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COMMENTARY: NEUROSCIENCE AND GENETICS

UNDERSTANDING THE HIGH MIND: HUMANS ARE STILL EVOLVING GENETICALLY

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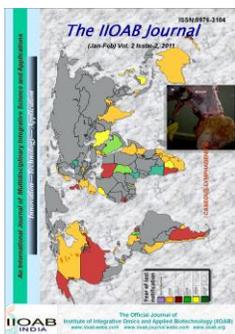
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ABSTRACT

The total population of the United States at the turn of the 21st century was 281,421,906. The total number of people above the age of 12 years old was estimated at 249 million. The National Institutes on Drug Abuse and the Substance Abuse and Mental Health Services Administration (SAMHSA) have surveyed persons age 12 and older and found that in the year 2001, a total of 104 million people have used illegal drugs in their life (ever used), 32 million used a psychoactive drug in the past year (2000-2001) and 18 million used a psychoactive drug in the past 30 days. Interestingly this does not include Alcohol. We must ask then, who are the people that could just say NO? When almost half-of the US population have indulged in illegal drug practices, when our presidential candidates are forced to dodge the tricky question of their past history involving illegal drug use, and when almost every American has slogged down a martini or two in their life time, there must be a reason, there must be a need, there must be a natural response for humans to imbibe at such high rates. There is even a more compelling question surrounding the millions who seek out high risk novelty. Why do millions have this innate drive in face of putting themselves in harms-way? Why are millions paying the price of their indiscretions in our jails, in hospitals, in wheel chairs and are lying dead in our cemeteries. What price must we pay for pleasure seeking or just plain getting "HIGH"? Maybe the answer lies within our brain. Maybe it is in our genome? Utilization of the candidate vs the common variant approach may be parsimonious as it relates to unraveling the addiction riddle. In this commentary we have discussed evidence, theories and conjecture about the "High Mind" and its relationship to evolutionary genetics and drug seeking behavior as impacted by genetic polymorphisms. We consider the meaning of recent findings in genetic research including an exploration of the candidate vs the common variant approach to addiction, epigenetics, genetic memory and the genotype-phenotype problem. We speculate about the neurological basis of pleasure seeking and addiction, the human condition and



the scope of societal judgments that effect multitudes in a global atmosphere where people are seeking "pleasure states".

Keywords: *evolution; genome; common variant hypothesis; candidate genes; reward deficiency syndrome (RDS); dopamine*

The mind of man is capable of anything- because everything is in it, all the past as well as all the future.

Joseph Conrad
Heart of Darkness

[I] INTRODUCTION

A fundamental premise about the brain is that its workings – sometimes referred to as the “mind” – are the result of its anatomy, physiology, neurochemistry, and genome, and that is all. The mind, therefore, is a consequence of the brain, and of the action of its constituents. Some people have difficulty accepting that premise, whether as an outgrowth of their religious upbringing, or their acceptance of other premises springing from tradition or folklore, their belief is that the mind is something magical. They perceive it as unidentifiable and quite separate from the body, as if it were made of quite different “stuff”. Some even refer to it as the “soul.” [1]

It is not our intent to argue or defend the mind/body dualism theories of the early days of psychology. Rather, this is an attempt to understand the mind in terms of alterations in its’ level of function.

It is interesting that as early *Homo sapiens* spread out from Africa starting around 60,000 years ago, they encountered environmental elements and challenges that they could not overcome with prehistoric technology. In this regard many scientists falsely expected that analyses of our genome would indicate that an explosion of evolutionary mutations would have spread quickly throughout different populations. They theorized that these beneficial mutations would confer a greater survivability. However recent analysis of by Jonathan K Pritchard [2] and others [3] suggest that recent human evolution has occurred at a far slower pace than biologists had envisioned. While there have been examples of strong genetic mutations that have resulted in adaption to environmental pressure such as observed in Tibet. There transition to high altitudes resulted in gene mutation that favors this environmental shift in Tibetans [4]. The genome actually contains few examples of very strong rapid natural selection. Instead most of the visible natural selection appears to have occurred over tens of thousands of years. It is noteworthy that the rate of change of most traits is very slow indeed and as such major adaptive shifts require stable conditions across millennia. According to Pritchard [5]: “*Thus 5,000 years from now the human milieu will no doubt be very different. But in the*

absence of large-scale genomic engineering, people themselves will probably be largely the same. With this in mind then it may not be surprising to find a fairly high genetic influence on drug/pleasure seeking behavior in Homo sapiens possibly due to carrying a gene form that sets-up the individual to be driven by a need to up-regulate specific proteins such as dopamine receptors to induce a feeling of well-being and happiness”.

[II] THE GENE MANUAL

Most recently we have seen an enormous advance in the breaking of the genetic code and the identification of some 30,000 genes in the human genome. The gene manual is now known to contain a parts list of about 20,000 genes –strings of DNA letters that spell out the information required to build proteins. About 2 percent of the human genome encodes proteins, and a roughly similar amount seems to be involved in gene regulation. Most of the rest of the genome has as yet no known role. Modern research suggests that the entire scope of recent history and biology points to an inescapable conclusion: that we are, to a remarkable degree, chemically identified (made-up) of nucleic acids, DNA and RNA, and other operational agents referred to as proteins as either receptors or enzymes [5,6].

