no effect on glycemia after irradiation of lower limbs or of thorax, whereas irradiation of liver raised blood sugar levels to a varying degree depending on the diet; (ii) there is a delay in a return to normal of the curve of glycemia induced by intravenous injection of sugar in rabbits, whose liver, thorax or limbs had been exposed to X-rays.

Rother (1928) irradiated, in vitro, isolated and perfused livers and observed no change in the biochemical reactions. He concluded that the integrity of vegetative liaisons of the gland with the body as a whole is necessary for roentgen hyperglycemia to arise.

Rother (1928) revealed that liver glycogen in rabbits is reduced after X-irradiation, although blood sugar levels are increased. Steadman and Grimaldi (1952) observed hyperglycemia in rabbits following irradiation. This hyperglycemia increased with increasing dose and at every dose (500-2000 r) maximum value reached at 4 hours after
irradiation, thereafter, declining to normal value within 24 hours. Hyperglycemia was completely prevented by insulin. They postulated that irradiation causes a mobilization of glycogen into glucose and that the normal supply of insulin in rabbits is not sufficient to prevent hyperglycemia.

It is now well established that irradiation of animals up to 2000 r result in an increase in the level of liver glycogen (Ross and Ely, 1951; McKee, 1952; Nims and Sutton, 1954; Kay and Entenman, 1956; Supplee et al., 1956; Coniglio et al., 1957; Bresciani et al., 1965; Movsesyan et al., 1968). According to Ord and Stocken (1960) increased accumulation of liver glycogen after irradiation may be due to enhanced tissue breakdown, and the consequent storage of amino acids carbon skeleton, which ultimately gets converted into glycogen. This is promoted by the presence of hormones controlled by pituitary-adrenal axis.

Dixit et al. (1976) observed a significant rise in the liver glycogen in house rat (Rattus rattus, Rufescens) exposed to 400 r Co\textsuperscript{60} external \(\gamma\)-irradiation on 6th postirradiation day. They have suggested that it may be due to the increased gluconeogenesis. Szysko (1976) observed an increase in glycogen content up to 12 times with a dosage of 650 r x-ray whole-body irradiation.
Khan (1980) found that liver glycogen level showed maximum increase at 24 hours, 3 and 5 day postirradiation after 250, 500 and 1000 r of gamma irradiation. Normal values were attained by 7th and 14th day postirradiation with 250 and 500 r, while in mice irradiated with 1000 r, though return to normal value was initiated, it was not attained as all animals died by 10th day postirradiation.

The amount of hepatic glycogen following irradiation differs from that of unirradiated controls. The post-irradiation anorexia and weight loss of rats is greater than many other species. Therefore, in most of the experiments, the rats have been fasted either before or at least after irradiation and compared with fasted unirradiated rats. Under these conditions, the glycogen level is found to be higher in irradiated than in unirradiated controls (North and Nims, 1949; Ross and Ely, 1951; Kay and Enteman, 1956; Hansen, 1967).

On the other hand, rats fed ad libitum, results are quite contradictory. Nims and Sutton (1954) found a decrease during the first 24 hours after 500 r, followed by an increase. The level of control was reached on 4th day postirradiation. Gordeyeva (1960) observed no change in the level of hepatic glycogen in the first 24 hours, on 3rd day...
postirradiation a decrease sets in which reached minimum value on 9th day after 650 r. Matsuba (1964) found that after 1000 r, there was a steady decrease in liver glycogen level for at least 72 hours.

It has been found that hypophysectomy prevents deposition of glycogen in the liver of fasted and irradiated rats (Nims and Sutton, 1954). It seems that stimulation of pituitary-adrenal system is necessary for the conversion of glucose precursors into glycogen. Thurber and Nims (1962) determined the liver glycogen and blood sugar levels in newborn rats. Uptil 6th day after birth, irradiation had no effect on the liver glycogen and the blood sugar levels were quite unstable. However, on the 7th day after birth, the blood sugar levels became stabilized and expected mild hyperglycemia and increase liver glycogen after whole-body X-irradiation were demonstrable. It, thus, appears that pituitary-adrenal regulation of carbohydrate metabolism becomes effective on or about 7th day in newborn rats.

Hameed and Haley (1964) measured the plasma and adrenal corticosterone levels after 650 r whole-body X-irradiation in rats fed ad libitum. They found a marked increase in both plasma and adrenal corticosteroids levels at 2.5 hours post-irradiation. The hormone level in plasma returned to normal
values at 24 hours and showed less marked but significant rise at 48 hours postirradiation, decreased on 5th and 7th day and returned to normal values by 14th day postirradiation. In hypophysectomized animals, no increase in the corticosterone levels in both plasma and adrenal glands was observed after X-irradiation. The involvement of intact pituitary for adrenal response was also described by Fatt et al. (1948) in rats.

