Research Article

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The Metabolic and Neurochemical Etiopathology of Passive Exposition to Alcohol Consumers

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Introduction

Second-hand smoking has been a battle in almost every field. Typically, a nonsmoker who is an alcohol consumer, complains of secondhand smoke, without even considering second-hand risk health tragedies and human rights violations due to ethanol consumption.

We expose here the concept, mainly unexplored, of tragic adverse health effects and human rights violations to third parties due to alcohol consumption by others; as well as disability due to chemical transient prefrontal lobotomy with alcohol consumption.

Alcohol has been an integrated part of the human diet for centuries, in part, due to the fact that alcoholic beverages have constituted a safe means of hydration whenever pure clear water was scarce[1].

Old patients could be part of the ethanol consumers and/or secondhand victims. However, before deciding to approach the geriatrical problems, we propose the allegorical pedagogical model, based on Scott, Ellison, and Sinclair, as published in Nature Aging, in July 2021. We divide the theoretical approach with four elemental alternatives[2]

Life extension (the Struldbrugg case). In Jonathan Swift's 1726 novel Gulliver's Travels, the struldbrugg are humans who are born seemingly normal. The Struldbruggs, are immortal but age normally, live in continuously worsening health. It takes us to the philosophical alternative of: "to live or to last"[2]

To Diminish morbidity (the Dorian Gray case). Accordingly The Picture of Dorian Gray is aphilosophical novel by Oscar Wilde. Dorian Gray possesses a portrait of himself and while the picture ages, Dorian Gray does not, keeping his health and appearance until death[2].

To Slow aging (the Peter Pan case), In the extreme case, where aging is not just slowed but eliminated, mortality and health become independent of age and the individual is 'forever young'. This refers to the 'Peter Pan' case, after the play and novel about a boy who never grows old. This corresponds to the Hypocaloric diet claim that slows aging[2].

Reversing aging biological damage is repaired rather than slowed. This is analogous to the Theseus Boat and the regeneration of salamanders and lizards and transplants from donors. Obviously, this is the future of organoids and the engineering of pluripotent cell[2].

Understanding the Social Determinants of the Passive Health Victims and Consequences

Ethanol consumption has been estimated to be responsible for more than 80,000 deaths a year in the United States. More than 50% of these deaths are made up of drunk driving accidents and ethanol-related homicides and suicides, and approximately 15,000 deaths per year are the result of cirrhosis[3]. Therefore, contrary to common beliefs, ethanol consumption is more of a cause of passive health casualties than cirrhosis in the consumer.

Social determinants are the product of composite behavior of the subset of the population that determines the effect on the passive health victims. Since all there is in the universe are the subatomic particles, namely leptons and quarks, Higgs Boson, and obeying the four only existing forces, gravitational, electromagnetic, nuclear weak, and strong nuclear. There has been no evidence of physical-chemical unique properties inside of the head different from the chemistry outside. Therefore as Peter W. Atkins, Fellow of Lincoln College at the University of Oxford and author of the most prestigious 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 thoughts, feelings, ideas, comprehension, logic, mathematics and, absolutely all human behavior.

All this is evidenced as accidents, abandonment of minors, breach of family and professional commitments (pacta sunt servanda), failure in the need for a reliable work team; as well as a decrease in the attention span in important aspects, intellectual, professionals in risk situations, etc. Additionally, there is a decrease in the acquisition of new concepts, high failure in complex tasks, underestimation of adverse consequences due to impaired judgment, greater willingness to take risks due to a damaging prefrontal effect; As can be seen, pilots, surgeons, bus drivers, taxi drivers, operation of high-risk machinery in factories and outdoors, and in general, being part of trusted teamwork becomes a cause of harm to third parties. This is hamartia and a tragedy.

The larger the damage to the patient due to ethanol consumption, the less probable is that the patient could produce a secondhand effect on passive subjects.

The older the patient with ethanol organic damage, the less probable it is that the patient could

produce a secondhand effect on passive subjects.

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].

