Second-Hand Risk Health Tragedies and Human Right Violations due to Ethanol Consumption. Biochemical basis for metabolic and behavioral Tragedies due to Ethanol Consumption

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Introduction

Everywhere a nonsmoker who is an alcohol consumer, complains of secondhand smoke, without being aware of second-hand risk health tragedies and human rights violations provoked by alcohol consumption.

Here we analyze the concept, mainly unexplored, of dramatic adverse health effects and of human rights violations against third
parties generated for alcohol consumption by others; and also, the harm due to the chemical transient prefrontal lobotomy generated by alcohol consumption.

Alcohol consumption has been a part of the everyday human diet for centuries, especially because of the fact that alcoholic beverages are a safe means of hydration wherever clear water has not been available [1].

Old patients could, simultaneously be part of the alcohol consumers and/or secondhand victims. Before deciding to analyze the geriatric problems, we propose the allegorical model, based on Scott, Ellison, and Sinclair, as it was published in Nature Aging, in July 2021. We divide the theoretical analysis with four fundamental alternatives [2]:

The extension of life (Struldbrug case). In Jonathan Swift’s 1726 novel “Gulliver’s Travels”, the struldbrugs were humans born apparently normal. The Struldbruggs, however immortal however they age normally, live in continuously deteriorating health. This takes us to the philosophical alternative of: “living or lasting” [2].

To lower morbidity (Dorian Gray case). Narratively, in “The Picture of Dorian Gray” a philosophical novel by Oscar Wilde, Dorian Gray owns a portrait of himself and while the picture ages, Dorian Gray does not change, maintaining his health and appearance until death [2]. Slowing aging (Peter Pan case). In this extreme case, where aging is not just slowed but canceled, the mortality and the health become independent of the age, and thus the individual is ‘forever young’. This constitutes the ‘Peter Pan’ case, after the play and novel about a boy who never grows old. This closely corresponds to the Hypocaloric diet claiming that it slows aging [2].

To reverse aging physical damage is repaired instead of slowed. This is a close analogy to the “Theseus Boat” as well as the regeneration of salamanders and lizards and transplants from donors. Desiderative, this is the future of organoids and the engineering of the pluripotent cell [2].

Social Determinants of the Passive Health Victims

Alcohol consumption has been calculated to cause more than 80,000 deaths yearly in the United States. More than half of these deaths are produced by drunk driving accidents and alcohol-vinculated homicides and suicides, and approximately fifteen thousand deaths yearly are the result of cirrhosis [3]. Dramatically, contrary to common doxastic beliefs, alcohol consumption is much more of a cause of passive health casualties in third parties than cirrhosis in the ethanol consumer.

The social determinants are thus the product of composite behavior of a subset of the population that provokes the effect on the passive health victims. Considering that all there is in the universe are subatomic particles, i.e., leptons and quarks, Higgs Boson, and additionally obeying the four only existing forces, the gravitational, the electromagnetic, the weak nuclear, and the strong nuclear. There is no evidence of physical-chemical unique properties inside of the cranium being different from the chemistry outside. Thus, as Peter W. Atkins, Fellow of Lincoln College at the University of Oxford and also the author of the classic text on physical chemistry: “Because our brains are made of elements, even our opinion is, in a sense, properties of the chemical [elements]” [4]. These concepts extend over doxas, thoughts, desiderata, feelings, ideas, comprehension, ideals, logic, mathematics and, absolutely all human behavior.

All of the above is instanced as accidents, abandonment of the minors, breach of family and professional commitments (pacta sunt servanda), failure in the structure for a reliable
work team, additionally as a decrease in the attention span in vital aspects, intellectual, professionals in high-risk situations, etc. Furthermore, there is a decrease in the acquisition of new concepts, high failure in complex tasks, underestimation of possible adverse consequences due to deteriorated judgment, greater willingness to accept risks due to the damage of prefrontal effect. Clearly, pilots, surgeons, bus drivers, taxi drivers, operation of high-risk machinery in factories and outdoors, and in general, being part of trusted teamwork, ideally, legislative activities become a giant cause of harm to third parties. This constitutes the worst hamartia. Paradoxically, the larger the damage to the patient due to alcohol consumption, the less probable that the patient could produce a secondhand effect on passive subjects. These patients are unable to drive or even leave their room in the hospital.

According to The Constitution of the World Health Organization, Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity [5]. The extension to all peoples of the benefits of medical, psychological, and related knowledge is essential to the fullest attainment of health [5]. The objective of the World Health Organization shall be the attainment by all peoples of the highest possible level of health [5]. It is dialectically evident that at the bottom of most etiologies it is a behavioral substrate which is determinant of the tragedies which tend to be superficially considered in most of the desiderative and doxastic analysis [6].

Francis Bacon, clearly the father of empiricism, and one of the founders of science, who was introduced to a French audience as the “father” of the scientific method in 1733 by Voltaire, strongly warned about the “idols of the mind” and the process of purging information. Bacon’s epagogical inference, probabilistic inductive inference insisting that the experience must be purged (pars destruens), as the precursor of John Stuart Mill’s methods, for the correct approach to understand nature [7].

All the principles and objectives of the CONSTITUTION OF THE WORLD HEALTH ORGANIZATION constitute desiderative and aspirational concepts. They are all Baconian Idols of the Tribe, according to which it is assumed order and purpose in things; as well as the Idols of the Theater, representing the world as a stage, the Idols of the theater are prejudices coming either from authority or from traditional philosophical systems, resembling plays in so far as they generate fictional worlds, which have never been exposed to the right experimental check. Therefore, the idols of the theater have their origin in a dogmatic philosophy or, even worse, in the wrong laws of demonstration [5].

It is pertinent to consider what was stated by the Director-General World Health Organization, Dr. Tedros Adhanom Ghebreyesus, in the Global status report on alcohol and health 2018 World Health Organization: Alcohol use is part of many cultural, religious, and social practices, and provides perceived pleasure to many users. This new report shows the other side of alcohol: the lives of its harmful use claims, the diseases it triggers, the violence and injuries it causes, and the pain and suffering endured as a result [5].

