INTRODUCTION
1. INTRODUCTION

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1. INTRODUCTION

1.1 ALCOHOL INGESTION AND ALCOHOLISM

1.1.1 The desire to alter reality and delve into fantasy is one of the most ancient, persistent and understandable part of human nature. Ever since civilisation, as we know it, began, alcohol had a unique position in man's life. A look at ancient history, a study of bygone cultures, confirms the universal presence and use, including abuse of alcohol. Man began to understand and appreciate the fact that alcohol not only, merely helped to satisfy hunger and thirst, it also had rather pleasing side effects, intoxicating, exciting and tranquilising.

1.1.2 Alcohol abuse and alcoholism is one extreme, in a continuum of drinking behaviour, rather than a distinct and separate, pathological identity. It represents one of the major health, social and economic issues, facing the world.

1.1.3 Alcoholism (alcohol dependence), is the third largest killer in the world to-day, cancer and heart disease being the first and second (Max Glatt, 1974). Survey carried out by Indian Council of Medical Research
in 1976 revealed that approximately, 30 percent of the total adult population suffer from alcohol abuse in India (WHO project, 1979).

1.1.4 American estimates on alcoholism and related expenditure (including losses) accounted for 44,000,000,000 U.S. dollars, for the year 1976 (Luce and Schweitzer, 1978). But the economic impact pales in comparison, with the psychological pain and anguish brought to alcoholics, and their family and friends.

1.1.5 Ethyl alcohol (ethanol), is a sedative hypnotic consumed basically as a social drug. The same, when consumed in large quantities has remarkably far reaching effects. Its study includes its effects on the various biochemical processes of the body, biochemistry and biophysics of membranes and cell organelles and its psychological impact.

1.2 ABSORPTION AND FATE OF ETHANOL IN THE BODY

1.2.1 Absorption of ethanol following ingestion takes place along the gastro-intestinal tract (GIT), by simple diffusion (Halsted et al. 1975). 80 percent of the ingested alcohol is absorbed, in the small intestine.

1.2.2 Routes of administration of ethanol markedly affects the speed of absorption, (Goldfarb, 1976).
Under ideal conditions, absorption of a single oral dose of ethanol may almost be complete within an hour. The blood ethanol level, usually reaches a maximum within 40-60 minutes and subsequently decreases to near zero in 8 to 10 hours (Ritchie, 1965). Inhalation of vapourised ethanol results in sufficient absorption through lungs, to produce fatal intoxication.

1.2.3 For acute experiments, intravenous or intra-arterial injections are used, (Erickson, 1979). A number of routes have been exploited for chronic administration of alcohol because of distaste of animals for ethanol. They include, oral consumption via ethanol containing liquid diet (Lieber and Decarli, 1973), schedule induced polydypsia of aqueous ethanol solution (Falk et al, 1972), gastric incubation (Majchrowicz, 1975) and inhalation (Goldstein and Pal, 1971).

1.2.4 The oral route is preferred in our laboratory, since our aim is to study the effect of the alcohol consumption, in a manner as close to the human pattern, as possible.

1.2.5 High concentrations of ethanol (>30%) tend to reduce gastric mobility and thereby, significantly slow absorption (Sedman et al, 1976). Absorption is most
rapid with ethanol in moderate concentration (10-15%) especially, when taken on an empty stomach (Ritchie, 1965).

1.2.6 Certain types of food may also alter absorption such as, high carbohydrate and high fat diet (Welling et al., 1977), glucose (Sedman et al., 1976) and fructose and galactose (Clark et al., 1973), which reduces blood ethanol concentrations, perhaps through increased oxidation or decreased ethanol absorption.

1.2.7 Alcohol may be distributed throughout the whole of the body water, that is about two-thirds of the body volume (Greenberg, 1968) and gets accumulated in tissues, with the highest water content (Harger et al., 1977). These authors have suggested that this might be due to the hydrophillic properties of the compound.

1.2.8 About 90-98 percent, of the total alcohol ingested is ultimately oxidised to carbon dioxide and water with the release of 7 calories/g, of alcohol. The remainder is excreted unchanged in the urine, expired air and also in sweat (Pawan, 1972).

1.3 ETHANOL METABOLISM

1.3.1 Liver is the major site of ethanol oxidation although other tissues such as lung, kidney, muscle,
intestine and possibly even brain may metabolise, small quantities (Pawan, 1972).