Accepting these Principles and for the purpose of co-operation among themselves and with others to promote and protect the health of all peoples, the Contracting Parties agree to the present Constitution and hereby establish the World Health Organization as a specialized agency within the terms of Article 57 of the Charter of the United Nations[5].

The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition. The health of all peoples is fundamental to the attainment of peace and security and is dependent upon the fullest cooperation of individuals and States[5].

The extension to all peoples of the benefits of medical, psychological, and related knowledge is essential to the fullest attainment of health5.

Chapter I

Objective

Article 1 The objective of the World Health Organization shall be the attainment by all peoples of the highest possible level of health[5].

Francis Bacon, the father of empirism, and thus one of the founders of science, introduced to a French audience as the "father" of the scientific method in 1733 by Voltaire himself, clearly warned about the idols of the mind and the process of purging information. All this constitutes incurring in the idols. Bacon's epagogic inference, probabilistic inductive inference insisting in that the experience must be purged (pars destruens), as precursors of John Stuart Mill`s methods, for the right approach to the understanding of every natural phenomenon[6].

He principles and objective of the CONSTITUTION OF THE WORLD HEALTH ORGANIZATION constitute desiderative and aspirational concepts, they are Baconian Idols of the Tribe, according to which we always assume order and purpose in things; as well as the Idols of the Theatre, considering the world as a stage, the Idols of the theatre are prejudices coming from authority or traditional philosophical systems, that resemble plays in so far as they render fictional worlds, which have never been exposed to an experimental check. The idols of the theatre, therefore, have their origin in a dogmatic philosophy or, worse, in wrong laws of demonstration[5].

As stated by Dr. Tedros Adhanom Ghebreyesus, Director-General World Health Organization 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 half of the world's adults have consumed alcohol in the last 12 months, the global burden of disease caused by its harmful use is enormous. Disturbingly, it exceeds those caused by many other risk factors and diseases high on the global health agenda. Over 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].

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 DALYs are due to non-communicable

and mental health conditions, and about 40% are due to injuries[5].

The Second-Hand Risk health Tragedies and Human Right Violations due to Ethanol Consumption, constitute a violation of human rights.

As established in 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[7].

Understanding the Physiopathological Condition of the Active Subject.

The three major overlapping lesions, Fatty Liver Disease, Alcoholic Hepatitis, and Cirrhosis are inversely related to the third-party passive injury. It is the intoxicated man with normal liver, after a binge drinking more than the cirrhotic patient with encephalopathy, who is the principal cause of death and lesions to the third parties[7]. Thus, the worse the hepatic damage, the less the probability of causing third-party injury.

Ethanol is a direct hepatotoxin; however, only 10 to 20 % of alcoholics will develop alcoholic hepatitis[8, 9, 10].

Ethanol is the third principal risk for disease burden. Cirrhosis and its complications are closely correlated with the volume of ethanol consumed; in both senses, per consumption, and cumulatively.

The most important risk factors in the development of alcoholic liver disease are quantity and duration[8]. These scientifically proven facts could mislead the consideration, already mentioned, that alcohol consumption produces more damage in third parties, mainly through accidents than in the consumers.

According to The National Institute on Alcohol Abuse and Alcoholism, in 2016, of all deaths attributable to alcohol consumption worldwide, 28.7 percent were due to injuries, 21.3 percent were due to digestive diseases (primarily cirrhosis of the liver and pancreatitis), 19 percent were due to cardiovascular diseases, 12.9 percent were due to infectious diseases (including tuberculosis, pneumonia, and HIV/AIDS), and 12.6 percent were due to cancers (most prominently those of the upper aerodigestive tract.)[11]

In addition, all the unconsidered effects in the number of incarcerated persons that are in jail for having produced health damage or death to third parties constitutes the basis for the rule that alcohol consumption takes more people to jail than to cirrhosis. Thus, we can say, like an adagio: the drinker should have more fear to end in jail than becoming cirrhotic.

Comparatively, approximately 12 g of alcohol are contained in one beer, four ounces of wine, or in one ounce of 80 proof spirit[11].