The basic needs of humans include sustenance, reproduction and safety. These needs are challenged on a daily basis and for many people replaced with hunger, lack of human contact and fear. Many drugs that have abuse potential and other natural stimuli such as food or sexual activity produce similar chemical changes in the brain. That change is an increase in extracellular dopamine (DA) in the shell of the nucleus accumbens (NAc). Moreover, the reward mechanism is at least very similar for all stimuli.

Presently the available information shows that the reward pathways involved are complex and have multiple elements. Multiple brain regions, multiple receptors, multiple distinct neurons, multiple transmitters, multiple transporters circuits peptides, proteins, metabolism of transmitters, and phosphorylation, all participate in reward mechanisms. Most

recently, a review of published literature on fMRI studies of love, illustrating brain regions associated with different forms of love revealed interesting results. Although all fMRI studies of love point to the subcortical dopaminergic reward-related brain systems (involving dopamine and oxytocin receptors) for motivating individuals in pair-bonding, a meta analysis newly demonstrated that different types of love involve distinct cerebral networks, including those for higher cognitive functions such as social cognition and bodily self-representation [7].

The sets of mechanisms involved in the reward from different drugs of abuse, are different from the mechanisms in the reward from natural stimuli such as food or sexual activity; thus there are different systems that distinguish different stimuli. Separate functions of the reward system such as anticipation, evaluation, consummation and identification; all contain function-specific elements. The level of the stimulus also influences the participation of the elements in the reward system. There are possible reactions to even below threshold stimuli, and excessive stimuli can change reward to aversion. Learning and memory of past reward is an important and integral element involved in reward and addictive behavior. Many of the reward elements are altered by repeated or chronic stimuli, and chronic exposure to one drug is likely to alter the response to another stimulus. To evaluate and identify the reward stimulus thus requires understanding of the heterogeneity of the reward components in the brain [8].

[III] HUMAN GENOME PROJECT: REVOLUTION OR FAILURE?

If the conclusion that we are made up basically of genetic material is feasible, and as such we are very complex then what makes us so different from other organisms of the universe? Is it our “mind” or is it the evolutionary impact of the environment on our genetic material. Do these concepts meld into a hybrid blend of biological and functional activity? We do now understand that there are mutations in various genes which have occurred ancestrally and are referred to as older gene forms, and there are other mutations in the same gene that are referred to as new gene forms. We also know that certain environmental elements could actually effect the expression of certain gene forms whether old or new. For example, Vitamin B12 can add methyl groups on a gene and change its expression. There are also epigenetic effects influencing drug seeking behavior, ADHD and even schizophrenia [9] [see epigenetics section below].

The Human Genome Project opened the pathway to solving the mysteries of disease, after a decade of arduous research from world class scientists while the future looks bright, there is a long way to go before we could achieve medical “miracles”. To many the Human Genome Project has failed so far to provide the medical miracles that scientists promised in 2000. In that year leaders of the Human Genome Project announced

completion of the first rough draft of the human genome. One of the predictions was that follow-up research could pave the way to personalized medicine within ten years. Accordingly to date few medical applications have emerged but important insights have already revolutionized medical research including psychiatric genetics. While some leading geneticists argue that a key strategy known as the “common variant” hypothesis for seeking medical insights into complex diseases such as addiction is fundamentally flawed, others say that the strategy is valid [10].

The obvious way to see who was right would have been to sequence the full genome of diseased and healthy individuals and, using powerful computers, identify DNA variations that turned up in patients with the given disease but not in control subjects. Using sophisticated techniques many scientists embarked on large scale studies, known as *genome-wide association studies* (often called GWAS) that relied on landmarks in DNA known as single-nucleotide polymorphisms or SNPS, to uncover gene variants important in disease.

These concepts led to the development of HapMap. [11]. Thus in the last five years genome-wide association studies have looked at hundreds of thousands of common SNPS in the genome of tens of thousands of individual subjects and controls in search of SNPS linked to common disease. While a number of leaders in the field believe that using this strategy has revealed important clues and uncovered pathways for a number of common diseases such as schizophrenia, type 2 diabetes, Alzheimers and hypertension no magic bullets have been developed. In fact it is astounding that being able to crack the human Genome allowing scientists to look at the entire compliment of common genetic variants has not led to any major breakthroughs especially in neurobiology. Moreover, in a recent interview [12] David Botstein of Princeton University (Hall 2010) discussing the HAPMAP stated “It had to have (been) done. If it had not been tried, no one would have known that it didn’t work” The 138 million HapMap he says was a “magnificent failure”. This has been further supported by Walter Bodmer who first proposed the genome project. He also believes that the common variant hypothesis is a dead end and suggests that the vast majority of common variants have shed no light on the biology of disease [12].