1.3.2 The main hepatic pathway for ethanol disposition involves alcohol dehydrogenase (ADH). Other non-ADH pathways include, peroxidase - xanthine - oxidase catalase (Thurman et al., 1975), NADPH cytochrome reductase (Ioannides et al., 1975) and microsomal ethanol oxidising system (Lieber and Decarli, 1972).

1.3.3 NAD dependent alcohol dehydrogenase is a zinc metallo enzyme, predominantly present in the cytosol of the liver and catalyses the reaction.

$$\text{CH}_3\text{CH}_2\text{OH} + \text{NAD}^+ \rightarrow \text{CH}_3\text{CHO} + \text{NAD} + \text{H}^+$$

Small amounts of ADH, is also found in the kidney and gastric mucosa (Kreb et al., 1969). Brain and heart, have no appreciable enzyme activity. Hence non-ADH pathway is adapted in these tissues to metabolise alcohol (Rognstad and Grunnet, 1979).

1.3.4 The second enzyme, aldehyde dehydrogenase ubiquitous in nature, catalyses the reaction

$$\text{CH}_3\text{CHO} + \text{NAD}^+ + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COO}^- + \text{NAD} + 2\text{H}^+$$

Acetaldehyde, formed from ethanol in the cytosol is primarily oxidised in the mitochondria (Rognstad, 1974).
The proportion of aldehyde oxidised to acetate by aldehyde oxidase in liver (Higgins, 1979), is marginal.

1.3.5 Chance et al (1952), outlined the mechanism of action of catalase as given below.

\[ \text{Catalase} + \text{H}_2\text{O}_2 \rightarrow \text{Enz} - \text{H}_2\text{O}_2. \]

\[ \text{Enz} - \text{H}_2\text{O}_2 + \text{H}_2\text{O}_2 \rightarrow \text{Enzyme} + \text{O}_2 + \text{H}_2\text{O}. \]

Enzyme - $\text{H}_2\text{O}_2$ complex in addition to reacting with another molecule, may also react with a number of hydrogen donors including ethanol (Keilin and Hartree, 1945), in a peroxidase type of reaction.

\[ \text{Enz} - \text{H}_2\text{O}_2 + \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{Enz} - \text{CH}_3\text{CHO} + 2\text{H}_2\text{O} \]

Most of the catalase activity in the liver is located in the peroxisomes (Maker and Mannering, 1968).

1.3.6 Orme Johnson and Zielger (1965), reported the oxidation of ethanol by the microsomal enzyme system, which utilizes NADPH as the cofactor.

\[ \text{NADPH} + \text{H}^+ + \text{O}_2 + \text{C}_2\text{H}_5\text{OH} \rightleftharpoons \text{CH}_3\text{CHO} + \text{NADP}^+ + 2\text{H}_2\text{O} \]

This enzyme system has since been studied extensively by Lieber and Decarli (1970), who subsequently named it as the microsomal ethanol oxidising system (MEOS). It is also known as the microsomal alcohol oxidising system (MAOS), (Rognstad and Grunnet, 1979).
Fig. 1. Pathways for ethanol elimination. Solid lines represent major routes believed to operate at this time. The MEOS and/or catalase pathways appear to operate at high ethanol concentrations (~60 mM). The percentage estimates for each pathway are crude but in accord with most findings.
1.3.7 The pathways of ethanol elimination are summarised in fig. 1. 60-90 percent of ingested ethanol is oxidised by cystolic ADH in liver, to aldehyde. About 5 percent of the ingested ethanol is oxidised by the ADH, of extrahepatic tissues and 3 percent is eliminated as such in urine and breath. The non-ADH pathways in liver oxidise, 0-30 percent of the ingested alcohol.

1.4 LIPID METABOLISM IN ALCOHOL INDUCED TOXICITY

1.4.1 Excessive oxidation of ethanol results in increased NADH generation. This is reflected in an enhanced NADH/NAD ratio, which in turn produces a change in the ratio of those metabolites, whose reduction is dependent on this redox system.

1.4.2 This increased NADH/NAD ratio, raises the concentration of α-glycerophosphate (Nikkila and Ojala, 1963), which favours hepatic triglyceride accumulation by trapping fatty acids. In addition, excess NADH promotes lipogenesis (Lieber and Schmid, 1961) possibly, by the mitochondrial elongation pathway or transhydrogenation to NADPH.