There is an evident paradoxical event such that, the more deteriorated is the patient due to ethanol consumption the less probability he has of causing secondhand damage to others. Therefore having a clear parallel picture of the physiopathological effects in the ethanol consumer, together with the neurochemical alterations causing the behavioral effects which constitute the deleterious condition caused by the consumer of ethanol in third parties, is paramount in this presentation.

Alcohol as a Direct Hepatotoxin

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 ethanol metabolism. The excess NADH signals that 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 first pathway for ethanol metabolism is by the enzyme alcohol dehydrogenase which oxidizes ethanol

to acetaldehyde reducing NAD+ to NADH. Then acetaldehyde is oxidized by the acetaldehyde dehydrogenase, again reducing NAD+ to NADH.

The second pathway for ethanol metabolism utilizes the cytochrome P450 enzymes, the microsomal ethanol-oxidizing system (MEOS) generates acetaldehyde and subsequently acetate while oxidizing biosynthetic reducing power, NADPH, to NADP+. The fact that oxygen is used in this pathway leads to the production of free radicals that damage tissue. This oxidative stress is exacerbated as NADPH is being consumed, decreasing the capacity to neutralize this oxygen reactive species by preventing the regeneration of glutathione[12].

The effects of the other metabolites of ethanol: Liver mitochondria can convert acetate into acetyl CoA in a reaction requiring ATP through a thiokinase[12] .

Additional processing of Acetyl-Co A by the Krebs cycle is blocked[1]

The accumulation of acetyl CoA has several consequences: First, ketone bodies will form and be released into the blood, worsening the acidic condition already resulting from the high lactic acidosis. The metabolism of lactate 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 ethanol is persistently consumed at high levels, acetaldehyde can importantly damage the liver and eventually produce cell death[1].

Ketone bodies are synthesized in the mitochondrial matrix. Acetyl-CoA formed in the liver during oxidation of fatty acids or metabolism of alcohol, can either enter the Krebs cycle or undergo conversion to the ketone bodies, D-β-hydroxybutyrate, acetoacetate, and acetone, that are exported to other tissues[13].

Since the Krebs Cycle is Inactive due to the Following

In an extremely fine-tuned regulatory process, the pyruvate dehydrogenase complex is specifically Inhibited by ATP, acetyl CoA, NADH, and fatty acids; the Citrate Synthase is inhibited by NADH, citrate, and ATP; the Isocitrate dehydrogenase is Inhibited by ATP; and, the α-ketoglutarate dehydrogenase complex is inhibited by NADH[13].

Then the surplus of acetyl CoA in the mitochondria enters the process of synthesis of ketone bodies that initiates from two molecules of acetyl-Co A.

The brain which preferentially uses glucose as a fuel can, if needed, adapt to the use of acetoacetate and β-hydroxybutyrate. The brain cannot utilize fatty acids as fuel because they are unable to cross the hematoencephalic barrier[13].

Fatty Acid Synthesis

Whenever a cell or organism possesses more than enough metabolic fuel to satisfy its energy requirements, the excess is usually converted to fatty acids and stored as lipids such as triacylglycerols. The reaction catalyzed by the enzyme acetyl CoA carboxylase constitutes the rate-limited step in the biosynthesis of the fatty acids. Whenever the acetyl CoA concentrations of mitochondrial and ATP are increased, citrate is transported outside of the mitochondria; it then becomes the precursor of cytosolic acetyl-Co A and an allosteric signal that activates acetyl CoA carboxylase.

Malonyl CoA is generated from acetyl Co-A and bicarbonate. A carboxyl group, which is derived from bicarbonate (HCO-3), is first transferred to biotin in an ATP-dependent reaction. The biotinyl group constitutes a temporary carrier of CO2, transferring it to acetyl CoA to produce malonyl-CoA.

The enzyme is in a collective manner denoted as fatty acid synthase. The reducing agent is NADPH, two per cycle (stoichiometrically) and the activating groups are two different -SH groups in the fatty acid synthase.

Fatty acid synthesis occurs in the cytosol. This location separates synthetic processes from degradative reactions.