It is self-evident that gluconeogenesis can proceed only when sufficient amounts of substrates are available. After irradiation, tissues in radiosensitive organs breakdown with the consequent liberation of glucogenic and ketogenic amino acids (Rust et al., 1963). Indeed some polypeptide fragments accumulate in liver (Nims and Sutton, 1954), and amino acids level in blood increase (Caster and Armstrong, 1956; Williams et al., 1957; Gerber et al., 1959). Liver, therefore, is exposed to an excess of amino acids and remove these from the blood stream via a stimulated transport system. However, the transport system which is stimulated after irradiation, does not appear to carry all the amino acids but rather may be specific for the neutral ones requiring Na⁺ and endogenous energy for their uptake (Flory and Jennewein, 1975). The specificity of the stimulated transport resembles the "A" system defined for Ehrlich cells by Oxender and Christensen.
(1963). The amino acids transported by "A" system are serine, threonine, asparagine, glutamine, glycine, proline and alanine and all these are glucogenic amino acids. Others, who have also observed such stimulation of amino acids transport are Flory and Neuhaus (1976), Kilberg and Neuhaus (1976). This transport increases the levels of hepatic amino acids, and, therefore, is a key factor in regulating the postirradiation glycogenesis (Kilberg and Neuhaus, 1976).

Aminotransferases play a central role in determining the metabolic fate of amino acids. They permit in conjunction with L-glutamate dehydrogenase, conversion of amino N of \( \alpha \)-amino acids to NH and, thus, provide a means for the biosynthesis of non-essential amino acids. Aminotransferases especially in the liver and muscle, respond readily to tissue damage and are released into the bloodstream. The activity of these enzymes is influenced by the nutritional level and increases markedly during starvation. Nevertheless, starvation is not the only factor responsible for the changes in the hepatic aminotransferases activities after irradiation. This is shown by the marked difference in the behaviour of various aminotransferases. Time and species also influence the radiation induced enzymatic activities (Streffer and Melching, 1965).
Exposure of fed mice to 530 r revealed no change in the aspartate aminotransferase (GOT) up to 12 days after exposure (Tonhazy et al., 1950).

Brin and McKee (1956) found no increase in the activity of GOT in the livers of rats fed high glucose (60 per cent) diet after exposure to 900 to 1000 r.

Fitch et al. (1961) exposed rats to 900 r and fed them with 60 per cent fructose or glucose diet. They observed a decrease of 16 per cent in the activity of GOT when fructose was given, however, no change in the enzymatic activity was observed when glucose was fed.

Braun et al. (1963) exposed fed mice to 450 r and found an increased activity of GOT of 28 to 65 per cent at 2, 4, 14 days after exposure. Slight decrease in the activity of this enzyme in rats following 600 r at 10 days interval was, however, observed by Braun et al. (1965).

Streffer and Melching (1965) exposed mice to total body irradiation of 690 r. The enzymatic activity was not changed considerably up to 12 days after irradiation in the cytoplasm of starved mice. There was a non-specific decrease between 8th and 10th day after irradiation in the mitochondria.
A significant increase in the GGT activity was, however, observed in the cytoplasm of fed animals between the 1st and 6th day after irradiation.

Fikulov and Yakubovick (1966) found a decrease in the activity of this enzyme in rats at 1, 2, 24 days following exposure to 100 r.

The activity of alanine aminotransferase (GPT) is also influenced by the nutritional state after irradiation. GPT seems to be more radiosensitive than GGT, and the activity of the former and not the later enzyme increases in liver of rats fed a high glucose (60 per cent) diet after exposure to 900-1000 r (Brin and McKee, 1956).

Exposure of fed mice to 450 to 690 r resulted in an increase in the activity of GPT, in liver of mice, by 27 per cent (Braun et al., 1965).

Streffer and Melching (1965) determined and compared the activity of GPT in the liver of starved and fed mice exposed to 690 r. The levels of GPT did not change considerably in the cytoplasm up to 12 days after exposure in the starved mice. However, a non-specific decrease in the GPT activity
between 8th and 10th day after irradiation in the mitochondria was observed.

Kilberg and Neuhaus (1976) exposed rats to 1500 r and 2500 r gamma irradiation. The level of enzyme activity between 12 to 48 hours postirradiation remained essentially constant. At 48 hours postirradiation, both the starved controls and irradiated rats showed a decrease in the level of GPT. They found no apparent induction of this enzyme in the liver of rats exposed to even 2500 r.

