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### RESEARCH ARTICLE

#### THE PATHOPHYSIOLOGY OF ALCOHOL AND THE ROLE OF NATURE AND NURTURE.

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#### Abstract

The spread of alcoholism at an epidemic rate is a cause of concern in the new millennium. As alcohol is a potential risk to both the health of an alcoholic and the society, an understanding of the factors that lead to the addiction, becomes very important. The addiction to alcohol had been considered to be primarily influenced by the nurturance factors for a very long time. The detection of the role of genetic factors and other physiological changes, in making a person addicted to alcohol, had been a breakthrough achievement. The research in this line has helped to ascertain that both nature and nurture play equally important roles in the pathophysiology of alcohol addiction. The origin of addiction is in the brain and is regulated by a complex interplay of neurotransmitters and genetic factors with the environmental factors. Many of the nurturance factors can be modulated by strong will. Knowledge about the genetic factors and physiological changes will help to design suitable therapeutic options for an alcoholic.

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#### Introduction:-

Life in the new millennium poses several challenges that question the survival of the human population. Some of these challenges include sweeping epidemics that claim the life of millions of people across the world. An addiction to drugs or alcohol is considered to be a personality disorder, but it is also seen as a worldwide epidemic of the new millennium, as the use of drugs and alcohol has reached an all-time high across the world (Saah, 2005). Alcoholism has been considered to be a character flaw, and it was believed that alcoholics are made by choice. However, multi-faceted research has shown that multiple factors like genetic, physiological and environmental influences play a role in controlling this behavior. This has allowed rephrasing the causes of alcoholism from "nature or nurture" to "nature and nurture". Alcoholism is now considered to be a health problem that arises as a consequence of several dynamic interactions between environmental conditions and the inherited genes (National institute of drug abuse, 2008). Due to the high occurrence of alcoholism in the relatives of alcoholics, alcoholism has been categorized as a familial disorder. Several studies grouped into five categories such as, twin studies, adoption studies, family studies, self-selection animal studies and genetic marker studies, have proved the role of heredity in alcoholism. Under twin studies, identical twins were found to be more concordant for alcoholism when compared to fraternal twins, as the identical twins are known to contain identical genetic constitution (Goodwin, 1971).

Influence of family members and other environmental factors such as poor economic status and poor social upbringings play a strong role in the development of alcoholism. However, research has shown that genes can also

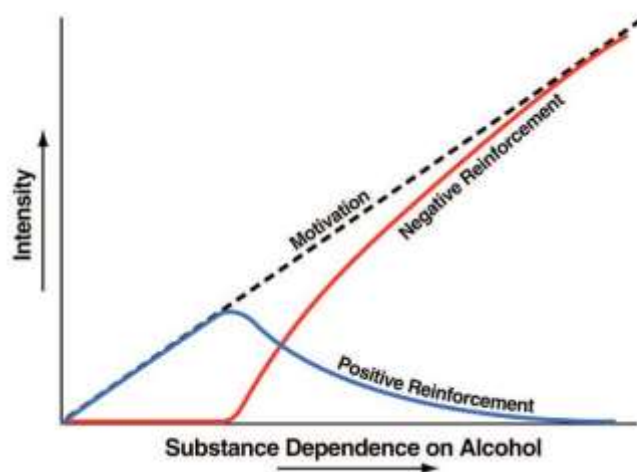
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control the response of the person towards various environmental factors. When the genes predisposed towards alcoholism are combined with poor social upbringing, the child has high chances of becoming alcoholic later in their life. Hence, both nature and nurture have a strong role in the pathophysiology of alcoholism.

#### **Addiction – its Meaning and its Neural Origin:-**

Addiction is characterized by compulsive, out-of-control desire for any substance despite serious negative consequences. The person gradually loses control in limiting his/her intake and reverts to a negative emotional state. Initially addiction is driven by impulsivity as the person gets attracted towards the positive reinforcement. Gradually addiction progresses towards compulsivity as the person is forced to drink alcohol to avoid negative reinforcement or withdrawal symptoms. The changes in positive and negative reinforcement with the progress of alcohol dependence are given in figure 1. The person starts showing withdrawal symptoms like anxiety, irritability and dysphoria, when he/she is deprived of the addictive substance such as drugs or alcohol. So addiction is alternatively known as substance dependence. Addiction is considered to be a chronic relapsing disorder during which a change in the neurobiological mechanism is observed as an individual moves from one domain to another. Alcoholism is also considered to be a substance abuse, as the person fails to meet the obligations at office and schools, affecting the performance of the person (Koob, 2011).