Typically NADPH is the electron carrier for anabolic reactions[13].

Biosynthesis of Triacylglycerols

Carbohydrates, fat, protein, and ethanol ingested in excess are stored in the form of triacylglycerols.

Urea Cycle

Ammonia is highly toxic to animals[13]. The catabolic production of ammonia constitutes a serious biochemical problem because ammonia is extremely toxic. The brain is particularly vulnerable; damage from ammonia toxicity causes clinically cognitive impairment, ataxia, and epileptic seizures. In extreme cases, swelling of the brain leads to death[13].

Clearing the cytosol from ammonia requires the reductive amination of α-ketoglutarate to glutamate by the enzyme glutamate dehydrogenase and the conversion of glutamate into glutamine by the enzyme glutamine synthetase. In the brain exclusively the astrocytes express glutamine synthetase. Glutamate and its derivative γ amino butyrate (GABA) are very important neurotransmitters; some of the high sensitivity of the brain to ammonia reflects depletion of glutamate in the glutamine synthetase reaction[13].

The Metabolic destine of the amino groups: Due to only a few microorganisms are able to convert N2 to NH3, amino groups are sophisticatedly husbanded in biological systems.

Four amino acids have fundamental roles in nitrogen metabolism: glutamate, glutamine, aspartate, and alanine. These amino acids are the most easily convertible into citric acid intermediates. Glutamate and glutamine are converted into α-ketoglutarate, alanine into pyruvate, and aspartic acid into oxaloacetate[1].

The cirrhotic liver is metabolically unable to convert ammonia into urea, and blood levels of ammonia rise continuously. Ammonia is highly toxic to the nervous system and can produce coma and death[1].

Retinol (Vitamin A) is converted into retinoic acid, which is an important signal molecule for growth and development in vertebrates, using the same dehydrogenase that metabolizes ethanol. Consequently, this activation does not take place in the presence of ethanol, because it acts as a competitive inhibitor. Furthermore, the p-450 enzymes induced by ethanol inactivate retinoic acid. These disruptions are probably responsible for fetal alcohol syndrome as well as the development of diverse types of cancers[1].

Wernicke Encephalopathy

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

Classically, Wernicke encephalopathy is structured by the triad: ophthalmoplegia, ataxia, and confusion[8].

Alcohol ingestion produces an initial inflammatory cascade because of its metabolism, resulting in steatosis produced by lipogenesis, fatty acid synthesis, and depletion of fatty acid oxidation 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 necrosis. The cell damage and the endotoxin release initiated by ethanol and its metabolites also produce activation of innate and adaptive immunity pathways, thus releasing proinflammatory cytokines (TNF-α) chemokines and proliferation of T and B cells[2, 8]. The net effect of chronic ethanol ingestion on intestinal permeability alters liposaccharide hepatic influx as well as microbiome dysbiosis, additionally contributing to the already existing pathogenic process[3]. The production of toxic protein-aldehyde adducts, the generation of reducing equivalents, and especially oxidative stress also 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 repertoire in response to injury. Fatty liver constitutes the initial and certainly most common response to hepatotoxic stimuli, including excessive ethanol consumption. Remarkably, the accumulation of fat within the perivenular hepatocytes is coincident with the location of the enzyme alcohol dehydrogenase, the major enzyme responsible for alcohol metabolism[14]. Continuing alcohol consumption results in fat accumulation throughout the whole hepatic lobule[14]. Despite extensive fatty change and distortion of the hepatocytes with macrovascular fat, unexpectedly, the cessation of drinking results in normalization of the hepatic parenchyma architecture and diminishing of fat content. Alcoholic fatty liver has historically been regarded as entirely 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[14].