Acid phosphatase is a hydrolytic enzyme and according to Novikoff and Essner (1960) this enzyme is localized in lysosomes. Upon release from lysosomes, these enzymes are capable of causing reparable or irreparable damage. Changes in the activities of lysosomal enzymes following whole-body irradiation have long been recognised (Douglas and Day, 1955; Okada et al., 1957). It has been suggested that radiation induces physical or functional changes in the lysosomal membranes permitting the release of hydrolytic enzymes and indirectly causing death by this mechanism (Alexander and Bacq, 1961; Goutier and Bacq, 1963). Increase in acid hydrolases after irradiation seems to be characteristic of tissue damage by irradiation and have been reported for thymus (Weymouth, 1958; Rahman, 1962); spleen
(Rahman, 1962; Roth et al., 1962): regenerating rat liver
(Goutier and Goutier, 1962) and in adrenals (Jonek et al.,
1964).

Goutier and Goutier (1962) observed increase in acid
phosphatase activity in the rat liver after whole-body
irradiation with 100 to 700 r. Noaman et al. (1968a) found
a significant increase in rat liver acid phosphatase after
750 rads on the 6th day postirradiation which remained
steady at 115% of the controls until last observations made
on the tenth day. Rene et al. (1971) found an increase in
acid phosphatase activity up to 143% of the controls after
whole-body exposure to 2 K rads in rats. Similar increase
was also observed by Zyss and Michalska (1972), Fiszer-Szafras
and Nadal (1977) and Kumar et al. (1979).

Significant increase in the value of acid phosphatase was
observed at 24 hours after irradiation with 250 and 500 r
and 5 days after irradiation with 1000 r in the liver of
Swiss albino mice (Khan, 1980).

Danpure and Taylor (1974) found an increase in acid
phosphatase activity 32-186 days after injection of colloidal
plutonium-239, B-radiation from injected gold-198, resulted
in higher specific activities between 14-62 days after treatment especially acid phosphatase and β-glucuronidase.

Hari Kumar et al. (1978) observed significant increase in the activities of lysosomal enzymes (except RNase) in rat liver exposed to 600 r. At the 8th day following irradiation, the activities of enzymes reverted to control values.

Several mechanisms have been suggested for the increased activities of lysosomal enzymes after irradiation. Wills and Wilkinson (1967) proposed that irradiation causes peroxidation of lysosomal membranes leading to its breakdown, which is followed by enzyme release.

Aikman and Wills (1974) proposed an alternative mechanism according to which lesions are produced in membrane lipids, possibly by peroxides, at the time of irradiation, which lead to activation of latent acid hydrolases which could result in the digestion of membrane itself with the consequent activation and release of other lysosomal enzymes.

Hepatic alkaline phosphatase is a zinc containing enzyme with molecular weight of 1,54,000. Partial hepatectomy, glucagon and cholera enterotoxin administration causes a significant increase in its activity that takes place
exclusively in the plasma membrane. One of the functions of alkaline phosphatase is to hydrolyse phosphorycholine, so that choline can be transported across the bile canaliculair membrane. It may be the same enzyme as calcium activated ATPase and may play a significant role in calcium transport across cell membranes.

Kuzin (1950) reported changes in the activity of alkaline phosphatase in several rat organs following whole-body irradiation with 0.3, 1.0 and 3.0 krad. He stated that no changes were detected in the levels of ATP in brain, pancreas, kidney or testes and only showed an increase in activity in spleen, thymus and duodenum. He also reported that inactivation was evident in liver and brain of white rats after 24 hours whole-body irradiation with 5 krad.

Ludewig and Chanutin (1950) found no change in alkaline phosphatase activity in the liver of rats receiving a total body X-ray exposure of 0.5 krad. However, majority of later workers have reported an increased activity of alkaline phosphatase after exposure to moderate to high doses (Rev and Vertekez, 1951; Noaman et al., 1968b; Hishida et al., 1979; Khan, 1980).
Nosman et al. (1968b) observed significant increase in AP activity in heart and liver within 3 hours after 500 r whole-body X-irradiation of rats and 750 r gamma rays. Maximum activity was noticed on 6th day postirradiation.

Dixit et al. (1976) exposed house rat and Indian desert gerbil (Meriones hurrianae, Jerdon) to 600 r gamma rays and observed significant increase in the serum alkaline phosphatase activity and attributed this increase to functional impairment of liver of these animals.

Hishida et al. (1979) observed significant rise in the value of AP from 2 to 7 days after irradiation of livers with 1000, 3,000, 5,000 and 10,000 rads. They attributed this increase to the radiation induced hyperaemia and congestion in early stages and degenerative changes in the later period following liver irradiation.