The current argument over the common variant hypothesis suggests at least one way forward for solving what many are calling the “missing” heritability problem. That is to search for rare genetic variants.

However, it is plausible that new approaches should consider re-exploring the older candidate approach instead of relying on GWAS for an answer. In this approach scientists pick and choose genes to examine in those people, based on prior knowledge of physiological processes as Blum and Noble [13] did in search of the “reward gene.” Using this approach they found at least one important variant of the dopamine- D2

receptor gene (Taq *AI*) that is associated with severe alcoholism. This apparently simple finding is complicated by the fact that many other genes in specific brain reward pathways [14] and their polymorphisms all work in concert to provide the end – genetically controlled phenotype. In this regard, Li [15] proposed that 396 genes work in a network of common pathways to influence the final net release of Dopamine and Glutamate in the reward center thus effecting drug seeking behavior.

3.1. Epigenetic changes

Interestingly, Joseph Nadeau, director of scientific development at the Institute for Systems Biology in Seattle, has tracked more than one hundred biochemical, physiological and behavioral traits that are affected by epigenetic changes. In addition, he has seen some of these changes passed down through four generations. This phenomena, which has been called the “*genotype-phenotype problem*” evokes the potential importance of the environment. However we have no evidence that in terms of addiction liability, for example, of what impact elements in society play in and to what extent these epigenetic effects impact future generations. However, we must keep an open mind and also realize that transgenerational genetic effects impact phenotypic expression and may confer disease risk [16]. Nadeau et al [16] suggests that some common illnesses may ultimately be traceable to a very large number of genes in a network or pathway whose effects may each vary. Various effects may depend on the gene variant whereby the presence of one gene variant can exacerbate or counteract the effect of another disease –related gene in the group. This takes on even more importance especially for the addiction field when we evoke the so called “domino effect” as observed in the cascade associated with brain reward” [14]. While we have not as yet seen medical miracles the genome project opened the doors and we should not predict a timetable for such miracles to occur but just imagine what Darwin and Mendel, for example, could do with this technology.

[IV] DNA AND REINCARNATION: GENE-ENVIRONMENTAL INTERACTION

In his book on the evolution of human intelligence, “The Dragons of Eden,” the late Carl Sagan as early as 1977, speculated that most complex organisms on earth today contain substantially more stored information, both genetic and extra-genetic, than the most complex organisms of two hundred million years ago. According to Sagan, the basic means for capturing this information lies within something termed “genetic memory” [17].

All organisms on planet Earth have chromosomes which contain the genetic material passed on from generation to generation, whether those organisms are fruit flies or human beings [18]. Indeed, there are those who speculate on the process of reincarnation as being nothing more than the passage

of information from one life form to another life form via DNA molecules. While no specific gene polymorphisms have ever been associated with an affinity for reincarnation per se, recent serious research on the relationship between child abuse and reincarnation has been investigated [19].

To gain an understanding of the psychosocial function of reincarnation among Druze, interviews were conducted with nine male subjects who had experienced reincarnation and with one or two of their family members. Analysis of these interviews revealed that the onset of experienced reincarnation typically occurs at between two and five years of age. Five of the subjects had displayed psychological distress in their childhood that was alleviated after the experience reincarnation.

Once the child has displayed initial indications of reincarnation, such as mentioning names that the family construes as being from a past life, the family takes an active role in constructing the past-life story and matching it to a known real story involving a tragic death. This match creates a new order in the life of the child, the family, and the past-life family. The findings support the sociocognitive notion of the constructing of past memories by the social environment.

In subsequent sections we discuss the relationship of genetic polymorphisms and potential positive and negative impacts on reward mechanisms that could influence long-term survival. An important question to ponder is why there is an increase in aggressive, addictive and other behavioral disorders and is our species in peril? In the past these trends have been attributed purely to environmental factors and to the stress of our increasingly complex and technological society. A new theory is emerging that just the opposite is occurring that our increasingly complex society, with its requirement for more and more years of higher education to compete, is selecting for the genes associated with these “reward” behavioral disorders, and that these genes are increasing infrequency in our society. In essence a breakdown of brain reward functioning has board implications for public policy –as well as the future of the human species.

It is feasible that a cave man imbibing his *mandragova* officinarum (mandrake root), a psychoactive substance with extreme aphrodisiacal powers, may have experienced an effect which was passed through “genetic memory” to his offspring and to subsequent offspring. The experience, being pleasant and stored, may or may not be experienced in the recipient offspring. However, appropriate extra-genetic stimuli may trigger awareness of that stored pleasure state, in one degree or another, for future generations.

Given that extra genetic triggering action (could be certain chemicals, toxins, etc); the recipient offspring may believe it to be a “fantasy” or “hallucinations”, whereas in reality the experience may have its origin as far back as recorded history, or as far back as the initial ingestion of the mandrake root.