**Figure 1:-** A graphical representation of the changes in positive and negative reinforcement as the dependence on alcohol proceeds (Koob, 2011).

The human brain contains a complex network of several million neurons that mutually communicate to give rise to various thoughts, perceptions, emotions and drives. Food, water, nurturing and sex are certain natural rewards that give the person a sense of pleasure when he/she is eating, drinking, being nurtured and procreating. These pleasurable feelings strengthen the behavior and the person has an urge to repeat it. Often, an addictive drug is taken for the first time by choice, to achieve a sense of pleasure, as these addictive substances are both rewarding and reinforcing. The reward pathway, also known as pleasure pathway or mesolimbic pathway, is located in the limbic system of the brain and is responsible for such behaviors. Major structures involved in the reward pathway are nucleus accumbens, ventral tegmental area (VTA) and prefrontal cortex. Neurons help in the transmission of messages between these structures. The neurotransmitter, dopamine, is present in the neurons of VTA, and gets released to nucleus accumbens and prefrontal cortex when the brain receives a rewarding stimulus. This surge in the levels of dopamine creates a feeling of pleasure and gets recorded in the brain. Gradually, a person enters into a compulsive behavioral state and starts feeling that the addictive substances are necessary for a comfortable survival. As the behavior is reinforcing, the person tries all means to procure the addictive substances, even though he encounters negative consequences. The addictive substances affect specific regions of the brain and hamper the control over desires and emotions. As a result, the person craves for these substances even when they have lost their power to reward (Volkow, n.d.) (National Institute of Drug Abuse, 2007).

#### **Statistics of Alcohol Addiction:-**

Alcohol is commonly consumed in social gatherings in many parts of the world. Unfortunately, many people succumb to alcohol abuse even though they have the knowledge about the negative effects associated with its

consumption. Moreover, drug and alcohol dependence has been often found together. Dependence on one substance increases the craving for the other. For example, drug users are more likely to become alcohol dependent in comparison to normal individuals.

According to a survey conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), 8.5 percent of adults were found to be alcoholics in the U.S. alone (National institute on alcohol abuse and alcoholism, 2008). The statistics provided by the World Health Organization (WHO) show that alcohol abuse leads to at least 1.8 million deaths and 58.3 million of Disability-Adjusted Life Years (DALYs) worldwide (Worldometers, n.d). The ratio of people suffering from psychiatric conditions is also very high amongst these people. The chance of becoming alcoholic has been estimated to be around 12% during the entire lifespan of an individual. Alcoholism is a cause of huge economic burden in the countries of its high prevalence. These economic losses are mainly considered to be due to the loss of workplace productivity, health care expenses, costs related to accidents and criminal justice expenses, as these persons have high chances of involvement in crimes. Table 1 shows a drastic increase in the alcohol-related hospital admissions in England, during the last decade. This accounts for huge increase in the hospital related expenditure, due to the consumption of alcohol. Excessive consumption of alcohol has devastating impacts on an individual's family, community and economy (Centers for Disease Control and Prevention, 2013). These statistics serve as alarming signals to prioritize the need to control alcoholism at early stages and spread awareness about the negative effects of alcoholism

England	Approx. number of admissions, by financial year									
	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12
Alcohol-related NHS hospital admissions based on primary and secondary diagnoses	510,700	570,100	644,700	736,000	802,000	863,500	945,400	1,056,900	1,168,300	1,220,300
NHS hospital admissions with a primary diagnosis wholly or partly	142,000	151,000	160,500	173,900	179,900	181,300	185,800	194,800	198,900	200,900

**Table 1:-** A table showing the increase in alcohol-related hospital admissions from the year 2002/2003 to 2011/2012 In England (Institute of Alcohol Studies, 2013).

### Signs and Symptoms of Alcohol Addiction:-

Alcoholism is considered to be a progressive disorder, as one usually starts as a social drinker and gradually rises up to become alcohol dependent. The transition period from a moderate or social use to alcohol dependence largely goes unnoticed. Hence, the knowledge about the warning signs and symptoms of alcoholism is very essential so that alcohol consumption can be stopped at the right time. Alcohol abusers are considered to be in their initial stages of the problem drinking as they have the capacity to set limits on their drinking. These people show some common symptoms like consumption of alcohol to relax or relieve stress, continue drinking even after encountering multiple problems and neglecting the responsibilities at workplace, home, school, etc. Being an alcohol abuser is a major risk factor for developing alcoholism (physical dependence on alcohol). Alcoholism is considered to be a more severe problem as it includes all the symptoms of alcohol abuse, along with the physical dependence on alcohol. The person starts feeling the necessity to drink more every day in comparison to the previous day to feel relaxed. An alcoholic tries to drink in large quantities in order to get relieved of stress or avoid withdrawal symptoms like anxiety, depression, sweating, nausea, vomiting, irritability, headache and shakiness. The person loses control over the quantity of alcohol consumed and fails to quit because of the unwanted withdrawal symptoms. The person starts retracting from all the activities that are liked by him or her, for example, pursuing hobbies. The alcoholic wastes a lot of productive time in drinking or recovering from its negative effects (Centers for Disease Control and Prevention, 2013). Sometimes, the withdrawal symptoms are very severe like hallucinations, seizures, fever and confusion. Hence, it is advisable to seek a doctor's help when an alcoholic wants to quit it.