1.4.3 Decreased activity of the citric acid cycle results, in the deposition in the liver of dietary fat, or of fatty acid derived from adipose tissue and endogenous
Fig. 2. Metabolism of ethanol in the hepatocyte and schematic representation of its link to fatty liver, hyperuricemia, hyperuricemia, hyperlactacidemia, ketosis, and hypoglycemia. Pathways which are decreased by ethanol are represented by dashed lines. ADH, alcohol dehydrogenase; MEOS, microsomal ethanol-oxidizing system; NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide, reduced form; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, nicotinamide adenine dinucleotide phosphate, reduced form.
synthesis, in the absence of dietary fat. It also promotes ketone body production, in association with other metabolic changes that develop after chronic alcohol consumption, (Lefevre et al., 1970). This effect aggravates the acidosis and the hyperuricemia resulting from hyperlactacidemia and on occasion, may lead to severe alcoholic ketosis, (Jenkins et al., 1971). The excess \( \alpha \)-glycerophosphate and fatty acids, combine to form triglycerides. This could be promoted by the increase in activity of the microsomal, \( L-\alpha \)-glycerophosphate acyl transferase, after ethanol consumption, (Joly et al., 1973).

1.4.4 Increases in plasma lipid levels, especially triglycerides, following ingestion of ethanol appears, to be a general phenomenon. Changes in metabolic process observed to occur after ethanol administration include, reduced oxidation of fatty acids, increased esterification of fatty acids, increased hepatic and intestinal production of lipoproteins and reduced peripheral utilisation of the circulating lipids (Barberiak and Menahan, 1979).

1.4.5 Ethanol induced hyperlipemia, results from enhanced lipoprotein production. Incorporation into
significantly increased by alcohol administration (Baraona and Lieber, 1970). These increases are also reflected in ethanol induced, higher VLDL levels both in man (Wilson et al., 1970) and in animals (Baraona et al., 1973).

1.4.6 Mistilis and Ockner (1972), have reported that ethanol stimulated the production of triglycerides rich, VLDL.

1.4.7 Lefevre et al. (1972), found that ethanol promotes, esterified cholesterol accumulation by enhancing cholesterologenesis and decreasing, bile acid excretion.

1.4.8 In rats, one large dose of ethanol has been reported to result in increased (Brodie et al., 1963), or unchanged (Elko et al., 1961), circulating levels of free fatty acids. This effect of ethanol on free fatty acid mobilisation was found to be mediated by acetate (Crouse et al., 1968), the end product of ethanol metabolism in the liver. Since, stressful doses of ethanol probably both stimulate fatty acid mobilisation (via catecholamine release) and depress it (via the acetate produced), the net effect may be dependent upon experimental conditions.
1.5 ROLE OF DIETARY FACTORS

1.5.1 Hartroft (1966), reported that the effect of alcohol depends as much or even more on the sources and proportions of the calories provided by fat, protein, carbohydrates than on the absolute amount and duration of alcohol intake.

1.5.2 A decrease in the fat content of the diet attenuates, whereas a severe protein and vitamin deficient diet potentiates, the effect of alcohol in liver (Porta, 1965).

1.5.3 Replacement of dietary triglycerides containing long chain fatty acids (LCT), by fat containing medium chain fatty acids (MCT), reduces the capacity of alcohol to produce a fatty liver in rats (Lieber and Decarli, 1966). The propensity of medium chain fatty acids to undergo oxidation rather than esterification probably explains this phenomenon (Lieber et al., 1967).

1.5.4 Gachev and Spiro (1982), have reported that there is activated triglyceride synthesis, when sucrose was mixed with ethanol solution.

1.5.5 A combination of ethanol and diet deficient in both, protein and lipotropic factors (choline and methionine), leads to a more pronounced hepatic steatosis
than either deficiency alone (Klatskin et al., 1954, Lieber et al., 1969).

1.5.6 In alcoholics with comparable ethanol consumption and liver injury, depressions of valine, leucine and isoleucine (25-28%) were observed, in those with dietary protein deficiency (<56 g/day of protein for greater than 2 weeks) compared to those without such deficiencies (Shaw and Lieber, 1978).

1.5.7 Vannucchi et al. (1974), reported that the chronic alcoholics with deficient dietary intake, show clinical and laboratory signs of significant alterations in metabolic and nutritional status.