[V] INSIDE THE BRAIN

“Of all animals, man has the largest brain in proportion to his size”

Aristotle

The Parts of Animals

With evolution came genetic mutations, and with mutations came *Homo sapiens*. Where is this genetic information stored? To protect against accident, we would expect natural selection to have evolved substantial redundancy, it is also scientifically apparent that the brain is not equipotent in its capacity to store bits of information for memory purposes.

Studies on the limbic system reveal that electrical activity of that part of the brain, termed “theta activity” appears to be related to short-term memory. Drugs which increase Theta Activity also have been found to increase memory [20].

A review of pertinent literature makes it difficult to resist the conclusion that – at least in humans – memories are stored somewhere in the cerebral cortex and activated within the limbic system. They involve chemical messengers, dopamine, gallanin, acetylcholine as well as the *fos* gene and wait to be retrieved by electrical impulses generated through endogenous substances or processes within the brain itself or the ingestion of psychoactive substances including drugs of abuse.

An increasing body of evidence shows that structural modifications of chromatin, the DNA-protein complex that packages genomic DNA, do not only participate in maintaining cellular memory (e.g., cell fate), but they may also underlie the strengthening and maintenance of the synaptic connections required for long-term changes in behavior. Accordingly, epigenetics has become a central topic in several neurobiological fields such as memory, drug addiction, and several psychiatric and mental disorders [21].

This interest is justified as dynamic chromatin modifications may provide not only transient but also stable (or even potentially permanent) epigenetic marks to facilitate, maintain, or block transcriptional processes, which in turn may participate in the molecular neural adaptations underlying behavioral changes. Through epigenetic mechanisms the genome may be indexed in response to environmental signals, resulting in specific neural modifications that largely determine the future behavior of an organism. In their review Malvaez et al. [21] discuss recent advances in our understanding of how epigenetic mechanisms contribute to the formation of long-term memory and drug-seeking behavior and potentially how to apply that knowledge to the extinction of memory and drug-seeking behavior.

[VI] THE HEMISPHERE CONNECTION

The human brain consists of a right and left hemisphere, both of which are connected via the corpus callosum. The complex cabling system represented by the corpus callosum underlines the fact that although the separate hemispheres have separate functions the interaction of the hemispheres is a vital human function which may have impact on one’s behavior such as, for example obsessive compulsive disorder [22].

Humans exhibit an interesting separation of musical and verbal skills [23]. Patients with lesions of the right hemisphere are significantly impaired in musical, but not verbal, ability. However, even when performance of musical abilities is hampered by right hemisphere lesions, the ability to read music is unimpaired.

In this regard, it has been stated by Sagan that evidence from scientifically sound experiments suggest that those functions we ordinarily describe as “rational” live mainly in the left hemisphere, while those we consider “intuitive” dwell mainly in the right [17].

As early as the 70’s, Robert Ornstein and David Galin of the Lanley Porter Neuropsychiatric Institute of San Francisco claim that as normal people change from analytic to creative intellectual activities, the EEG activity of the corresponding cerebral hemispheres varies in the predicted way: for example, when a subject is performing mental arithmetic, the right hemisphere exhibits the alpha rhythm characteristic of an “idling” cerebral hemisphere [24].

According to Ornstein and Galin, the Western world is left hemisphere oriented. They suggests that our awareness of right hemisphere function is a little like our ability to see stars in the daytime. Sagan further describes Ornstein’s hypothesis:

The sun is so bright that the stars are invisible, despite the fact that they are just as present in our sky in the daytime as at night. When the sun sets, we are able to perceive the stars. In the same way, the brilliance of our most recent evolutionary accretion, the verbal abilities of the left hemisphere, obscures our awareness of the functions of the intuitive right hemisphere, which in our ancestors must have been the principle means of perceiving the world [17].

In essence, then, inhibition of the left hemisphere releases our potent “intuitive” side of the brain, reflecting our most primitive desires, feelings and appetites. This has been described by some as the coming out party of our ‘reptilian brain”

In 1962, William Barrett, in his *Irrational Man*, described the historical transition from intuitive to rational dominance of human consciousness as a traumatic turning point in human development, both as a source of power on one hand, and as an alienation from more primitive powers on the other.

“This capacity for loving easily and familiarly at an extraordinary level of abstraction is the source of modern man’s powers. With it he has transformed the planet, annihilated space, and trebled the world’s population. But it is also a power which has, like everything human, its negative side, in the desolating sense of rootlessness, vacuity, and lack of concrete feeling that assails modern man in his moments of real anxiety” [26].

It is not surprising that such moments of real anxiety should drive modern man to experimentation with consciousness-altering substances with hopes that can touch the roots of his intuitive powers.