### Influence of Various Natural Factors on Alcoholism:-

Various factors such as gender, age, race and the age of maturity have been found to influence the tendency to become alcoholic. These factors have been discussed below.

**Influence of Gender on Alcoholism:-**

The manifestations of certain risk factors for alcohol use and problems are found to be naturally less in women when compared to men. Some psychosocial factors like acquiring social sanction for drinking and their inherent capacity to play multiple roles in society, act as protective factors and prevent them from getting succumbed to excessive drinking. Research across different races has shown that the proportion of women drinking alcohol is less compared to men. As a result, the alcohol-related problems have also found to be less in women when compared to men. Biological factors such as genetics and alcohol sensitivity or reactivity have been recognized to be the cause behind gender differences in alcoholism. Some studies suggest that genetics plays a stronger role in alcoholism for men in comparison to women. However, contradictory results like, the equal contribution of genetics to alcoholism in both men and women, has been observed in some studies. Hence, further research is required to ascertain the role of genetics. Low alcohol reactivity in men has been found to be associated with the history of familial risk for alcohol-related problems. Hence, low alcohol reactivity could be involved in the development of alcohol-use disorders in men. Cognitive and motor impairment is found to be high in women even when they consume low doses of alcohol. This suggests that women exhibit greater alcohol reactivity. In many societies, drinking by women is discouraged and drinking is strongly considered to be a part of male gender role. Women who show certain traditional feminine traits as a nurturance, emotional expressivity are less involved in drinking. Males have a natural tendency to start drinking to avoid negative feelings such as depression or stress, but women usually do not report such motives. Unfortunately, these psychosocial factors and biological factors are not able to inhibit the women of the current generations from drinking, as some recent studies have shown that this gender difference in alcoholism is gradually decreasing (Nolen-Hoeksema, 2004).

**Influence of Age on Alcoholism:-**

The use of alcohol and other drugs is found to be more prevalent in adolescents than adults. According to a national survey, a high percentage of students have been reported to have used alcohol during their lifetime (54% of 8th graders and 82% of 12th graders). Reports show that some of them have been involved in heavy drinking, that is, consumption of 5 or more drinks in a single occasion. Underage drinking strongly influences alcohol abuse and alcohol dependence in adults. In fact, children who start drinking at an early age of 14 years or below are more likely to become alcohol dependent in their lifetime in comparison to children who start drinking at the age of 20 years or later. Many factors such as lack of awareness, immaturity and a desire to explore something new such as alcohol, drives adolescents towards alcohol. Alcohol impairs the neural development and affects the adolescent brain. Hence, educating children about the negatives of alcohol consumption can reduce the incidences of abuse to some extent.

**Influence of Race on Alcoholism:-**

Variations in drinking and alcohol related problems have been observed across ethnicities, during national surveys. Amongst the various ethnic minorities (blacks, Asian-Americans, Hispanics and Native Americans), high-risk drinking was associated with Native Americans and Hispanics to a greater extent. However, gender and age group related differences exist within ethnic minorities. The risk for developing alcohol-use disorders is more in Whites and Native Americans in comparison to other ethnic groups. The chances of recurrent alcohol dependence or persistent dependence are more in Blacks and Hispanics in comparison to Whites. The consequences of drinking are more prominent in the minority groups, and the need for alcohol treatment is also more in these populations in comparison to Whites. Research has shown that a single variable cannot explain the observed pattern of drinking in minorities. Rather, multiple factors are involved in shaping the drinking patterns. Historical and cultural factors and individual environment influence the drinking pattern. People belonging to minorities often face problems like minority stress and socioeconomic stress as their financial resources are limited. Moreover, these people face a feeling of insecurity as they have migrated from their homeland and face difficulty in adapting to the new society. This insecurity leads to acculturative stress. Low ethnic identification and unfair treatment add to their stress. The high risk for alcohol abuse in these minorities is usually associated with the inability to cope up with these types of stresses. In contrast to the other minority groups, Asian-Americans show low rates of heavy alcohol use and hence, are also considered to be a model minority group. Certain biological factors such as the presence of ALDH2\*2 allele for alcohol dependence in Asians explains the low rates of heavy alcohol use in this minority group. Due to the presence of this allele, people belonging to this minority group show facial flushing and other aversive symptoms to alcohol. This allele is responsible for the protective effects against alcoholism, as the person tries to avoid alcohol consumption (Chartier and Caetano, n.d) (Caetano et al. 1998).