1.6 LUNG METABOLISM AND LUNG FUNCTION

1.6.1 In the lung, glycolysis is accomplished in the cellular cytoplasm, while the aerobic phase which produces thirteen times more energy, is carried out in the mitochondria. Ninety percent of the succinate oxidase in the lungs is found in the mitochondria. The lung accounts for 10 percent of the total body, oxygen consumption (Slonim and Chapin 1967).

1.6.2 Energy is obtained chiefly from blood glucose and fatty acids. In rabbit lung slices, incubated at
37°C in Krebs—Ringer medium, with a glucose concentration (1 mg/ml of medium) Yaeger et al. (1972), showed an uptake of 1.83 mg glucose per g wet wt. per hour. Lactic acid production was 0.55 mg per g wet wt. per hour. After 2 hours incubation with glucose – U-14C, 19 percent of radioactivity taken up appeared in carbon dioxide, 29.7 in lactic acid, 4.4 in lipid, 0.4 in nucleic acid and 1.4 percent in protein of the glucose taken up. Less than 5 percent was metabolised via the hexose monophosphate pathway. Pasteur effect has been observed in rat lung slices implying a competition for adenosine diphosphate (ADP).

1.6.3 Albumin and Immunoglobulin G are the normal alveolar protein components of the rat lung. Fibrinogen was not found under normal conditions (Bignon et al, 1976). In a comparative invivo study in rats by Witschi and Hanspeter (1972), lung was found to be about as effective in synthesising RNA and protein as the liver. The incorporation of radioactive orotic acid was 10 times higher in RNA of liver than lung, while labelled uridine was twice as much in lung than in the liver. The activity of enzyme on the main pathway for pyrimidine synthesis (asparate transcarbamylase and orotidene 5’-phosphate pyrophosphorylase and decarboxylase), was higher in liver while II kinase and II phosphorylase were more active in the lung.
1.6.4 A major substrate for oxidative metabolism in many body tissues is the plasma free fatty acids, derived from adipose tissue storage depots. While liver converts a large fraction of free fatty acids into triglyceride molecules, lung converts them predominantly, to phospholipids, of this 85 to 90 percent is found in the lecithin component (Slonim and Chapin, 1967).

1.6.4.1 Using glycerol $^{14}$C label, the *de novo* synthesis of lipids in the lung was reported by Hidetaka (1976), to follow the pathway: glycerol $\rightarrow$ glycerophosphate $\rightarrow$ phosphatidic acid $\rightarrow$ diglycerides $\rightarrow$ triglycerides $\rightarrow$ phospholipids.

1.6.4.2 In lung, *de novo* synthesis contributes to the linoleic acid containing lecithins, though it also represents an important pathway for the synthesis of tetraenoic, monoenoic and perhaps to a lesser extent disaturated lecithins.

1.6.4.3 A deacylation - reacylation mechanism, may contribute significantly to the formation of dipalmitoyl lecithin, a major constituent of lung pulmonary surfactant. Acylation of the palmitoyl - Sn - glycerol - 3 phosphorylcholine with various labelled fatty acids or acyl COA esters, was studied in the presence of microsomes from rat lung. A significant uptake of palmitic
acid was observed in 2 position of lecithin. The result endorses the findings from the *in vivo* studies, that the acylation of monoacyl-Sn-glycero-3-phosphoryl choline may play an important role in maintaining the high level of dipalmitoyl lecithin in lungs (Vereyken *et al.*, 1977).

1.6.5. The biosynthesis of pulmonary glycoconjugates was studied by Levrat and Louisat (1982), in sheep lungs microsomes. Glucosyltransferases catalyse the transfer of glucose from UDP - glucose to 4 different acceptors. These include a) glucosyl phosphoryl polyproenol, b) a product mixture of 5 glycolipids, one of them having a chromatographic behaviour, similar to hexosylceramide (asialo - GM₁), c) a glycoprotein of molecular weight 160,000 d) a glycoprotein insoluble in water and organic solvents.

1.6.5.1 Levrat *et al.* 1973, demonstrated the presence of a mannosyl enzyme system which catalyses the transfer of mannose from GDP - mannose to an endogenous acceptor, in the membrane fraction of the alveolar cells of the lung.

1.6.5.2 Pasquier *et al.* (1976), observed a similar glycoprotein constitution, but different dominant hexoses, for the glycolipids (glucose for rat, galactose
for rabbit and galactose for monkey) in the broncho-alveolar lavage.