While less than 50% of the world’s adults have consumed alcohol in the last 12 years, the global burden of disease caused by its harmful use is enormous. It exceeds those caused by many other risk factors and diseases high on the global health agenda. More than 200 health conditions are linked to harmful alcohol use, ranging from liver diseases, road injuries and violence, to cancers, cardiovascular diseases, suicides, tuberculosis, and HIV/AIDS. We have no time to waste; it is time to deliver on alcohol control [4].
We maintain that alcohol control is not limited to enforcing restrictive laws. We need behavior engineering to apply thoroughly.

Dramatically, in 2016, of all deaths attributable to alcohol consumption worldwide, 28.7% were due to injuries, 21.3% due to digestive diseases, 19% due to cardiovascular diseases, 12.9% due to infectious diseases, and 12.6% due to cancers. About 49% of alcohol-attributable causes are due to non-communicable and mental health conditions, and about 40% are due to injuries [5].

It is clear that the Second-Hand Risk health Tragedies and Human Rights Violations due to Alcohol Consumption, constitute a violation of human rights. According to the Universal Declaration of Human Rights in its Article 25.1: Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing, and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control [8].

Physiopathology of alcohol consumption

There are three major overlapping pathological lesions, Fatty Liver Disease, Alcoholic Hepatitis, and Cirrhosis, which paradoxically are inversely related to the third-party passive injury. It is the intoxicated man with a normal liver function, after an excessive ethanol drinking event, much more than the cirrhotic patient who already has encephalopathy, who constitutes the principal cause of death and the harm to the third parties. Therefore, the greater the hepatopathy, the less the probability of provoking third-party injury.

Alcohol is clearly a direct hepatotoxin; however, less than 20% of alcoholics will eventually develop alcoholic hepatitis [9-11]. Alcohol is also the third principal risk for disease burden. The cirrhosis and the related complications are closely correlated with the amount of alcohol consumed; both, per consumption, and cumulatively.

The most significant risk factors in developing the alcoholic liver disease are quantity and duration 8. These are scientifically proven facts that could mislead the consideration, already mentioned, that alcohol consumption produces more damage to third parties, mainly through accidents than the direct effect on the consumers.

Referred by The National Institute on Alcohol Abuse and Alcoholism, during the year 2016, of all deaths assignable to alcohol consumption worldwide, 28.7% were due to injuries, 21.3% were due to digestive diseases (primarily cirrhosis of the liver as well as pancreatitis), 19% were due to cardiovascular diseases, 12.9% were due to infectious diseases (including tuberculosis, pneumonia, and HIV/AIDS), and 12.6% were due to neoplasias (the most significant being those of the upper aerodigestive tract) [12].

Furthermore, all the non-considered effects in the number of incarcerated persons that are in jail for having provoked illness or death to third parties, constitute the basis for the adage that alcohol consumption takes more people to jail than to cirrhosis. Thus, we can teach the experts and the general population at large: the drinker should have more fear of ending in jail than becoming cirrhotic.

Approximately 12 g of alcohol are contained in one beer, in four ounces of wine, or just one ounce of 80 proof spirit [12].

Exists an evident paradoxical event such that, the more deteriorated the patient's liver is due to alcohol consumption the less the probability he has of provoking secondhand damage to others. Thus, having a clear conceptual image
of the physiopathological effects in the alcohol user, together with the neurochemical changes causing the behavioral effects which constitute the tragic condition caused by the consumer of alcohol in third parties, is essential in this presentation.

**Alcohol constitutes a direct Hepatotoxic**

Once acetyl-CoA is generated, it enters the normal Krebs cycle [1].

The excess of NADH also inhibits fatty acid oxidation. A fundamental metabolic result of fatty acid oxidation is the generation of NADH for ATP production through the electron transport chain, but alcohol consumers' NADH needs are met by alcohol metabolism. The excess NADH signals those conditions are appropriate for fatty acid synthesis. Therefore, triacylglycerols accumulate in the liver, leading to fatty liver, all of which is exacerbated in obese patients [3].

The initial step in the main pathway of alcohol metabolism is by the enzyme alcohol dehydrogenase which oxidizes alcohol to acetaldehyde and reduces NAD+ to NADH. Then acetaldehyde is oxidized by the enzyme acetaldehyde dehydrogenase, reducing more NAD+ to NADH.

The second most relevant pathway for alcohol metabolism is where it is subjected to the cytochrome P450 enzymes, the microsomal alcohol-oxidizing system (MEOS) produces acetaldehyde and subsequently acetate while oxidizing biosynthetic extreme reducing power, NADPH, to NADP+. The essential fact that the oxygen molecule is used in this pathway leads to the production of free radicals that tragically damage tissue. This extreme oxidative stress is potentiated as NADPH is being consumed, consequently decreasing the ability to neutralize this very extreme oxygen reactive species by avoiding the regeneration of glutathione molecule [13].

The cumulative effects of the other metabolites of alcohol: The hepatic mitochondria can convert the acetate into acetyl CoA by a reaction that requires ATP through a thiolkinase [13].

The Additional processing of Acetyl-CoA by the Krebs cycle is blocked [1]. The accumulation of acetyl CoA has extreme consequences: First, ketone bodies are formed and released into the blood, worsening the acidic situation already resulting from the high lactic acidosis. The metabolism of the lactate molecule in the liver becomes inefficient, leading to the accumulation of acetaldehyde, which is a very reactive compound that forms covalent bonds with many essential functional groups in proteins, damaging protein function. When alcohol is persistently consumed at high levels, acetaldehyde can importantly damage the liver and eventually produce cell death [1].

The ketone bodies are synthesized in the mitochondrial matrix. Acetyl-CoA is formed in the liver during oxidation of fatty acids or metabolism of alcohol, can either enter the Krebs cycle or suffer conversion to the three main ketone bodies, D-β-hydroxybutyrate, acetoacetate, and acetone, which are exported to other tissues [14].