For example, since the early sixties and now even in the first part of the millennium, a closer look at the plant psychotropic marijuana reveals that it is often described as improving our appreciation for music, the arts, dance, sex, sign and symbol recognition and our sensitivity for nonverbal communications. Today we know that cannabinoid receptors in the brain are laid down by certain genes. The brain cannabinoid receptor (CB1) was first isolated in 1988 by W.A. Devane and associates. Then in 1990, L.A. Matsuda, cloned the CB1 receptor gene (CNR1). Some have thought that short-term memory is lost with high doses of cannabinoids. This assertion has been borne out because there is a relationship between a decrease amplitude of a certain evoked related potential (ERP) called the P300 and frequent marijuana smokers. Decreased amplitude of the P300 and prolonged latency has already been associated with memory deficits as well as alcohol and drug dependence. Nevertheless, this effect of marijuana has not kept millions from its daily use. There are even some who proclaim that they function better while using it. For example, some have called for individualized substance use counseling for persons suffering from schizophrenia, citing the observation that in some cases use of marijuana might help a client "feel calmer and happier" and actually prevent stress-related relapse.[25] For yet other patients, the drug might have deleterious effects. Advocating this degree of individualization of treatment takes considerable courage and is certainly not the conventional wisdom or the textbook approach.

In this regard, however, marijuana is seldom, if ever, reported to improve our cognitive abilities. It seems a certainty that marijuana does not enhance our abilities for cognitive calculation, whether represented by our appreciation of Einstein’s theory of relativity, the calculation of a rocket trajectory, or the computation of a Nernst equation [26].

It is more commonly observed that rather than enhancing human powers, the cannabinoids (active ingredients of marijuana) simply suppress the left hemisphere and permit the stars to come out. Such inhibition to the left hemisphere may be similar for other psychoactive substances, such as opiates derived from poppy, cocaine from cocoa root, alcohol from fermented sugar, nicotine from tobacco and sugar from sugar

cane. The neurochemical similarity of all these left – hemisphere suppressors induce presynaptic dopamine release from the reward site of the brain in the *meso-limbic system* called the *nucleus accumbens*.

This inhibition/release mechanism may even be the objective of not only the meditative states of many eastern religions it may also provide the basis for the seeking of pleasure states via natural or unnatural means. In other words, is the “high” we seek simply the suppression of the left hemisphere and preferential dopamine release?

Barrett has suggested that man’s preoccupation with left-hemisphere concerns in contemporary society drives him to alienation and loneliness that must somehow be relieved.

“---man’s feeling of loneliness or alienation has been intensified in the midst of a bureaucratized, impersonal mass society He has come to feel himself an outsider even within his own human society--- But the worst and final form of alienation--- is man’s alienation from his own self. In a society that requires of man only (that) he performs competently his own particular social function, man becomes identified with this function, and the rest of his being is allowed to subsist as best it can- usually to be dropped below the surface of consciousness and forgotten”[26].

Likewise, Harvard neuroanatomist Jill Bolte Taylor described her subjective experience of the aftermath of her left-sided stroke in the following manner:

“Because I could not identify the position of my body in space, I felt enormous and expansive, like a genie just liberated from her bottle. And my spirit soared free like a great whale gliding through the sea of silent euphoria. I remember thinking there’s no way I would ever be able to squeeze the enormity of myself back inside this tiny little body. But I realized “But I’m still alive! I’m still alive and I have found Nirvana. And if I have found Nirvana and I’m still alive, then everyone who is alive can find Nirvana.” I picture a world filled with beautiful, peaceful, compassionate, loving people who knew that they could come to this space at any time. And that they could purposely choose to step to the right of their left hemispheres and find this peace” [27]

The ways and means of returning to delve again into those forgotten regions of the subconscious which house “the rest of his/her being,” are many and varied. Whether the “high” is sought to suppress left hemisphere dominance is “narcotic” or “natural”, the end is identical. In a recent study by Baloch et al. [28] fifty one children and adolescents with DSM-IV Pediatric bipolar disorder and 41 healthy comparison subjects underwent 1.5 T structural magnetic resonance imaging brain scans. Exploratory analysis showed pediatric bipolar disorder subjects who had one or more first degree relatives with mood disorders had significantly smaller left hemisphere SGPFC compared to healthy controls (p = 0.03 Sidak corrected).

From 1987 – 1990, one of us (KB) had the fortunate experience of directing a research project at the University of Texas Health Science Center in San Antonio, Texas, and UCLA in search for genes that may associate with severe alcoholism. In 1990, Ernest Noble (former Director of NIAAA) and KB published their findings in the prestigious *Journal of the American Medical Association*. In essence they found the first “defective” gene that associated with severe alcoholism. The press wrongly labeled the finding as “EXPERTS FIND THE ALCOHOLISM GENE” [13].

This was wrong because there is nothing in the brain that is particular to alcohol per se. Instead Blum and Noble and associates found a gene form that really associates with brain reward or feelings of well-being. After many years of additional research and a lot of controversy their work has now withstood the test of time. While there are many genes involved in causing impulsive, compulsive and addictive behavior, it is interesting that these genes work in concert and predispose an individual to these destructive behaviors. There is a common genetic thread that causes alcoholism, drug dependence, nicotine dependence, carbohydrate cravings, and other behaviors such as pathological gambling, sex addiction and even serial killing. Being perplexed with the field of biological psychiatry KB coined the term “Reward Deficiency Syndrome (RDS)” to describe this common genetic thread linking all the addictions [29].