The transition between the fatty liver and the development of alcoholic hepatitis is continuous, smooth, and blurred. The significant hallmark of alcoholic hepatitis is represented by hepatocyte injury which is characterized by ballooning degeneration, spotty necrosis, polymorphonuclear infiltrate, and increasing fibrosis in perivenular and perisinusoidal space of Disse[14]. Mallory Denk bodies are frequently present in florid cases but are neither considered specific nor necessary to establish the diagnosis[14]. Alcoholic hepatitis is considered to be a precursor of cirrhosis[14]. However, like fatty liver, it is potentially reversible with cessation of alcohol consumption. Cirrhosis is present in approximately 50% of the patients with biopsy-proven alcoholic hepatitis, and its regeneration is uncertain, even with absolute abstention[14].

Understanding the Clinical Condition of the Active Subject

Usually, the clinical manifestations of alcoholic fatty liver are subtle and detected during a medical visit for an apparently unrelated matter. Previously unsuspected hepatomegaly is often the only clinical finding. Occasionally patients with fatty liver could present with right upper quadrant discomfort, nausea, and rarely, jaundice[8].

Alcoholic hepatitis is manifested as a gamut of clinical features[8]. Fever, spider nevi, jaundice, and abdominal pain, apparently an acute abdomen, constituted the extreme end of the spectrum, while many patients will be absolutely asymptomatic[8]. The 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 pivotal to the initiation of an effective and adequate diagnostic and therapeutic approach[8].

Gastric alcohol dehydrogenase initiates alcohol metabolism. There are three enzyme systems in the liver: Cytoplasmic alcohol dehydrogenase, Microsomal Ethanol oxidizing System (MEOS), and Perixosomal Catalase. Acetaldehyde is a highly reactive molecule that is metabolized, in the mitochondria, to acetate by aldehyde dehydrogenase[2]

The alcohol oxidation by the alcohol dehydrogenase causes 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[8].

ROS generation: The metabolism of ethanol in the liver by CYP2E1 produces ROS, which causes lipid

peroxidation of hepatocyte membranes[8]. Alcohol also generates the release of the endotoxin (lipopolysaccharide) from 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 injur[8].

Ethanol consumption augments the intracellular triglyceride accumulation by increasing fatty acids' cellular intake and by suspending the fatty acid oxidation and lipoprotein secretion.

The protein synthesis, glycosylation, and secretion are altered[7]. The oxidative damage to the adipocyte membrane occurs as a result of the formation of reactive oxygen species[7].

Acetaldehyde is a very reactive molecule that reacts with proteins forming protein acetaldehyde molecular additions. These adducts 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 of extracellular matrix[8]. The connective tissue appears simultaneously in periportal and pericentral zones and eventually unites portal triads with central veins, thus forming regenerative nodules. Hepatocyte loss tends to occur, as well as collagen production and deposition, and, additionally continuing the hepatocyte destruction[8]. Then the liver contracts and shrinks[8].

T*he Microsomal Ethanol Oxidizing System (MEOS)*

Consists of an alternate pathway of the ethanol catabolism that occurs in the smooth endoplasmic reticulum in the process of oxidation of ethanol molecule to acetaldehyde[8]. Playing only a minor role in ethanol metabolism in normal individuals, the MEOS activity increases with chronic alcohol consumption. The MEOS pathway requires the CYP2E1 enzyme, (part of the cytochrome P450 family), in order to convert the ethanol to the molecule of acetaldehyde[8]. The ethanol's affinity for CYP2E1 is 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[8].

The MEOS pathway metabolizes the ethanol to acetaldehyde by a redox reaction, where ethanol is oxidized (losing two hydrogens) and molecular oxygen is reduced (accepting hydrogen) to form water[8]. NADPH 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[8].

The increment in the rest energy expenditure has been hypothesized as if the MEOS would expend 9 Cal/ gram of ethanol to catabolize versus 7 Cal/ per gram of the ingested ethanol[2]. Therefore this would produce a net loss of 2 Cal/gram of the ethanol that has been ingested. So ethanol unexpectedly would make lose weight[3].

Ethanol (CH_3CH_2OH) in a direct manner affects different types of neurochemical systems and many signaling cascades and, especially has powerful rewarding and addictive properties. It is without any doubt the oldest recreational drug and probably contributes to more morbidity, mortality, and public health cost than all the rest of illicit drugs combined[11]. The last Diagnostic and Statistical Manual of mental disorders (DSM-5) has integrated alcohol abuse and alcohol dependence into a single disorder: alcohol use disorder (AUD), with subclassifications as mild, moderate, and severe[12].