Given the fact that the Krebs cycle is inactive due to the following:

In a precisely fine-tuned regulatory mechanism, the pyruvate dehydrogenase complex is uniquely inhibited by ATP, acetyl CoA, NADH, and fatty acids; Furthermore, the Citrate Synthase is inhibited by NADH, citrate, and ATP; additionally, the Isocitrate dehydrogenase is inhibited by ATP; and also, the α-ketoglutarate dehydrogenase complex is inhibited by NADH [14]. Then the excess of acetyl CoA in the mitochondria enters the synthesis of ketone bodies initiating from two molecules of acetyl-CoA.
The brain tissue which preferentially uses glucose as a fuel, is able, in extreme situations, to adapt to the utilization of acetoacetate and β-hydroxybutyrate. The brain cannot utilize fatty acids since fatty acids are incapable to cross the hematoencephalic barrier [14].

The Fatty Acid Synthesis

In all the cases in which a cell or organism possesses more than enough metabolic fuel to satisfy its energy demand, the excess tends to be converted to fatty acids and thus stored as lipids such as triacylglycerols. The reaction catalyzed by the enzyme acetyl CoA carboxylase is representative of the rate-limited step in the biosynthesis of the fatty acids. Every time the acetyl CoA concentrations of mitochondrial and ATP are elevated, then citrate is transported outside of the mitochondria where it then becomes the precursor of cytosolic acetyl-CoA and an allosteric determinant that activates acetyl CoA carboxylase.

The Malonyl CoA intermediate is thus generated from acetyl Co-A and bicarbonate. A carboxyl group, derivated from bicarbonate (HCO-3), is initially transferred to biotin in an absolute ATP-dependent reaction. The biotinyl group is a temporary carrier of CO2, transferring it to acetyl CoA consequently producing malonyl-CoA. This enzyme is denoted as fatty acid synthase. The reducing agent is then NADPH, two per cycle (stoichiometrically) and the activating groups are chemically two different -SH groups in the fatty acid synthase. The fatty acid synthesis occurs in the cytosol. Thus, having separated synthetic processes from degradative reactions. Typically, NADPH is the electron carrier for anabolic reactions [14].

The biosynthesis of triacylglycerols

All the carbohydrates, fat, protein, and alcohol consumed in excess are stored as triacylglycerols.

THE UREA CYCLE: The Ammonia molecule is extremely toxic to animals [14]. The catabolism of ammonia is a challenging evolutionary biochemical problem because ammonia is extremely toxic. The brain is extremely vulnerable; damage from ammonia toxicity produces clinically cognitive impairment, ataxia, and epileptic seizures. In extreme cases, swelling of the brain terminates as death [14].

To clear the cytosol from ammonia requires the reductive amination of α-ketoglutarate to glutamate by the enzyme glutamate dehydrogenase Furthermore, the conversion of glutamate into glutamine by-glutamine synthetase. In the brain exclusively the astrocytes express glutamine synthetase. Glutamate and its derivative γ amino butyrate (GABA) are fundamental neurotransmitters; some of the high sensitivity of the brain to ammonia is due to depletion of glutamate in the glutamine synthetase reaction [14].

The Metabolic hemodynamic favored destine of the amino groups: Due to the fact that only a few microorganisms can convert N2 to NH3, amino groups are sophisticatedly husbanded in biological systems. Four amino acids play fundamental roles in nitrogen metabolism: glutamate, glutamine, aspartate, and alanine. These amino acids are thermodynamically favored to be convertible into citric acid intermediates. Glutamate and glutamine tend to be converted into α-ketoglutarate, alanine into pyruvate, and aspartic acid into oxaloacetate [1].

Fundamentally, the cirrhotic liver is metabolically unable to convert the ammonia molecule into urea, therefore blood levels of
ammonia rise unboundedly. Ammonia is highly toxic to the nervous system and tends to produce coma and death [1].

Importantly retinol (Vitamin A) is converted into retinoic acid; an important signal molecule for growth and development in vertebrates, using the same dehydrogenase molecule that catabolizes alcohol. This activation does not take place in the presence of alcohol, due to it acting as a competitive inhibitor. Thus, the p-450 enzymes induced by alcohol inactivates retinoic acid. These specific disruptions are responsible for fetal alcohol syndrome and the development of multiple types of cancers [1].

The Wernicke encephalopathy is responsible for the existence of neurological symptoms caused by biochemical alterations of the central nervous system after exhausting the B-vitamin reserves, mainly thiamine (vitamin B1). This condition forms part of a larger group of thiamine deficiency disorders, including beriberi in all its forms, and alcoholic Korsakoff syndrome. When it occurs simultaneously with alcoholic Korsakoff syndrome it is called Wernicke–Korsakoff syndrome.

Wernicke encephalopathy is classically structured by the triad: ophthalmoplegia, ataxia, and confusion. The alcohol ingestion produces an initial inflammatory cascade of its metabolism, resulting in steatosis generated by lipogenesis, fatty acid synthesis, and depletion of fatty acid oxidation which appears as secondary to effects on the sterol regulatory transcription factor and the peroxisome proliferator-activated receptor α (PPAR-α). The intestinal-derived endotoxin initiates a pathogenic cascade through toll-like receptor 4 and tumor necrosis factor α (TNF-α) that promotes hepatocyte apoptosis and also necrosis. The cell damage and the endotoxin release initiated by alcohol and its metabolites additionally produce activation of innate and adaptive immunity pathways, therefore releasing proinflammatory cytokines (TNF-α) chemokines and proliferation of T and B cells 2, 9. The net result of chronic alcohol ingestion on intestinal permeability alters lipopolysaccharide hepatic influx and microbiome dysbiosis, additionally contributing to the existing pathogenic process [3]. The production of protein-aldehyde adducts, the generation of reducing equivalents, and especially oxidative stress play a definitive role. The hepatocyte injury and the regeneration following chronic alcohol ingestion are ultimately associated with the stellate cell activation and collagen production which are key events in fibrogenesis [3]. The resulting fibrosis from continuing alcohol consumption determines the architectural derangement of the liver and the consequent pathophysiology [3].