**Influence of Early Pregnancy on Alcoholism:-**

The early onset of puberty has been identified to be a significant risk factor for early pregnancy and several other negative outcomes as early sexual initiation, early substance use, depression and conduct problems. Adolescent pregnancy is directly associated with negative consequences such as reduced educational achievement and low income-earning potential. These negative outcomes impede the success of the early-maturing girl. A girl maturing at an early age is not prepared for this transition, both cognitively and emotionally. As a result, her coping resources are also too immature. The chances of using alcohol and cigarette by these girls are more when compared to the girls who experience menarche at the proper time. Research suggests that many young women use alcohol prior to sexual intercourse to avoid the usage of contraceptives. Hence, alcohol usage increases the likelihood of sexual intercourse in adolescents. However, as young girls enter into unplanned sexual intercourse, the chances of risky sexual behaviors and pregnancy are high. The alcohol use and age of sexual initiation play a significant role in determining the timing of pregnancy in girls who become pregnant in their young age (Deardorff et al. 2005).

**Pathophysiology of Alcohol Addiction:-**

Alcohol acts as a depressant on the central nervous system (CNS). Even though initial stages of drinking are marked by behavioral arousal, the continuation of drinking impairs the judgment and reaction time. These effects of alcohol on CNS were presumed to be due to the non-selective disruption of the lipid bilayers of the neurons. Current research has shown that alcohol acts by binding with and altering the function of specific proteins. These proteins belong to the voltage-dependent ion channels and membrane-bound ligand-gated ion channels (LGIC). The actions of alcohol are modulated through their effect on various neurotransmitters/ neuromodulators.

**Role of GABA<sub>A</sub> Receptors in Alcohol Addiction:-**

The major inhibitory transmitter of the brain is called Gamma aminobutyric acid (GABA) and GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub> are the three types of GABA receptors present in the brain. These receptors regulate neuronal excitability by mediating the fast inhibitory synaptic transmissions. Out of these receptors, GABA<sub>A</sub> receptors play a primary role in both short-term effects and long term effects of alcohol in CNS. As this receptor is a member of the family of transmembrane LGICs, it stimulates rapid neuronal transmission in the CNS of mammals. In the presence of the ligand such as alcohol, the ion channel of the GABA<sub>A</sub> receptors opens up, facilitating the transport of chloride ions. GABA is considered to be an inhibitory neurotransmitter, as its binding with the receptor reduces the ability of that neuron to conduct a neural impulse. The chloride ions released from the ion pores reach the postsynaptic cell after activation of the GABA<sub>A</sub> receptors. This moves the postsynaptic membrane potential far away from attaining its firing threshold. During acute exposure of GABA<sub>A</sub> receptors to alcohol, GABA-gated current is observed. GABAergic system has also been observed to be involved in self-administration of ethanol, hence proving its stimulatory role in the reward circuit in the mesolimbic system. GABA<sub>A</sub> receptors play a significant role in mediating the levels of dopamine in the mesolimbic dopamine system. GABA<sub>A</sub> receptor  $\alpha 1$  sub-units present in ventral tegmental area (VTA) of the mesolimbic pathway are decreased due to the long term exposure to alcohol. This stimulates the dopamine release, hence stimulating the reward circuit (Davies, 2003).