1.6.6 The metabolism of the lung, supports a number of functions. The general functions include 1) performance of external work, including mechanical, osmotic and electrical work, 2) the maintenance of gradients and unstable structures and 3) the maintenance of lung temperature in its exposed situation.

The specific functions include 1) the maintenance and repair of structure, 2) smooth muscle contraction, including the normal tonus of bronchial smooth muscle, 3) ciliary activity, 4) phagocytic activity of alveolar macrophages, 5) synthesis of phospholipids which act as pulmonary surfactant, 6) active transport, 7) nerve conduction and 8) synthesis of protein, DNA and RNA.

1.6.7 Three basic types of cells are observed, in normal pulmonary alveoli. a) alveolar epithelial cells, which form the pulmonary surface epithelium, termed small, type A or type I cells, b) alveolar epithelial cell termed type B or type II. They contain cytoplasmic laminar bodies which are suggested to produce the alveolar surfactant (Bhattacharya et al., 1974). c) alveolar macrophages.
1.6.8 The alveoli of the lungs are lined with a layer of lipoprotein which by lowering the surface tension, prevents collapse of the lungs, and transudation of fluid, from the capillaries.

1.6.8.1 The surfactant is a phospholipid containing, lipoprotein of about \( \frac{1}{4} \) to \( \frac{3}{4} \) protein : lipid ratio that behaves electro-phoretically, as an alpha globulin.

Shelley et al (1982), studied the biochemical composition of the surface active material of adult human lung. It was found to contain 12 mg of phospholipid/mg protein. Of the phospholipids, 80 percent was phosphatidyl choline and 9 percent was phosphatidyl glycerol. The phosphatidyl cholines, 55 percent of which were disaturated, contained more than 70 percent palmitic acid. In contrast, phosphatidyl glycerol contained 22 percent palmitic acid and 52 percent olio acid, suggesting the importance of phosphatidyl glycerol in surfactant function, relates to its acidic head group.

The most abundant proteins were high molecular weight (> 400,000), glycoproteins. A low molecular weight protein was also present in surfactant subfractions, which had higher phospholipid/protein ratios.

1.6.8.2 The surfactant performs two important functions.

1) It decreases the work of breathing by decreasing the
surface tension of the fluid/air interface in the alveoli.

2. Because of its variable surface tension, it prevents the alveoli emptying and collapsing. With alveolar expansion, surface tension increases. Should this go unmodified in the lung, small alveoli would be more difficult to inflate and would tend to empty into larger alveoli with less surface tension, causing it to collapse. High pressure is needed to overcome the high cohesive forces and open closed (atelactic) alveoli. If open alveoli are exposed to these high pressures, they may burst (David and Horrobin, 1968).

1.6.8.3 Mendenhall et al (1967), found marked local surface turbulence in their hysteresis studies and suggested that this condition plays an important part in transport mechanisms across the surface.

1.6.9 The glycolipids are primarily concentrated on the plasma membrane and are the minor lipid components of the membrane, accounting for about 0.5-5% of the total membrane lipid (Weinstein et al, 1970).

The glycosphingolipids are usually divided into three groups.

1) The neutral glycosphingolipids. These include the cerebrosides and sulfatides.
2) Hexosamine containing glycosphingolipids without sialic acid.

3) Gangliosides which contain one or more sialic acid residues.

1.6.9.1 The glycoproteins are present as integral components of the plasma membrane of mammalian cells. Both glycoproteins and glycolipids are asymmetrically oriented in cell membranes with their saccharide chains projecting outwards from the membrane (Bretscher and Raff, 1975).

1.6.9.2 The specific functions of glycoproteins and glycolipids include roles in immunogenicity (Oxley and Griffin, 1971), interaction of hormone with target cells (Haskar et al., 1973), blood clot formation (Vermyler et al., 1974), reproductive process (Gould et al., 1971) and certain surface enzyme activities (Stefanovic et al., 1976).

1.6.9.3 Glycolipids and glycoproteins also function play an active role in sodium translocation (Wiegandt, 1971). The glycoproteins conduct transport by undergoing conformational changes (Guidotti, 1976).

1.6.9.4 They are also involved in the aggregation (of cells) mechanism (McGuire and Edward, 1976),
and in inducing membrane fusion by interaction with the phospholipids (Maggio et al., 1978). Information encoded in specific sugar residues of membrane glycoproteins plays an important role in cell to cell recognition (Morell Anatol, 1977).