The hepatic parenchyma has a limited resource in response to injury. Fatty liver constitutes the initial and most common response to hepatotoxic stimuli, including excessive alcohol consumption. Remarkably, the accumulation of fat within the perivenular hepatocytes is coincident with the location of the enzyme alcohol dehydrogenase [15]. Continuing alcohol consumption results in fat accumulation the whole hepatic lobule [15]. Despite extensive fatty change and distortion of the hepatocytes with macrovascular fat, paradoxically, the cessation of drinking results in normalization of the hepatic parenchyma architecture and diminishing of fat content. The alcoholic fatty liver has historically been regarded as benign, and similarly to the spectrum of nonalcoholic liver disease, the appearance of steatohepatitis and other specific pathological features such as giant mitochondria, perivascular fibrosis, and macrovascular fat could be associated with progressive liver injury [15].

The smooth transition between the fatty liver and the development of alcoholic hepatitis is continuous and blurred. The significant hallmark of alcoholic hepatitis is hepatocyte injury, which is characterized by ballooning...
degeneration, spotty necrosis, polymorphonuclear infiltrate, and increasing fibrosis in perivenular and perisinusoidal space of Disse [15]. Mallory Denk bodies are present in florid cases but are neither considered specific nor necessary to establish the diagnosis15. Alcoholic hepatitis is customarily considered to be a precursor of cirrhosis. However, as fatty liver, it is potentially reversible with cessation of alcohol consumption. Cirrhosis is present in approximately half of the patients with biopsy-proven alcoholic hepatitis, and its regeneration is uncertain, even with total abstention [15].

The clinical condition of the active alcohol consumer. The clinical manifestations of alcoholic fatty liver are subtle and discovered during a medical visit for an apparently unrelated matter. Previously unsuspected hepatomegaly is the only clinical finding. Sometimes patients with fatty liver could present with right upper quadrant discomfort, nausea, and rarely, jaundice [9].

The alcoholic hepatitis is evidenced as a set of clinical features [8]. Fever, spider nevi, jaundice, and abdominal pain, apparently an acute abdomen, represent the extreme end of the spectrum, while many patients may be asymptomatic [8]. The unexpected presence of portal hypertension, ascites, and or variceal bleeding may occur in the absence of cirrhosis. The recognition of the clinical features of alcoholic hepatitis is fundamental to the initiation of an effective and adequate diagnostic and therapeutic approach [9].

The gastric alcohol dehydrogenase initiates alcohol metabolism. There are three enzyme systems located in the liver: Cytoplasmic alcohol dehydrogenase, Microsomal alcohol oxidizing System (MEOS), and Peroxisomal Catalase. Acetaldehyde is a highly reactive molecule that is metabolized, in the mitochondria, to acetate by aldehyde dehydrogenase.

The alcohol oxidation by the alcohol dehydrogenase generates the reduction of NAD+ to NADH, with a consequent decrease in NAD+ and an increase in NADH. NAD+ is required for fatty oxidation in the liver and also for the conversion of lactate into pyruvate. Its deficit is a main cause of the deposition of fat in the liver of alcohol consumers. The increase in NADH/NAD_ ratio in alcohol consumers also produces lactic acidosis. NAD+ is needed for the conversion of glyceraldehyde 3 phosphate to 1, 3 bisphosphoglycerate, by the enzyme glyceraldehyde 3 phosphate dehydrogenase.

ROS generation: The metabolism of alcohol in the liver by CYP2E1 generates ROS, which causes lipid peroxidation of hepatocyte membranes [8]. Alcohol additionally generates the release of the endotoxin (lipopolysaccharide) from the gram-negative bacteria in the intestinal flora, which consequently stimulates the production of tumor necrosis factor (TNF) and other cytokines from macrophage and Kupffer cells, thus leading to hepatic injury [8].

Alcohol consumption augments the intracellular triglyceride accumulation by increasing fatty acids' cellular intake and by suspending the fatty acid oxidation and lipoprotein secretion are simplistic. The protein synthesis, glycosylation, and secretion are altered [8]. The oxidative damage to the adipocyte membrane occurs as a result of the formation of reactive oxygen species [8].

Acetaldehyde is a highly reactive molecule that reacts with proteins forming protein acetaldehyde molecular effects. These adducts, sadly, might interfere with some specific enzyme activities, including the microtubular formation and the hepatic trafficking of proteins. With the acetaldehyde-mediated hepatocyte damage, several reactive oxygen species could result in the Kupffer cell activation with the consequent production of excess collagen and extracellular matrix [9].
The connective tissue appears histologically in perportal and pericentral zones and eventually unites portal triads with central veins, thus forming regenerative nodules. Hepatocyte loss have a tendency to occur, as well as collagen production and deposition, and, additionally continuing the hepatocyte destruction. Then sadly the liver contracts and shrinks [9].

The microsomal alcohol oxidizing system (MEOS) is an alternate pathway of the alcohol catabolism that secondarily occurs in the smooth endoplasmic reticulum in the process of oxidation of alcohol molecule to acetaldehyde [9]. Falsely believed that is playing only a minor role in alcohol metabolism in normal individuals, the MEOS activity clearly increases with chronic alcohol consumption. The MEOS pathway specifically requires the CYP2E1 enzyme, (Part of the cytochrome P450 family), to convert the alcohol to the molecule of acetaldehyde [9]. The alcohol’s affinity for CYP2E1 is paradoxically lower than its affinity for the enzyme alcohol dehydrogenase. Importantly, it has a delayed activity in the non-alcohol consumption states since the increase in MEOS activity is clearly correlated with an increase in the production of CYP2E1, which is seen most conclusively in the alcohol dehydrogenase negative case of the deer mice [9].

Clearly, the MEOS pathway metabolizes the alcohol to acetaldehyde by a redox reaction, where alcohol is oxidized (losing two hydrogens) and molecular oxygen is reduced (accepting hydrogen) to form water [9]. NAD+ PH is the donor of hydrogen, forming NADP+. The process consumes ATP and also dissipates heat, leading to the hypothesis that long-term drinkers see an increase in resting energy expenditure [9].