**Role of Serotonin Receptors (5 HT<sub>3</sub>) in Alcohol Addiction:-**

Serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter that is used by many neurons throughout the brain. The detection of serotonin metabolites in the cerebrospinal fluid and urine of alcoholic human beings paved the way for the discovery of the role of 5-HT in alcohol addiction. The 5-HT<sub>3</sub> receptor of the serotonergic (5-HT) system is unique as it directly gates an ion channel. The opening of the ion channel causes a rapid depolarization, stimulating the release of neurotransmitters and/or peptides. The mesolimbic dopamine (DA) pathway is regulated by the 5-HT<sub>3</sub> receptor that controls the addictive properties of drugs of abuse. The 5-HT inputs received by VTA and nucleus accumbens lead to an increase in the extracellular levels of both 5-HT and dopamine in the nucleus accumbens. Hence, the 5-HT<sub>3</sub> receptor regulates the alcohol consumption by regulating the alcohol's rewarding effects. The electrical signals generated by the 5-HT<sub>3</sub> receptor are further enhanced during acute alcohol exposure. Increased functioning of the 5-HT<sub>3</sub> receptor leads to excessive stimulation of neurons in the regions of the brain that receive information from serotonergic neurons. The ultimate effect of this excessive stimulation is the release of other neurotransmitters that are involved in alcohol intoxication. A prolonged exposure to alcohol stimulates adaption-related changes in the brain cells. For example, when the functioning of the neurotransmitter receptor is inhibited due to exposure to alcohol, the brain cells try to compensate this loss by increasing the number of receptors, or by changing the molecular makeup of the receptors. This type of adaptive change is observed in the 5-HT<sub>2</sub> receptor that increases in number to compensate for the loss of functioning of the neurotransmitter receptor (Engleman et al. 2008) (Loving, 1999).

**Role of N-methyl-d-aspartic acid (NMDA) receptors in Alcohol Addiction:-**

N-methyl-d-aspartic acid (NMDA) receptors are a type of glutamate receptors that play an important role in alcohol addiction. Prolonged exposure to ethanol inhibits the activity of these receptors leading to an upregulation of NMDAR mediated functions. This decreased sensitivity to alcohol is associated with acute tolerance and dependence to alcohol along with the delayed signs of alcohol withdrawal. The expression of certain sub-units of NMDAR is found to be altered under prolonged exposure to alcohol, for example, an increased expression of the splice variant forms of the NR1 sub-units and the expression of the NR2B. These changes in the sub-unit composition alter the NMDA ion channels so that the permeability for calcium ions is increased and the closing kinetics of the ion channel become slow. These changes are the underlying mechanisms behind the enhanced NMDAR activation after prolonged exposure to alcohol. The increase in the expression of the NR2B sub-unit leads to the increase in the inhibitory potential of the NMDAR antagonists that are NR2B subunit-selective. This demonstrates the role of NMDAR against alcohol withdrawal. Hence, selective NMDAR antagonists offer a high therapeutic potential against in pharmacotherapy of alcohol dependence (Nagy, 2005).

**Role of  $\delta$ -opiate receptors in Alcohol Addiction:-**

Studies suggest that endogenous opioids play a vital role in enhancing the rewarding properties of alcohol. The opioidergic transmission is affected by ethanol at multiple levels. Ethanol affects the biosynthesis and release of the opioid peptides that act as ligands to these receptors. It also effects the degradation and binding of these peptides to the receptors. The physiological action of alcohol is mediated via enkephalins and beta-endorphin (opioid peptides) that act as ligands to mu- and delta- opioid receptors. The binding of these ligands to receptors activates the mesolimbic dopamine system and positively reinforces the reward circuit of the brain. Acute or light alcohol consumption triggers the increased release of opioid peptides in different regions of the brain that ultimately increase the dopamine levels. However, a central opioid deficiency is observed during chronic heavy alcohol consumption. The opioid deficiency might be correlated to opioid withdrawal that promotes alcohol consumption through negative reinforcement. A clear understanding of the combined action of endogenous opioids, neurotransmitters and alcohol can help to design novel treatment options (Gianoulakis, 2001).

**Role of nicotinic receptors in Alcohol Addiction:-**

Due to the high co-morbidity between nicotine and alcohol abuse, it was presumed that nicotinic acetylcholine receptors (nAChRs) also played a vital role in alcohol dependence. The genomic regions that codes for  $\alpha 5^*$  nAChR subtype has been detected to be associated with alcohol dependence in human beings. nAChR is a member of the superfamily of ligand-gated ion channels that exists in three different states. It exists in resting, open or desensitized state at any given point of time. The transition from the resting to the open state allows an influx of the cations that depolarize the cell membranes. This increases the neuronal excitability. nACh receptors are expressed at the peri-synaptic, extra-synaptic and presynaptic sites of synapses that explains their role in modulating the neurotransmitter release. The direct effect of ethanol on the ion channel stimulates the release of a wide array of neurotransmitter/peptide systems that play a vital role in the initiation of the drinking behavior. Pharmacological manipulation of the subunit,  $\beta 2^*$  nAChRs can help in the modulation of the acute alcohol-responsive behaviors such as recovery-time and hypnosis (Dawson, 2008).