The mechanisms of the ethanol effects in the central nervous system constitute the basis for understanding the rewards, disease processes, and treatment for ethanol-related conditions[12].

Aspirin use inhibits gastric alcohol dehydrogenase and increases the bioavailability of ethanol[12].

The main enzymes involved in ethanol

metabolism are Alcohol dehydrogenase and aldehyde dehydrogenase, followed by catalase and CYP2E1, CYPs 1A2, and 3A4 in some metabolic instances[12].

Each step of metabolism requires two molecules of NAD+ stoichiometrically to oxidize it, reducing them to NADH. Oxidation of one mole of ethanol (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 ethanol to approximately 8 grams per hour, maintaining it in zero-order kinetics[12].

The results of the oxidation of ethanol 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 Bisphophoglycerate by the glyceraldehyde 3 phosphate dehydrogenase requires NAD+ to convert into NADH

Increase Acetyl CoA from ethanol derived acetic acid decrease Krebs cycle activity and increase of fatty acid synthesis is a cytosolic process[12].

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[12].

NADH, acetyl-CoA, and ATP are expected to be increased[13].

As explained, cytoplasmic ADH and mitochondrial ALDH, stoichiometrically convert 2 NAD+ to 2 NADH for each molecule of ethanol. Ethanol is eventually converted to acetic acid[13].

Two thiokinases 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[13].

The Complete Reaction with all the Substrates and Products Included is[13]

ATP + Acetate + CoA <=> AMP + Pyrophosphate + Acetyl-CoA

Ethanol has many diverse and widespread effects on the whole body and impacts directly or indirectly almost on every neurochemical system in the CNS[16].

Even at relatively low doses, alcohol can exacerbate most clinical problems and perturbates the medications metabolized in the liver, and at higher doses can, per se, transitively mimic many medical (diabetes) and also psychiatric (depression) diagnoses[16].

Alcohol use disorders, as a such, decrease the lifespan by approximately ten years[17].

Congeners could include other alcohols like methanol and butanol, acetaldehyde, histamine, tannins, and the metals iron, and lead[16]. Ethanol decreases neuronal activity and has similar behavioral effects and also cross-tolerance with several other depressants, like benzodiazepines and barbiturates[16].

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[16].

Fasting heavy drinking in a healthy individual may produce transient hypoglycemia within six to thirty-six hours, secondary to the acute actions of ethanol which decreases gluconeogenesis. All this could result in temporary abnormal glucose tolerance tests (diabetes mellitus[16]).

A glucose load can not 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[16].

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[16]. 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[16].

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-ethanol consuming population[15]. 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[15]. These participate in an increase in fat hepatic accumulation. In healthy individuals, these changes are thoroughly reversible, however, with repeated consumption of ethanol, 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[15]. Probably, through an increased susceptibility to infections, subjects with alcohol use disorders have an increased rate of hepatitis C[16].

Hematopoietic System

Ethanol 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[16]. With chronic heavy ethanol 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[16]. Associated immune deficiencies could contribute to the vulnerability to infections, such as hepatitis and HIV, and also interfere with their appropriate treatment[16]. 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, ethanol 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[16]. 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[16].

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[16]. 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 ethanol on heart myocytes[16]. 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 ethanol consumption in individuals with no other evidence of heart pathology, which constitutes a syndrome known as “holiday heart”[16].

Heavy Drinking in Teens can Affect Normal Sexual Development and also Reproductive Onset[16].

As effects in other systems, between 50%-75% of

individuals with ethanol 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[16]. Among the effects of repeat, heavy ethanol 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 ethanol 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[16]. These hormone abnormalities usually disappear after several weeks of total ethanol consumption abstinence.

The Prefrontal Cortex Constitutes the Target of all Preventive and Therapeutic Behavioral Interventions

The fundamental concepts of the cognitive control and the executive function could be defined in terms of their relationships with the goal-directed behavior rather than habits and controlled rather automatic processing, and also related to the functions of the prefrontal cortex (PFC) as well as other related regions and networks[17,18].