Thermodynamically, the increment in the rest energy expenditure has been hypothesized as if the MEOS would expend 9 Cal/gram of alcohol to catabolize versus 7 Cal/ per gram of the ingested alcohol [2]. Therefore, this would produce a net loss of 2 Cal/gram of the alcohol that has been ingested. So, alcohol unexpectedly would make lose weight.

Alcohol (CH3CH2OH) through a direct mechanism alters different types of neurochemical systems and several signaling cascades and, unexpectedly, has very powerful rewarding and addictive properties. It is, the oldest recreational drug and contributes to more morbidity, mortality, and public health cost than all the rest of illicit drugs together [12]. The Diagnostic and Statistical Manual of mental disorders (DSM-5) has included alcohol abuse and alcohol dependence into a single disorder: alcohol use disorder (AUD), and with classify as mild, moderate, and severe [14]. The mechanisms of the effects in the central nervous system constitute the fundamentals for comprehending the rewards, disease processes, and the treatment for alcohol-related problems [14]. Salicylates use inhibits the gastric alcohol dehydrogenase and also increases the bioavailability of alcohol [13]. The principal enzymes involved in alcohol catabolism are alcohol dehydrogenase and aldehyde dehydrogenase, followed by catalase and CYP2E1, CYPs 1A2, and 3A4 in some metabolic situations [13]. Each step of metabolism takes two molecules of NAD+ stoichiometrically to oxidize it, reducing them to NADH. Oxidation of one mole of alcohol (46 gr), the equivalent to three glasses of wine, requires 1.3 Kg of NAD+. This highly exceeds the availability of NAD in the liver. Thus, the bioavailability of the NAD+ limits the metabolism of alcohol to approximately 8 grams per hour, maintaining it in zero-order kinetics [13]. The results of the oxidation of alcohol are increase NADH; increase lactate by lactate dehydrogenase; reducing pyruvate into lactate and converting NADH into NAD+. The conversion of glyceraldehyde 3-phosphate into 1,3 Bisphosphoglycerate by the glyceraldehyde 3 phosphate dehydrogenase requires NAD+ to convert into NADH Increase Acetyl CoA from...
alcohol derived acetic acid decrease Krebs cycle activity and increase of fatty acid synthesis is a cytosolic process [13]. In the synthesis of fatty acids, each step of two carbon additions comes from the molecule of malonyl-CoA, which is produced by the enzyme Acetyl-CoA carboxylase [13].

NADH, acetyl-CoA, and ATP are expected to be increased [14]. As explained, cytoplasmic ADH and mitochondrial ALDH, stoichiometrically convert 2 NAD+ to 2 NADH for each molecule of alcohol. Alcohol is eventually converted to acetic acid [14]. Two thio kinases are associated with the conversion of acetic acid to acetyl-CoA1). Acyl-CoA synthetase short-chain family member 2 ACSS2 (EC 6.2.1.1) and acetyl-CoA synthase 2 (confusingly also called ACSS1) which is localized in mitochondria [14]. The complete reaction with all the substrates and products included is [14]: ATP + Acetate + CoA <=> AMP + Pyrophosphate + Acetyl-CoA. Alcohol has many diverse and widespread effects on the whole body and impacts directly or indirectly almost on every neurochemical system in the CNS [15-17].

Even at relatively low doses, alcohol can exacerbate most clinical problems and perturbs the medications metabolized in the liver, and at higher doses can, per se, transitorily mimic many medical (diabetes) and also psychiatric (depression) diagnoses [17]. Alcohol use disorders, as a such, decrease the lifespan by approximately ten years [18].

Congeners could include other alcohols like methanol and butanol, acetaldehyde, histamine, tannins, and the metals iron, and lead[17]. Alcohol decreases neuronal activity and has similar behavioral effects and also cross-tolerance with several other depressants, like benzodiazepines and barbiturates [17]. Alcohol also interferes with the absorption of diverse vitamins in the small intestine and decreases their amount stored in the liver, with some effects on vitamin A, folate, thiamine, pyridoxine, and nicotinic acid [17].

Fasting heavy drinking in a healthy individual may produce transient hypoglycemia within six to thirty-six hours, secondary to the acute actions of alcohol which decreases gluconeogenesis. All this could result in temporary abnormal glucose tolerance tests (diabetes mellitus).

A glucose load cannot be totally catabolized into pyruvate, through glycolysis, because there are no enough NAD+ available, which is required in order to convert glyceraldehyde 3 phosphoglycerate into 1,3 bisphosphoglycerate by the enzyme glyceraldehyde 3 phosphate dehydrogenase, which incorporates inorganic phosphate and is considered the substrate-level phosphorylation for antonomasia, stopping glycolysis, because NAD+ is being used in the metabolism of alcohol, depleting the cell of NAD+ and giving a high level of glucose evidenced in the glucose tolerance test [18].

The alcohol ketoacidosis, probably as a result of diminished fatty acid oxidation coupled with inadequate diet and/or persistent vomiting can be wrongly diagnosed as diabetic ketosis [17]. With alcohol-related ketoacidosis, patients could show an increment in serum ketones along with a mild increase in the level of glucose but with a large anion gap, a mild to moderate increase in lactate in serum, and a β-hydroxybutyrate/lactate ratio of between 2:1 and 9:1 instead the normal of 1:1 [17].

**Effects on pancreas and liver**

The incidence of acute pancreatitis is roughly 25 per 1,000/year and is almost three times higher in patients with alcohol use disorders than in the non-alcohol consuming population [16]. Alcohol disturbs gluconeogenesis in the liver, producing a fall in the glucose produced from glycogen, an increase in lactate production, and an elevation in fatty acids.
oxidation. These participate in an increase in fat hepatic accumulation. In healthy individuals, these changes are thoroughly reversible, however, with repeated consumption of alcohol, mainly daily heavy drinking, more severe changes in the liver would appear, including alcohol-produced hepatitis, perivenular sclerosis, and eventually cirrhosis, which is observed in 15% of individuals categorized as alcohol use disorder patients. Probably, through an increased susceptibility to infections, subjects with alcohol use disorders have an increased rate of hepatitis C.