**Role of Alcohol dehydrogenase (ADH) in Alcohol Addiction:-**

Mitochondrial aldehyde dehydrogenase (ALDH2) and alcohol dehydrogenase (ADH) are the two vital enzymes that participate in the metabolism of the bulk of alcohol. These enzymes help in the elimination of the small quantities of alcohol consumed along with the diet. These enzymes are present in high concentrations in the liver and this pathway has evolved to detoxify environmental alcohols. However, the primary target of this pathway gets altered when one consumes alcohol in large quantities, as; under these conditions the oxidation of ethanol becomes the major energy source in the liver and affects the metabolism of other nutrients in the liver. Genetic studies have shown that the genes located on chromosome 4q (the region associated with the expression of alcohol dehydrogenase) are linked to alcoholism. Polymorphisms in these genes were noticed in families containing multiple members as alcoholics. The enzymes encoded by these polymorphic variants showed altered kinetic properties. Variations in *ADH4* gene were strongly associated with alcoholism. The pathophysiological effects of these variants are observed in the form of accumulation of acetaldehyde. *ADH* genotypes such as those showing the presence of an *ADH2\*2* allele govern the risk of development of alcoholism. The *ADH2\*2* codes for high-activity ADH  $\beta 2$ , and the inactive form of this gene is associated with a reduced risk for alcoholism. Other environmental factors such as national origin affect the association of these genes with alcoholism (Crabb et al. 2004).

**Role of Aldehyde Dehydrogenase (ALDH) in Alcohol Addiction:-**

Aldehyde dehydrogenases (ALDHs) promote the metabolism of both endogenous and exogenous aldehydes. ALDH2 plays a vital role in alcohol metabolism as it oxidizes acetaldehyde. A deficiency of ALDH2 was associated with the reduced risk of alcoholism in men. The deficiency also reduced the quantity and frequency of alcohol consumption by men. Individuals heterozygous for *ALDH2*\*2 showed protective effect against alcoholism (Crabb et al. 2004).

**Role of Microsomal Oxidation System (MEOS) in Alcohol Addiction:-**

Even though, the oxidation of ethanol through alcohol dehydrogenase (ADH) explains the effects of alcohol in our body, the role of the enzyme, alcohol dehydrogenase, in alcohol tolerance could not be proved. Moreover, it was observed that smooth endoplasmic reticulum (SER) gets proliferated during the post alcohol consumption stages. This suggests that an additional pathway known as the microsomal ethanol oxidizing system (MEOS) cytochrome P450 might be actually involved in alcohol tolerance. The activity of MEOS has been observed to increase after chronic alcohol consumption. This increased activity is associated with the rise in cytochrome P450 and CYP2E1. Free radicals are released in significant quantities due to metabolism by CYP2E1. These free radicals impact the defense systems of the body that act against oxidative stress, hence playing a vital role in the pathogenesis of the alcoholic liver disease (Lieber, 2004).

**Genetics in Alcohol Addiction:-**

The co-occurrence of the dependence to alcohol and any other drug suggests the role of genetic factors behind alcohol addiction. Moreover, the inheritance of the trait for alcohol dependence has been detected in 40 and 70% of people. Genetic factors, along with environment, determine the susceptibility to alcohol dependence.

**Role of Alcohol Dehydrogenase Allele ADH1 B\*3 in Alcohol Addiction:-**

ADH and aldehyde dehydrogenase (ALDH) play a vital role in alcohol metabolism, and the genes that encode these enzymes exist in several variants or alleles. The variant forms of these enzymes are known as isoforms and they differ in their ability to metabolize alcohol. ADH1B is one variant isoform of ADH and is encoded by several alleles. *ADH1B*\*3 is one such allele that encodes for this variant isoform. This allele has been detected only in the people of Native American tribes and in people of African descent. The ADH isoform encoded by *ADH1B*\*3 allele causes a more rapid breakdown of alcohol, hence leading to a temporary accumulation of acetaldehyde. The chances of family history of alcoholism are less in people carrying this allele. The response to alcohol is less rewarding in these people, and hence keeps them away from alcohol (Scott and Taylor, 2007).

**Role of Dopamine Receptor Gene, DRD2 in Alcohol Addiction:-**

Out of the several genes that code for the receptors of dopamine, DRD2 (dopamine receptor gene) has been detected to influence the reinforcing and motivating effects of alcohol. The quantity of the DRD2 protein in an individual depends on the expression of both alleles. Polymorphism in its alleles affects the expression of the receptors. Each allele of DRD2 represents a distinct haplotype. Studies suggest that haplotypes composed of polymorphisms in DRD2 alleles are associated with the decreased expression of the receptors. Such polymorphisms are more common in alcoholics than in healthy individuals. Further, haplotypes leading to the decreased expression of DRD2 were also correlated with alcohol dependence (Kraschewski et al. 2009).