So basically, the junkie on the street making a heroin run is neurochemically similar to the executive gulping down five martinis at a business lunch. The main difference is the stigma attached to the heroin addict compared to the respected business person. The reason why these individuals are neurochemically similar is that both heroin and alcohol stimulate the same brain reward site and cause the nerve cell release of a substance called dopamine. Regulation of dopamine plays a crucial role in our mental and physical health. In addition to affecting brain processes that control movement, emotional response, and ability to experience pleasure and pain, Dopamine’s two major functions are as an anti-stress molecule and a pleasure inducing molecule [30].

Drug addiction is a chronically relapsing disorder that has been characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (for example, dysphoria, anxiety, irritability) reflecting a withdrawal syndrome when access to the drug is prevented. Drug addiction has been conceptualized as a disorder that involves elements of both impulsivity and compulsivity that yield a composite addiction cycle composed of three stages: 'binge/ intoxication', 'withdrawal/ negative affect', and 'preoccupation/ anticipation' (craving) [31].

Animal and human imaging studies have revealed discrete circuits that mediate the three stages of the addiction cycle. The ventral tegmental area and ventral striatum is a focal point for the binge/intoxication stage. The extended amygdala is the key

area in the withdrawal/negative affect stage. The preoccupation/anticipation stage involves a widely distributed network including the orbitofrontal cortex-dorsal striatum, prefrontal cortex, basolateral amygdala, hippocampus, and insula, involved in craving and the cingulate gyrus, dorsolateral prefrontal, and inferior frontal cortices involved in disrupted inhibitory control [32].

The transition to addiction involves neuroplasticity in all of these structures that may begin with changes in the mesolimbic dopamine system and a cascade of neuroadaptations from the ventral striatum to dorsal striatum and orbitofrontal cortex and eventually dysregulation of the prefrontal cortex, cingulate gyrus, and extended amygdala. The delineation of the neurocircuitry of the evolving stages of the addiction syndrome forms a heuristic basis for the search for the molecular, genetic, and neuropharmacological neuroadaptations that are key to vulnerability for developing and maintaining addiction [31].

Thus, imagine the world without dopamine and you would find an individual caught up in a very anxious non pleasurable and totally frustrated state. When there is a lack of dopamine receptors the individual seeks out substances that will fix the problem by stimulating dopaminergic pathways.

[VII] BRAIN REWARD MECHANISMS

In his book “Alcohol and the Addictive Brain” with James Payne [33] KB provided a look at how the brain may function leading to either well-being/euphoria or dys-ease/dysphoria. Many more recent experiments confirm these ideas.

It is well known that in the brain reward site, the chemical messenger dopamine works to maintain our normal drives: hunger, thirst, and sex. In fact, dopamine has come to be known as the “pleasure molecule” and/or “anti-stress molecule.” When dopamine is released into the synapse, it stimulates a number of dopamine receptors (D1-D5) that results in a feeling of well-being and stress reduction. This is the result of the interaction of numerous transmitters-serotonin (5HT), endorphins (END), GABA (GB), dopamine (DA), norepinephrine (NE), and acetylcholine (ACH).

The process of the interactions at the brain “reward site” is called: the reward cascade [14]. A consensus of the literature suggests that when there is a dysfunction in the “brain reward cascade,” especially in the dopamine system causing a low or hypo-dopaminergic trait, the brain of that person requires dopamine to feel good. This high-risk genetic trait leads to multiple drug-seeking behaviors. This is so because alcohol, cocaine, heroin, marijuana, nicotine and glucose all activate release of dopamine, which can heal the abnormal cravings [34]. Moreover, this genetic trait is due to a form of a gene (DRD2A1 allele), which prevents the expression of, the normal laying down, of dopamine receptors in the brain reward site [13].

This gene and others involved in neurophysiological processing reward neurotransmitters (i.e. 5HT, END, GB, DA, NE, ACH etc), have been associated with deficient functions and predispose individuals to have a high risk for addictive, impulsive, and compulsive behavioral propensities. These include: severe alcoholism, cocaine, heroin, marijuana, and nicotine addictions, glucose bingeing, pathological gambling, sex addiction, ADHD, Tourette syndrome, autism, chronic violence, post traumatic stress disorder, schizoid avoidance disorder, conduct disorder, and antisocial behavior [35].

It has been proposed that genetic variants of the D2 dopamine receptor gene and other "reward genes" are important common genetic determinants of the emerging concept Reward Deficiency Syndrome (RDS) [36]. Ongoing current research involved in chromosomal marking and candidate gene analysis has supported the concept of "polygenic inheritance" and epistasis. While certain pharmaceutical approaches include targeting of single neurotransmitter deficits (e.g. SSRI's), as well as blocking dopaminergic activity to reduce drug effects (e.g. Haloperidol), our approach includes multiple neuropharmacological targets and enhancement of dopaminergic function as a life-long goal.