**Hematopoietic System**

Alcohol consumption causes an increase in red cells’ mean corpuscular volume, which might reflect its effects on the stem cells. If heavy drinking is coincident with folic acid deficiency, there can additionally be hypersegmented neutrophils, reticulopenia, and hyperplastic bone marrow; if additionally, malnutrition is present, sideroblastic changes could appear. With chronic heavy alcohol drinking, a decrease in the production of blood cells, decrease granulocyte mobility and adherence and impair delayed hypersensitivity responses to novel antigens and a possible false-negative tuberculin skin test may result. Associated immune deficiencies could contribute to the vulnerability to infections, such as hepatitis and HIV, and also interfere with their appropriate treatment. Finally, many patients with alcohol use disorders might have mild thrombocytopenia, which may resolve within weeks of abstinence unless there is already hepatic cirrhosis or congestive splenomegaly.

**Cardiovascular System**

In the acute case, alcohol diminishes myocardial contractility and produces peripheral vasodilation, thus resulting in a mild decrease in blood pressure and a compensatory increase in cardiac output. Exercise-induced increases in the consumption of cardiac oxygen are higher after alcohol consumption. These acute effects do not have important clinical significance for the average healthy drinker but can become very problematic when there is concomitant cardiac disease.

The consumption of three or more drinks per day produces in a dose-dependent fashion an increase in blood pressure, which tends to return to normal after weeks of abstinence. Therefore, heavy drinking is a main factor in mild to moderate hypertension. Chronic heavy drinkers may also have a sixfold increased risk of coronary artery disease, partially related to an increase in low-density lipoprotein cholesterol, and also carry an increased risk for cardiomyopathy through the direct effects of alcohol on heart myocytes. Symptoms could include arrhythmias in the presence of left ventricular impairment, heart failure, hypercontractility of myocardial cells, and dilation of the four heart chambers, also with an associated potential mural thrombus and probable mitral valve regurgitation. Atrial or ventricular arrhythmias, especially paroxysmal tachycardia, can also occur temporarily after events of heavy alcohol consumption in individuals with no other evidence of heart pathology, which constitutes a syndrome known as “holiday heart.”

Heavy drinking in teens can affect normal sexual development and also reproductive onset. As effects in other systems, between 50% 75% of individuals with alcohol use disorders, develop progressive skeletal muscle weakness produced by acute alcoholic myopathy, which is a condition that improves but might not fully remit with abstinence. Among the effects of repeat, heavy alcohol consumption on the skeletal system changes in calcium metabolism diminished bone density, and a decreased growth in the epiphysis, therefore leading to an increased risk for fractures and also...
osteonecrosis of the femoral head. Among hormonal changes, an increase in the cortisol levels, which could remain elevated during heavy alcohol drinking; an inhibition of vasopressin secretion at high plasma alcohol concentrations and increased secretion during falling blood alcohol consumption and falling blood alcohol concentrations (with the final result that the majority of the patients with alcohol use disorders are lightly overhydrated); also minor and reversible decrease in serum thyroxine with a more marked decrease in the serum triiodothyronine [17]. These hormone abnormalities usually disappear after several weeks of total alcohol consumption abstinence. The neurobiological substrate of the active subject. Mesocorticolimbic dopaminergic reward pathway and the addiction phenomenon.

The mesocorticolimbic reward pathway is activated when we encounter new stimuli that are advantageous for our survival which are evolutionary determinants of successful reproduction: As an epiphenomenon, it enhances well-being (food, sexual mate) [18,19]. The experience of the reward stimuli would be encoded into regions of the brain involved in memory and planning, permitting that our ancestors continued to actively feed and procreate, despite many lurking dangers of the time [18-19].

Alcohol and other drugs work exploiting the mesocorticolimbic reward pathway, the same pathway that has served and permitted humans to learn, survive and reproduce successfully for many generations [20-22]. All addictive drugs either directly or indirectly modulate the dopamine signaling in the mesocorticolimbic reward pathway. Importantly, not everyone who uses or abuses these drugs will become an addict [9]. On the other hand, for some individuals, a first-time experience can dramatically turn into a lifelong addiction [9]. The first stage of addiction: binge and intoxication. Often, when an individual consumes a drug for the first time, he experiences an unknown sense of euphoria that could be, in some circumstances, beyond that of any natural reward such as food or sex. Often, as predicted by behavior analysis, the reinforcement which has the feeling of intoxication as an epiphenomenon drives a user to take more of the same drug [10]. This behavior is considered representative of the first stage of addiction: binge and intoxication [10].

During the first stage of addiction, the alcohol or the drug targets a region of the midbrain, known as the ventral tegmental area (VTA), producing the release of dopamine into the nucleus accumbens [10]. Endorphins, which are our body’s primary natural opioids, are also released. It is believed that the combined activation of both dopamine and endorphins is what underlies the reinforcement and the sensation of pleasure following drug use [10,19,20].

**Reward:** The reinforcer is constituted by the drug and sometimes could be more powerful than any other natural reinforce [10]. This is especially the case in binge and Intoxication. The neuroanatomical substrate is constituted of the mesolimbic dopaminergic circuit, from the ventral tegmental area to the nucleus accumbens. Additionally, endorphins are liberated in these instances of addiction [10]. The globus pallidus is also activated and it is associated with the formation of the habit; The prefrontal cortex, corresponding to the Freudian superego, normally regulates the activity from the nucleus accumbens, but not during the drug's effects [4]. The nucleus accumbens and the olfactory tubercle collectively form the ventral striatum. The ventral striatum and dorsal striatum collectively form the striatum, which is the main component of the basal ganglia [19].
Other brain regions are also activated:

During this first stage, alcohol and the drugs of abuse, make the globus pallidus encode drug-related behaviors as habits. The globus pallidus is associated with the formation of habits and automatic behaviors [4]. The prefrontal cortex is a region responsible for the executive functions as are planning and decision making [4,10,11]. Normally, the prefrontal cortex inhibits the lower brain regions such as the nucleus accumbens; however, alcohol and drugs of abuse weaken this control, thus disinhibiting the nucleus accumbens [4,18]. This is thought to underlie the impulsivity that is characteristic of the binge and intoxication stage [4].