1.6.9.5 Transmembrane interactions of surface glycoproteins with the high molecular weight polypeptides, is considered an important factor in controlling cell morphology (Huggins et al., 1976). Sialic acid is shown to act as a binding ligand to LDL (the bulk carrier of cholesterol) (Goldstein and Chapman, 1981).

1.6.9.6 Bhattacharya et al., (1974) reported the presence of two glycopeptides of molecular weights, 6200 and 3600 in the alveolar lavage. Of these, the latter was the major one, in the lung tissues of man, dogs, rats and rabbits. These peptides were also found in isolated lamellar bodies from type II alveolar cells of rats and are probably used for packaging, storage in lamellar bodies and secretion of surfactant, by alveolar type II cells.

1.6.9.7 A cold insoluble globulin (CIG), immunochemically indistinguishable from the fibroblast surface protein, known as large external transformation-sensitive glycoprotein and fibronectin, was detected in
connective tissue fraction of adult human lung. It is thought to influence the function of the alveoli (Bray and Anderson, 1978).

1.7 ETHANOL TOXICITY AND PATHOLOGY OF THE LUNG

1.7.1 Ethyl alcohol, when taken in excessive amounts, results in a variety of toxic injuries leaving no tissue in the body untouched (Lieber, 1983).

1.7.1.1 A recent study by Bernstein (1982), showed that rat lung slices incubated in a Krebs-Kinger bicarbonate buffer was able to metabolise ethanol at a concentration of 10 mM, at a rate which is 10 times more than that of liver. The ability of lung to metabolise ethanol was not observed in the absence of oxygen. Calculations by him, indicated that lung tissue accounted for approximately, 30-40% invivo rates of ethanol oxidation.

1.7.1.2 A microsomal ethanol oxidising system was present in the lungs of rats, the activity of which was increased 25 percent by feeding rats, ethanol for 4 weeks. This system had properties similar to the liver MEOS. Inhibitor studies, showed that the ethanol oxidising activity was not due to catalase or alcohol dehydrogenase (Seitz. H et al, 1980).

1.7.1.3 Chronic non-tuberculous pulmonary disease such
as bronchitis, emphysema, pulmonary fibrosis, bronchiectasis, chronic airway obstruction and impairment of gas diffusion have been described in association with alcoholism (Banner, 1973; Emirgil et al., 1974; Cohen et al., 1979).

1.7.1.4 According to Tadeusz et al. (1973), two types of respiratory insufficiencies were observed in dogs after acute ethanol poisoning, an initial obturation due to occlusion of the respiratory pathway and a subsequent restriction due to the effects of ethanol on the nerve muscle pathway.

1.7.1.5 The administration of ethanol, 30% in aqueous solution to rats, at 3 ml/day for 8 weeks intragastrically, affected lung surfactant activity as shown by an increase in surface tension and a decrease in phospholipid content of the lung. (Krishnan and Ramakrishnan, 1973).

1.7.2 Pathological lipid accumulation within alveolar spaces occur in several conditions, such as in a rare human disease, alveolar proteinosis (Davidson and Macleod, 1969), in response to inhaled silica in high doses in rats (Heppleston et al., 1972).

1.7.3 A common condition affecting the lung is the Respiratory Distress Syndrome, also called the Hyaline
Membrane Disease (HMD). In this condition the pulmonary surfactant is grossly diminished and the lungs are unstable and tend to collapse.

1.7.3.1 The major surface tension lowering lecithin, present in the normal fetal lung is dipalmitoyl lecithin. Gluck et al (1972) have reported that surface active lecithins disappear from tracheal aspirate, during the time when the infant is developing HMD.

1.7.3.2 Infants of diabetic mothers developed HMD, as a result of delayed activation of the dipalmitoyl lecithin synthetic pathway (Whitfield et al, 1973).

1.7.4 In pig lung homogenates, cholesterol was reported by Suzuki et al (1976), to be the most active inhibitory material in the formation of a stable alveolar lining, by the lung surfactant. Free fatty acids, also had a marked inhibitory activity. The findings are highly significant in pathological lung conditions, such as atelectasis, in the newborn.

1.7.5 Human lung carcinoma tissues of various histological types, showed a marked increase in the glycolipid fractions (Yoda Yuhachiro, 1979).