The ventromedial and the dorsolateral prefrontal cortex are two fundamental prefrontal regions that typically interact in different cognitive functions[19, 20,21]. These regions are also involved in cognitive processing of emotions; however, their participation in emotional processing is not well- studied.

Ethanol abuse is pervasive in many societies worldwide and is also associated with extensive morbidity and mortality[22]. The underlying biochemistry of the development of ethanol abuse is heavily studied. Growing evidence suggests that alcohol consumption is strongly associated with alterations in DNA methylation[22].

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)[23, 24].

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[23,24].

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[25, 26, 27].

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[8].

On the other hand, for some individuals, a first-time experience can dramatically turn into a lifelong addiction[8].

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[9].

This behavior is considered representative of the first stage of addiction: binge and intoxication[9].

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[9].

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[9, 24, 25].

Reward

The reinforcer is constituted by the drug and sometimes could be more powerful than any other natural reinforce[9]. 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[9].

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[24].

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, 9, 10]. 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, 23]. This is thought to underlie the impulsivity that is characteristic of the binge and intoxication stage[4].

Stage 2: Withdrawal and negative affect

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 ethanol 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[4,23].

The neural systems that underlie this negative affective state include a group of midbrain structures conceptualized as the extended amygdala[3].

Learning which environmental conditioned stimuli predict danger is essential for survival through Pavlovian fear conditioning. In both, humans and rodents, fear conditioning is amygdala-dependent and rests on analogous neurocircuitry[28]. Rodent research has epagogically inferred a causative role for dopamine in the amygdala in fear memory formation; however, the participation of dopamine in aversive conditioned stimulus learning in humans is less clear[28]. It has been discovered that dopamine is released in the amygdala and the striatum during the process of fear learning in humans[28,29]. By using simultaneously positron emission tomography and functional magnetic resonance imaging, it has been recently demonstrated that the amount of dopamine release is directly linked to the magnitude of conditioned fear responses and linearly coupled to learning-induced activity in the amygdala[30]. Thus, like in rodents, the formation of amygdala-dependent fear memories in humans appears to be supported by the endogenous dopamine release, consistent with an evolutionary conserved neurochemical mechanism responsible for aversive memory

formation[28].

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[31].

The activations of these systems tend to increase the production of stress hormones[3,23]. Eventually, consuming ethanol 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, 16].

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, 8, 26].

Therefore the last stage of the ethanol and drug addiction cycle is the anticipation and craving stage, which frequently means the level whereby an individual`s chronic ethanol or drug consumption may lead to the development of a substance abuse disorder[7]. While this phase is conceptualized commonly as craving, it does not, by itself, lead to relapse and another cycle[8, 26]. This final stage is characterized by a significant loss of prefrontal control and continued ethanol and drug use compromises frontal lobe structures that are critical for evaluation, judgment, and decision making[8, 9, 26]. This stage is characterized by altered glutamatergic signaling[8, 26, 31]. Glutamate plays a principal role in memory formation and consolidation as well as in the initiation of behavior[8, 26, 31].

During the anticipation and craving stage, the large amount of dopamine received by the prefrontal cortex during drug and ethanol 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 ethanol 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, ethanol-related cues (reinforced conditioned stimulus)[3, 31]. 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 ethanol 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, 8, 26].

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 avoid the withdrawal to appear!

In the brain, ethanol affects almost all neurotransmitters 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 GABAA receptors[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[8]. The Acute administration of ethanol 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[3,8]. Of Equal importance is the ability of acute ethanol consumption to inhibit the post-synaptic 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[8]. The relationships between greater GABA and diminished NMDA receptor activity during the acute ethanol intoxication and diminished GABA with enhanced NMDA actions during ethanol withdrawal let us understand much of the ethanol intoxication and the withdrawal phenomena[8].