Stage 2:

Withdrawal and negative effects. A completely different subset of neuronal structures is involved in the withdrawal, and negative affect, which is considered the second stage in the addiction cycle [4]. Because drug use increases dopamine levels beyond what is normal, the chronic consumption of alcohol and other drugs leads to a number of compensatory responses [4]. The result is that when the consumer is not intoxicated the dopamine signal is lower than normal, leaving the user feeling awful and unhappy and much less able to be reinforced by natural reinforcers [4,18]. The neural systems that underlie this negative affective state include a group of midbrain structures conceptualized as the extended amygdala [3]. The behavior has become compulsive rather than the original pleasurable desire. Thus, the behavioral changes from impulsive to compulsive. The bed nucleus of the stria terminalis constitutes the anatomical substrate of this condition [23]. The activations of these systems tend to increase the production of stress hormones [3,18]. Eventually, consuming alcohol or the drug no longer produces pleasure but instead is now used in an effort to escape or evade the highly unpleasant psychological and physiological symptoms of the withdrawal [3,17]. Skinnerian escape and avoidance responses characterize this stage. Therefore, alcohol and drug consumption has become a highly compulsive need rather than the pleasurable impulsive desire of the beginning.

Stage 3:

Constitutes constant anticipation and severe craving, significant loss of prefrontal cortex function, and altered glutamatergic signaling [3,9,21]. Therefore, the last stage of the alcohol and drug addiction cycle is the anticipation and craving stage, which frequently means the level whereby an individual’s chronic alcohol or drug consumption may lead to the development of a substance abuse disorder [9]. While this phase is conceptualized commonly as craving, it does not, by itself, lead to relapse and another cycle [9,21] This final stage is characterized by a significant loss of prefrontal control and continued alcohol and drug use compromises frontal lobe structures that are critical for evaluation, judgment, and decision making [9,10]. This stage is characterized by altered glutamatergic signaling [9,21,23]. Glutamate plays a principal role in memory formation and consolidation as well as in the initiation of behavior [9,21,23].

During the anticipation and craving stage, the large amount of dopamine received by the prefrontal cortex during drug and alcohol consumption promotes the reciprocal release of glutamate in the midbrain, thus committing the alcohol or the drug, and the experience to memory [3]. As the plasticity of the brain is continuously shaped and reshaped by the consumption of alcohol and drugs, new paths become consolidated as alcohol-related contextual information is stored by the hippocampus, through the establishment of operant behavior and activation of the basolateral amygdala leads to conditioned responses to a highly specific, alcohol-related cues (reinforced conditioned stimulus) [3,23].
In this manner, chronic alcohol consumption can be considered as a dysfunctional adaptive form of learning whereby alcohol capitalizes on the highly plastic nature of the brain [3]. Extended alcohol consumption then leads to the exploitation and the restructure of the neural circuitry consolidating memories, habits, and goals that place much greater importance on alcohol and drug consumption behavior rather than on the natural rewards [3,9,21].

The total amount of satisfaction diminishes with the drug. However, all the satisfaction is drug-related. The drug becomes a powerful negative reinforcer. The reinforcement is remembered as produced by the consumption of the drug. The consumption of the drug prevents withdrawal. When the withdrawal is already present the response of drug consumption constitutes the behavior of escape. In one situation the subject escapes from the withdrawal syndrome and in the other avoids the withdrawal to appear. In the brain, alcohol affects almost all neurotransmitter systems, with acute effects that are frequently the opposite of those following desistance after a period of heavy consumption. The most profound acute actions relate to boosting γ-aminobutyric acid (GABA) activity, especially at the GABA receptor 3. Enhancement of this very complex chloride channel system significantly contributes to anticonvulsant, sleep-inducing, anti-anxiety, and the muscle-relaxing effects of all GABA-boosting drugs ⁹. The Acute administration of alcohol produces a release of GABA, and the continued consumption increases the density of GABAA receptors, whereas alcohol withdrawal states, are clearly characterized by a decrease in GABA-related activity [3,9]. Of Equal importance is the ability of acute alcohol consumption to inhibit the postsynaptic N-acetyl-D-aspartate (NMDA) excitatory glutamate receptors, whereas chronic alcohol consumption and desistance are associated with an upregulation of the excitatory receptors’ subunits described [9]. The relationships between greater GABA and diminished NMDA receptor activity during the acute alcohol intoxication and diminished GABA with enhanced NMDA actions during alcohol withdrawal let us understand much of the alcohol intoxication and the withdrawal phenomena [9].

As happens with all pleasurable activities, alcohol consumption acutely increases the dopamine levels in the ventral tegmentum and in the related brain regions, also this effect plays a major role in continued alcohol consumption, craving, and relapse [9]. The changes in dopamine pathways are also related to increases in cortisol and adrenocorticotropic hormone (ACTH) during acute alcohol intoxication and in the context of withdrawal [9]. Such alterations are probably to contribute to both the feelings of reward during acute intoxication and the depression during falling blood alcohol concentrations [9]. Also very closely linked to alteration in the dopamine in the nucleus accumbens are alcohol-induced changes in the opioid receptors, with acute alcohol consumption causing the release of β-endorphins [3,9]. Several additional neurochemical alterations include an increase in the synaptic levels of the neurotransmitter serotonin during acute alcohol consumption and subsequent upregulation of serotonin receptors [3,9]. The acute increases in the nicotinic acetylcholine systems contribute to the impact of alcohol in the ventral tegmental region, which occurs in concomitant with enhancing dopamine activity; in the same regions, alcohol impacts on the cannabinoid receptors, which results in the release of dopamine, glutamate, and GABA as well as consequent impacts on the brain reward circuits [3,9].