1.7.6 The sialate content of mouse lung cancer cells were found to be markedly elevated when compared to their normal counterparts (Vilarem et al, 1981).
1. **AVAILABLE THERAPEUTIC MEASURES**

1.8.1 Alcoholism, is now considered as a treatable disorder. Apart from psychiatric treatment, some drugs are employed to detoxify ethanol in the body systems. Drug therapy can be employed both for relieving the acute bout of alcoholism and as a valuable adjunct in the rehabilitation programme.

1.8.2 Abstinence from alcohol and the provision of diet with sufficient calories, vitamins and protein are the mainstays of therapy, for alcoholic liver disease *(Volwiler et al, 1948)*.

1.8.3 Minor tranquilisers such as chlordiazepoxide or hydroxyzine are used in acute alcoholic intoxication to eliminate anxiety, tension, agitation, apprehension and confusion without affecting mental alertness.

1.8.3.1 Tricyclic antidepressant agents like amphetamine, ametryptiline and caffeine have also been tested. Diphenylhydantion is used in treating the convulsions but the side effects, include nystagmus, dizziness, muscular inordination and insomnia.

1.8.3.2 Thyrotropin releasing hormone (TRH) and
other peptides have been found to antagonise ethanol depression (Porter et al., 1977). The action is not related to thyroid hormone action. The use of pyrazoles, an alcohol dehydrogenase inhibitor has been discontinued lately, due to undesirable side effects.

1.8.3.3 Propranolol, has been tested as a 'sobering pill'. Studies by Noble et al. (1973), however, revealed that propranolol, showed significant synergistic effect with alcohol and their reports point to possible danger of alcohol ingestion by patients, who take propranolol for cardiac arrhythmias.

1.8.4 Rehabilitation of alcoholics is primarily aimed at overcoming the depressions and withdrawal symptoms, common in most alcoholics with the lowering of blood alcohol levels. This is done mainly with the help of psychiatric treatment and use of antidepressants, which produce a noted drug alcohol interaction.

1.8.4.1 One such is disulfiram (bis-(diethyl thio carbamyl disulphide)) sold under the trade name 'Antabuse'. Disulfiram is a strong inhibitor of aldehyde dehydrogenase and causes an increased blood acetaldehyde levels. It is relatively inert in the
body, but when alcohol is drunk, unpleasant symptoms set in. They include, flushing, headache, nausea, vomiting, sweating, tachycardia, chest pain, dyspnea and occasionally hypotension syncope or even death.

1.8.4.2 Other drugs which produce an effect similar to the disulfiram - ethanol reaction, include calcium cyanamide, hypoglycemic agents such as tolbutamide, chlorpropamide, analgesic and antiarthritic agents such as phenylbutazone.

1.8.5 Santos - Ruiz et al (1983), reported the role of lipotropic factors, UDP-glucose, CDP-choline, S-adenosylmethionine and coenzyme A in decreasing, the lipid content of tissues and plasma and increasing the fat mobilization. Bobboi et al (1984), have shown the efficacy of garlic oil in reducing the hyperlipemic effects of ethanol.

1.8.6 In the traditional Indian medicine, drug and alcohol dependence are considered to be similar ailments and in the control of alcohol addiction, the therapeutic measures were aimed at reducing burning sensation, arrest of thirst, to stimulate the function of liver and spleen, increase digestion, promote appetite and improve health.
1.8.6.1 A popular mode of vehicle for alcohol based liquid formula is obtained by fermenting sugar solutions with herbal mixture of roots, barks, leaves stems, flowers or fruits, having the appropriate pharmacological property. The product obtained will have extracted the active drugs, in the herbal ingredients.

1.8.6.2 The search for drugs to combat alcohol related disorders, should be aimed at obtaining therapeutic measures alongwith access to alcohol, but which will inhibit the desire or craving for the drink. Our drug 'SKV', is designed to work on these lines in accordance with the Indian concept of medicine.

1.9 SCOPE OF THE PRESENT INVESTIGATIONS

1.9.1 Plasma and tissue lipid variations in ethanol induced toxicity in lungs has centred around the investigation of free and ester cholesterol, phospholipid, triglycerides and their free fatty acids. Not much has been understood about glycolipid changes. In the present investigations, attention was focussed on the carbohydrate components of glycolipid and glycoproteins and the effect of 'SKV', upon these alterations.