Gene therapy studies by Nora Volkow revealed that over expression of D2 receptors in the NAc of alcohol drinking rodents results in a significant reduction of both alcohol preference and craving [37]. Similar findings have been obtained in animals with high cocaine preference [38]. While the goal of treatment is the early diagnosis of one's genetic propensity to substance seeking behavior with the possible potential of CNS gene therapy, current diagnosis and treatment includes, limited non-invasive DNA testing as well as precursor amino-acid -enkephalinase inhibitory therapy [39,40].

We propose that, based on this previous evidence, substance abuse treatment must involve physiological, psychological, and spiritual modalities. With reference to the physiology, we propose a biogenetic model for the diagnosis, treatment and prevention of relapse for RDS behaviors. Thus, genotyping, pharmaceutical interventions, nutraceutical therapies, neurofeedback, auricular therapy, acupuncture, chiropractic and certain natural forms of healing provide a unifying approach to reduce aberrant cravings and enhance recovery and well being by altering brain chemistry.

While the above is based on some scientific concepts, there are other approaches that can be used to look at the age old question of "why do we like to get "HIGH"? Before we suggest a further answer to the question of the why and how of "High", there are other concepts which must first be taken into considerations.

[VIII] THE TRIUNE CONCEPT

Historically, MacLean in 1973, pointed out three basic components of the human brain, which for the most part have not really changed over the last 30 years, except for more defined functions and the discovery of a plethora of exciting genomic/phenotype topology. These functions include: 1) neocortex, 2) limbic and 3) reptilian complex (R-Complex). [41].

Accordingly it has been shown that the R-Complex plays an important role in aggressive behavior, territoriality, ritual and the establishment of social hierarchies. In some sense, the R-complex still performs dinosaur functions.

The limbic system generates strong or vivid emotions. Electrical discharges in the limbic system result in signs similar to those of psychoses or those produced by psychedelic or hallucinogenic drugs. The limbic system is the site of reward behaviors. It is the site where our desire for pleasure takes place. In a sense it is the pleasure center and by the exaggerated release of neuronal dopamine or possibly even opioid release, we perceive euphoria. All cravings occur at this site.

Human action is strongly influenced by expectations of pleasure. Making decisions, ranging from which products to buy to which job offer to accept, requires an estimation of how good (or bad) the likely outcomes will make us feel. Yet, little is known about the biological basis of subjective estimations of future hedonic reactions. Sharot et al [42] show that administration of a drug that enhances dopaminergic function (dihydroxy-L-phenylalanine; L-DOPA) during the imaginative construction of positive future life events subsequently enhances estimates of the hedonic pleasure to be derived from these same events. According to the authors these findings provide the first direct evidence for the role of dopamine in the modulation of subjective hedonic expectations in humans. The human cerebral neocortex is believed to be the seat of human cognition. It is frequently discussed in terms of four major regions or lobes: *frontal, parietal, temporal and occipital lobes*. Lesions in the neocortical areas often destroy initiative and creative traits.

Many Psychiatrists now believe that understanding the triune concept or brain part functions, and its interactions, albeit having separate but interrelated functions of the brain, may hold clues to the relationship between drugs and induced dreamlike states.

Based on the triune brain model, a new approach to psychopathology has taken shape. It is the evolutionary perspective of mental diseases such as the major psychoses, anorexia nervosa, anxiety disorders, and also brain diseases such as Parkinson's disease or Huntington's disease. Many mental illnesses are marked by severe deficits in social behavior and social communication. The social communication system disintegrates, especially in the major psychoses. The response choices to social or other external signals in a given situation

become limited or even distorted, and reasoning is no longer part of decision making [43].

The emphasis of this contribution is on the disintegration of social behavior in psychopathology, based on evolutionary psychiatry. In terms of mind-body-soul, MacLean's concept provides valuable insight for understanding the biological roots of human social behavior and communication. It is time to uncover the ties between the natural and the social sciences [43, 44].

[IX] DREAMS

Dreams may be a way in which humans communicate with the right hemisphere. A major aspect of the dream state might be the unleashing of the R-complex processes that had been suppressed by the neocortex during the wakeful periods.

One of the most famous dreams known to have solved a difficult intellectual problem is that of the German chemist Friederich Kekule von Stradowitz in 1865. The dream allowed Kekule to determine the molecular nature of the benzene ring. Kekule was dozing when he had a dream of dancing atoms in linear arrangement, and the tail of a chain of atoms attached itself to the head and formed a rotating ring.

This is an example of pattern recognition and not an analytic activity, and as such is typical of almost all of the famous creative acts accomplished in the dream state. These manifestations are right hemisphere and not left hemisphere activities.

In trying to understand the “high” mind, we might consider the possibility that psychotropic substances induce in the subject dream-like states of a creative nature- sometimes referred to as hallucinations. However, holding that thought, we can also glean wisdom from individuals who imbibe because they believe and maybe rightly so, that their most creative moments have occurred under the influence of one or more psychoactive drugs. Should we limit our minds? Should we think inside the box? Should we have bounds? Some of the best music, art and scripts have been generated by pleasure seekers with great talent that is unleashed without bounds. Lenny Kravitz wrote- *“I have a pocket full of money and a pocket full of- keys without any bounds”*. Maybe we should be able to fly away and feel good at will – what a thought! In essence, our mental freedom is all that we come into this world with.