As happens with all pleasurable activities, ethanol 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 ethanol consumption, craving, and relapse[8]. The changes in dopamine pathways are also related to increases in cortisol and adrenocorticotropic hormone (ACTH) during acute ethanol intoxication and in the context of withdrawal[8]. Such alterations are probably to contribute to both the feelings of reward during acute intoxication and the depression during falling blood alcohol concentrations[8]. Also very close linked to alteration in the dopamine in the nucleus accumbens are ethanol-induced changes in the opioid receptors, with acute ethanol consumption causing the release of β-endorphins[3, 8].

Several additional neurochemical alterations include an increase in the synaptic levels of the neurotransmitter serotonin during acute ethanol consumption and subsequent upregulation of serotonin receptors[3,8]. The acute increases in the nicotinic acetylcholine systems contribute to the impact of ethanol in the ventral tegmental region, which occurs in concomitant with enhancing dopamine activity; in the same regions, ethanol 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, 8].

Behavioral Effect. Tolerance and Withdrawal

The Behavioral Changes from Impulsive to Compulsive

Beverage ethanol is perhaps responsible for more overdose than other drugs[7]. Dependent consumption of ethanol 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[8]. 1) after 10 days of daily ethanol consumption, metabolic or pharmacokinetic tolerance appears, with up to 30% increases in the rate of hepatic ethanol catabolism[8]. This perturbation regresses almost as rapidly as it develops[7]. 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 ethanol, which contributes to the syndrome of withdrawal[8]. 3) individuals learn to adapt their behavior so that they can apparently function better than expected under the toxic influence of the ethanol or the drug which is considered learned or behavioral tolerance[8].

The cellular biochemical perturbations caused by chronic ethanol consumption may not resolve for a month several or longer following cessations of ethanol consumption. Rapidly decrease in blood ethanol 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[8].

It is considered that any potential healthful effect attributed to ethanol consumption, is overridden by continuous consumption of three or more daily drinks[8].

Nervous System

The subject with acute ethanol 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[8].

Another very common problem that is seen after as few as one or two drinks before bedtime is a state of disturbed sleep[8]. Even though ethanol 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[7]. Ethanol 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 ethanol use disorders that are older than 60 years. The patients can experience very prominent and sometimes highly disturbing dreams later in the night[8]. All these sleep perturbations could contribute to relapse to ethanol consumption[8].

Another common very significant adverse consequence of ethanol 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[8].

Heavy ethanol 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[8].

The chronic high ethanol 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[8]. 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[7]. 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 conditions[8]. These are produced from low levels of thiamine, especially in those predisposed individuals with transketolase deficiencies[8]. The repeated heavy ethanol 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[8]. The adolescents are especially vulnerable to ethanol-related brain derangements[8]. 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[8].

Ethanol 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 ethanol daily through fermentation. Catabolism of ethanol is thus essential, not only of humans but of all organisms. Several amino acid sequences in the enzymes used to oxidize ethanol 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 , 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 [13].

Survival by augmenting the capacity for fructose present in dwindling fruit to be stored as triglycerides, as a consequence of increased uric acid production during the fructose metabolism that emulated lipogenesis and also blocked the fatty acid oxidation[32]. Furthermore, a mutation in class IV alcohol dehydrogenase ~10 MYA produced a 40-fold increase in the ability to oxidize ethanol, which helped our ancestors to ingest fermenting fruit from the ground. The ethanol ingested would have activated aldose reductase that consequently stimulates the conversion of glucose to fructose, while uric acid produced during ethanol metabolism could further enhance the fructose production and its metabolism[32]. Aiding survival, and in turn evolutionary reproductive advantage of their genes, these mutations would have allowed our ancestors to produce more fat, mainly from fructose, to survive and to reproduce the very same mutated advantageous genes[32]. Sadly, the augmented ability to metabolize and utilize ethanol may now be increasing our risk for alcoholism, another consequence of the once-adaptive successfully reproduced thrifty genes[32].

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[33, 34, 35, 36].

We must be dialectical. If the experimental results are against our expectations, against our desires, against our ideology; furthermore, if our ideas about democracy[37,38], 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[39].

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