**Specific Nature of the ALDH2 Gene Variation:-**

The conversion of the acetaldehyde to acetate and water takes place in the presence of ALDH enzyme (more specifically in the presence of mitochondrial ALDH2 isozyme). Individuals with ALDH2 variants show alterations in the rate of ethanol oxidation. Facial flushing after alcohol consumption has been observed in people belonging to some areas, such as people belonging to China, Japan and Korea. This negative reaction to alcohol was also observed in Asian infants who were fed with alcohol, suggesting a genetic link behind this reaction. The inheritance pattern of the flush reaction was studied. It was detected that this reaction was inherited as a dominant trait. The accumulation of acetaldehyde causes flushing reaction. The mutant allele ALDH2 is created due to the G→A substitution, leading to the replacement of glutamate with lysine in ALDH2 enzyme at position 487. Individuals heterozygous for *ALDH2*\*2 show a reduced ALDH2 activity, whereas individuals homozygous to this allele do not show any ALDH2 activity at all. Individuals having a dominant negative allele for *ALDH2*\*2 show a reduced risk for alcoholism. Hence, individuals heterozygous for *ALDH2*\*2 show a protective effect against alcoholism (Crabb et al. 2004).

**Susceptibility to Alcohol Addiction is the Result of Interaction between Many Genes:-**

Using an approach that combines genome-wide association studies (GWAS) with the information about the proteins that interact with each other, it was possible to identify at least 39 genes that work in a complex network and are associated with alcohol dependence. Firstly, these genes that influence the alcohol metabolism are mostly those genes that encode for the enzymes involved in the metabolism of alcohol. Secondly, the genes coding for the proteins involved in the neurotransmission are also responsible for alcohol addiction. An association between some other types of genes such as taste receptor genes and alcohol addiction has also been detected. A complex interaction between these genes decides the risk of alcohol addiction in an individual.

**The Role of Nurture in Alcohol Addiction:-**

Even though natural factors such as race, gender, age and genetics influence the pathophysiology of alcohol addiction, nurturance also contributes towards the development of alcohol addiction to a great extent. The environment in which a person grows and the people with whom he is associated with, also decide whether a person ends up as an alcoholic. During adoption studies, twins born to alcoholic parents were separated and nurtured in different environments. The child who was nurtured in a healthy environment and kept away from alcohol did not develop alcohol addiction when compared to his other counterpart.

**The Role of Food and Drinks in Alcohol Addiction:-**

In many parts of the world, alcohol is directly used as an ingredient while cooking. It is used to tenderize meat or sometimes just to add flavor. Vinegars made of alcohol are also added to food substances. Some chocolates and desert items also contain alcohol, and eating such food stuffs can increase the craving for alcohol. Consumption of highly processed foods and sugar-rich foods and drinks leads to quick sugar flush in the body followed by a sharp fall in the sugar levels that increases the craving for alcohol. It is better to take foods containing complex carbohydrates and fiber that keep the sugar levels in our body at a constant level. Consumption of sodas and juices should also be avoided as far as possible. A healthy balanced diet rich in fruits and vegetables can control alcohol addiction to a great extent (Curinga, n.d.).

**The Role of Environment in Alcohol Addiction:-**

The cultural patterns of people living in cold countries suit their requirement that is, getting adapted to extreme cold. Under such cold conditions, people often develop hypothermia. This condition is marked by a drop in the core temperature of the body to subnormal levels that may prove to be life threatening. In order to cope up with such a situation, people end up taking a drink so that they can keep their body warm. But, there are high chances to become alcohol addicted thereafter. In countries like America, consumption of alcohol by elders during religious occasions and social gatherings is highly acceptable. Moreover, people belonging to these areas feel that adults can handle alcohol intake and control it whenever they want. Self-imposed protocols of drinking rituals, in some parts of the world, influence the levels of drinking. In countries like the U.S and the U.K., alcohol is used to celebrate the transition from work to play. Alcohol is associated with responsibility and recreation (Social Issues Research Centre, n.d.).

**The Role of Stresses in Alcohol Addiction:-**

The initiation and continuation of the addiction to alcohol is mainly influenced by stress. The reasons behind stress can be of many types like economic crunch, job problems or clash with the spouse. However, stress has been reported to be the cause of the initiation of alcohol addiction. Stress alters the activities of certain brain regions and alters the activity of the hypothalamic-pituitary-adrenal (HPA) axis and promotes addiction to alcohol. Stressful conditions can reinstate a person to consume alcohol even after a brief period of abstinence.