**Behavioral effect: Tolerance and Withdrawal**

The behavioral changes from impulsive to compulsive. Beverage alcohol is perhaps...
responsible for more overdose than other drugs [8]. Dependent consumption of alcohol contributes to the need for a larger number of standard drinks to generate effects initially obtained with fewer drinks, which represents acquired tolerance, a phenomenon constituted of at least three compensatory mechanisms [9]. 1) After 10 days of daily alcohol consumption, metabolic or pharmacokinetic tolerance appears, with up to 30% increases in the rate of hepatic alcohol catabolism [9]. This perturbation regresses almost as rapidly as it develops [8]. 2) Cellular or pharmacodynamics tolerance develops through several neurochemical compensatory changes that keep relatively normal physiologic functioning despite the existence of a subsequent decrease in the blood levels of alcohol, which contributes to the syndrome of withdrawal [9]. 3) Individuals learn to adapt their behavior so that they can apparently function better than expected under the toxic influence of the alcohol or the drug which is considered learned or behavioral tolerance [9].

The cellular biochemical perturbations caused by chronic alcohol consumption may not resolve for a month several or longer following cessations of alcohol consumption. Rapidly decrease in blood alcohol levels before the time can produce a withdrawal syndrome, which is most intense during the first week, but with some symptoms as disturbed sleep and anxiety lasting probably up to 4-6 months as a component of a protracted withdrawal syndrome [9]. It is considered that any potential healthful effect attributed to alcohol consumption, is overridden by continuous consumption of three or more daily drinks [9].

Nervous System

The subject with acute alcohol intoxication may experience a blackout which is an episode of anterograde amnesia, even though the person was awake but has forgotten all of what occurred during the acute drinking period [9]. Another very common problem that is seen after as few as one or two drinks before bedtime is a state of disturbed sleep [9]. Even though alcohol could initially help a subject to fall asleep, it alters sleep through for the rest of the night. The stages of sleep are disturbed, and the periods spent in rapid eye movements (REM) and deep sleep initially in the night are diminished [8]. Alcohol produces relaxation in the muscles of the pharynx which may produce snoring and also exacerbate sleep apnea. The Symptoms of this apnea occur in 75% of men with alcohol use disorders that are older than 60 years. The patients can experience very prominent and sometimes highly disturbing dreams later in the night [9]. All these sleep perturbations could contribute to relapse to alcohol consumption [9]. Another common very significant adverse consequence of alcohol consumption even at relatively low concentration is impaired mathematical and logical judgment, as well as coordination, which increases the risk of injuries and other personal adverse consequences [9].

Heavy alcohol consumption could also be associated with headache, thirst, nausea, vomiting, and fatigue the next day, also, the hangover syndrome that is responsible for much-missed time in work and l time, and much more important, with temporary cognitive deficits [9]. The chronic high alcohol doses produce peripheral neuropathy in around 10% of patients with alcohol use disorders which is similar to diabetes, experiencing bilateral limb numbness, tingling, and paresthesias, all being more pronounced distally [9]. Close to 1% of individuals with alcohol use disorder can develop cerebellar degeneration or atrophy thus producing a syndrome consisting of progressive unsteady stance and gait frequently accompanied by mild nystagmus, neuroimaging studies would demonstrate atrophy of the cerebellar vermis [9]. Probably as few as 1 in 500 patients with alcohol use disorders would develop total Wernicke's (ophthalmoparesis, ataxia, and encephalopathy)
and Korsakoff’s (severe retrograde and anterograde amnesia) syndromes, but a higher proportion would manifest has one or more neuropathological altered states related to these conditions⁹. These are produced from low levels of thiamine, especially in those predisposed individuals with transketolase deficiency [8]. The repeated heavy alcohol consumption could significantly contribute to progressive cognitive problems and the temporary memory impairment that can last for weeks to months after abstinence [8]. Brain atrophy, as evidenced by the ventricular system enlargement and widened of the cortical sulci on magnetic resonance scans appears in half of the patients with long-term alcohol use disorders; these derangements tend to be typically reversible if abstinence is strictly maintained. The adolescents are especially vulnerable to alcohol-related brain derangements [9]. Thus, there is no unique so-called syndrome of “alcohol dementia”; rather, this general label describes patients who have reached irreversible cognitive derangements from several causes in the frame of chronic alcohol use disorders [9].

**Alcohol and Evolution**

Humans inadvertently have produced an artificial selection of organisms that are producers of substances that release dopamine in the nucleus accumbens. Humans have artificially selected organisms that produce substances that activate the mesocortical-limbic dopamine reward pathway. The ability to produce these substances has been selected. It is the evolutionary historical origin of all-natural drugs. Furthermore, synthetic or artificial drugs are specifically designed to activate the mesocortical-limbic Dopamine reward pathway.

The human digestive system produces approximately 3 g of alcohol daily through fermentation. Catabolism of alcohol is thus essential, not only of humans but of all organisms. Several amino acid sequences in the enzymes used to oxidize alcohol are evolutionary, going back to the last common ancestor more than 3.5 billion years ago. This function is necessary since all organisms produce small amounts of alcohol by several pathways, mainly through fatty acid synthesis, the metabolism of glycerolipids, and the biosynthesis of bile acid pathways. Without this mechanism for catabolizing the alcohols, the body would build up alcohol and become toxic. This is evidence of evolutionary advantage for alcohol catabolism and by sulfotransferase too [14].

**Corollary**

We must ask ourselves in the frame of evolution by natural selection: Cui bono? Cui prodest?: Saccharomyces cerevisiae and other types of yeast in winemaking. These microorganisms have evolutionary hijacked mesocortical-limbic dopamine reward pathway in the human brain, as has happened with D. dendriticum in ant Formica fusca and, toxoplasma gondii in rats or even more dramatically, dogs which have evolved and hijack in a manner analogous to drugs, the same mechanisms in our brains that create the strongest social bonds, including those between mother and child [24-27]. We must be dialectical. If the experimental results are against our expectations, against our desires, against our ideology; furthermore, if our ideas about democracy [28,29] overpopulation, global warming, etcetera, are rebutted, we better acknowledge the phenomenological reality of the universe. Therefore, Man, at last, knows that he is alone in the unfeeling immensity of the universe, out of which he emerged only by chance. Neither his destiny nor his duty have been written down. The kingdom above or the darkness below: it is for him to choose [30].
Second-Hand Risk Health Tragedies and Human Right Violations due to Ethanol Consumption. Biochemical basis for metabolic and behavioral Tragedies due to Ethanol Consumption


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