**Role of Family and Friends in Alcohol Addiction:-**

Studies have shown that children who grow up seeing their elders consuming alcohol are more likely to become alcoholic, as drinking is an acceptable norm for them and they easily get the permission for the same. Multiple members of the same family turn out to be alcoholic, as they are all nurtured under a similar kind of environment and interact with similar people. An easy access to alcoholic drinks through friends and family members also decides whether a child develops to become an alcoholic. Children who have developmental or behavioral issues tend to become alcoholic. Many adolescents and children become misguided by certain messages like alcohol can do good when consumed in small quantities, or it relaxes the body and relieves a person of all the stress (Social Issues Research Centre, n.d.).

**Diseases and Disorders with Alcohol Addiction:-**

Alcohol gets transported through the blood to all parts of the body, and hence affects the body systems in different ways. Liver damage is mainly associated with alcohol consumption as the liver is the main site of alcohol metabolism. The byproducts of alcohol, mainly free radicals, remain in the liver, leading to inflammation or scarring of the liver, and causing diseases like alcoholic hepatitis and cirrhosis. Inflammation of the esophagus is also observed in alcoholic patients. In acute cases, it leads to esophageal cancer. Cancers in various parts of the body like mouth, throat, breast, and pancreas are associated with the increased consumption of alcohol. Heavy drinkers have high chances of developing gastritis or inflammation of the stomach. The chances of being attacked by the bacterium *Helicobacter pylori* (*H. pylori*) are high in such people. Alcohol affects the pumping action of the heart by interfering with the sodium-potassium pump. This pump allows the electrical impulse to travel through the heart. Long term effects of alcohol involve the effect on the mitochondria of the heart cells. People who drink more than four drinks per day suffer from high blood pressure or hypertension. Alcohol changes the levels of various hormones and neurotransmitters that are involved in the regulation of the cardiac functions. High rates of deaths caused by coronary artery disease have also been noticed in alcoholics. Children born to alcoholics have been found to suffer from fetal alcohol syndrome (FAS). Alcohol impacts the behavior of a person too, as its effects in brain are long standing. The person becomes aggressing and loses control over his/her actions.

**Treatment and Medications for alcohol addiction:-**

An understanding about the pathophysiology of alcohol addiction had helped in the treatment of this chronic disease. The treatment plan should combine both behavioral therapy and pharmacological treatments, as the treatment cannot be complete without psychological component. Under behavioral treatment, patients who are resistant to treatment are motivated, and under cognitive-behavioral therapy, people are educated about the skills that help them to stay away from alcohol. The positive behavior of these patients is encouraged during contingency management interventions. Pharmacological treatment is done with the help of certain drugs that inhibit the pathophysiology of addiction in a number of ways. The drug Disulfiram is given to alcoholics as it interferes with the metabolism of alcohol. If a person consumes alcohol while taking this drug, the concentration of alcohol increases in the body. A person suffers from unpleasant effects such as flushing of face, nervousness and nausea. Naltrexone is another successful drug in this line, as it blocks the action of the opiate receptors. Naltrexone blocks the action of receptors for endorphins that are the hormones involved in the craving for alcohol. As a result, the person loses the desire for alcohol. This drug also inhibits the relapse of the drinking habit. Acamprosate affects the functioning of the neurotransmitters. This drug has proven success in reducing the risk of heavy drinking. Anticonvulsant medications like Topiramate have proved to be effective in treating alcohol dependence. Treatment of an alcoholic can only be complete with the support of the family members and self-determination of the person (National institute on alcohol abuse and alcoholism, 2008).

**Conclusion:-**

Alcoholism is a public health problem that affects the well being of many people across the world. Heavy drinking not only hampers the individual's health, but also affects the life of the people associated with the person. The loss in the working capacity of an alcoholic directly affects his/her earning potential and productivity. This, in turn, disturbs relationships. Even though limited alcohol intake is encouraged in some societies, one should always keep in mind that an invisible line separates pleasure drinking from alcohol addiction. Many people fail to recognize when they have crossed the barrier. Hence, it is always advisable to avoid alcohol. Current research has shown that both nature and nurture are involved in developing an alcoholic. Research has helped to understand the pathway of addiction so that drugs that can interfere at specific locations can be designed. An understanding of the alterations in the genetic factors that lead to alcohol addiction can also help in designing proper therapeutic measures. Understanding of the various factors that contribute towards proper nurturing like proper food, good friends and proper guidance by the family members is also very essential to reduce the frequency of alcoholism. Alcohol addiction can be effectively controlled only when the contributions by nature and nurture are analyzed together.