To continue, it may follow that if indeed dreams are the result of right hemisphere dominance and if there is an alteration of the level of consciousness in a positive way (feeling good – being high) then the “high” one obtains from drugs or herbs may be due to their effect of inhibiting the left hemisphere, as suggested earlier.

Sagan points out that in dreams “we are sometimes aware that a small portion of us is placidly watching; often in a corner of the dream, there is a kind of observer” [17]. In a nightmare, we may say to ourselves: “This is only a dream”. Maybe this entire universe is a dream and someone else is dreaming this dream and we are just a part of it!! This idea becomes more vivid when we consider the movie *“Inception”*.

According to Bruce Charlton, the Peak experiences in science could therefore be considered the result of a 'significance alarm' going off in the brain and their objective value depends on the specialized cognitive quality of that specific brain. So scientists may be correct to take peak experiences seriously. Perhaps the best approach is to regard the scientific peak experience as a signal from the self to the self (occurring in a dream state), a subjectively evaluated and auto-administered emotional reward for good thinking [45].

It is noteworthy that in psychedelic drug experiences –for example liquid Tetrahydrocannabinol (THC) or lysergic acid (LSD) the presence of such a “watcher” is frequently reported. Even today, years after Hoffman, Huxley, Leary, Ram Das, and Cohen, LSD experiences may be quite terrifying, and it is the “watcher” who acts to buffer the terrifying experiences. The “watcher” would say: “Hey man- this is just a dream”. “The easy induction of pseudo-profound insights by intoxicants serves as a warning of the potential pitfalls. An arbitrary object becomes labeled with an obscure sense of delight and personal relevance in a process that could be termed the Colonel Flastratus! Phenomenon” [45]

As intelligent humans seeking knowledge attempting to uncover the mysteries of the mind, we must ask are drug-induced hallucinations fragmented bits of stored information having a direct link to our many pasts, or are they images of our future? Remember Conrad's statement –*“everything is in it (the mind), all the past as well as all the future-”*

[X] GETTING “HIGH”

In 1972, Andrew Weil, in the bestselling book *“THE NATURAL MIND”*, [46] proclaimed that getting “high” is a time-honored tradition. Human beings are born with an innate need to get high, to experience periodically other states of consciousness, and the capacity for this experience is a capacity of the human nervous system. Often, external things, such as psycho active drugs, like strong marijuana, seem to cause highs, but this is an illusion. In fact it is due to the interaction of the drug and meso-limbic chemical messengers with the net effect of releasing dopamine at the reward site. Indeed it is a pleasurable activity likened to a pre-orgasmic experience increasing one's libido. Most importantly, the great thinkers and teaches of meditation, believe that it is possible to be high spontaneously and to learn to get high with less and less external stimulation.

In terms of science the act of being high depends on one's receptor sensitivity to interaction with certain chemical messengers including serotonin, endorphins and dopamine. In reality unless there is sufficient quanta of the so called "high" molecules in the synapse, no high will be achieved. In essence the genome of each individual may have a lot to do with one's sensitivity, need and innate tolerance for the psycho active effects of any substance [47, 48].

Therefore, most people do not want to train their mind and slowly increase their ability to get high naturally. We must accept the fact that many people are going to rely on external things, including drugs and plants psychotropics, for their highs.

From the beginning, mankind has devoted considerable energy and ingenuity to "turning on" under such labels as "altering levels of consciousness" or as it use to be noted by Aldous Huxley the "opening the doors of perception". Through smoking, snorting, sniffing, eating, drinking, or main-lining, people of all cultures have sought a little more than the standard view of reality.

We could argue that today the problem of substance use disorder is symptomatic of more general societal problems, but we now know that certain gene forms can express a phenotype which actually predisposes an individual to wanting to get high compared to others that do not like to get high. In this regard, we know that individuals who carry the DRD2 A1 gene form love psychostimulants (cocaine) and those that carry the DRD2 A2 hate psychostimulants [49].

The continued understanding of neurogenetics and its role in drug seeking behavior will be the subject of many experiments in the future extending our existing knowledge of "Psychiatric Genetics".

[XI] DRUGS: HAVE IT YOUR WAY

The drug scene is nothing new and seems to be increasing in our younger generation. It is the American way, a trillion dollar complex that pushes and pumps its produce into all facets of our life. Burger King cannot compare to the blazing R_x sign in the sky. "If you have a pain, we have a pill", is not so odd to rejoin to, "Have it your way" (at Burger King). The only real difference is that corporate drug dealers shy from the figures of how many "pill-burgers" they have actually dealt us. The question of "Should we give drugs to people?" -then takes on an expo factor value and echoes the empty ring of political "would have's, should have's". The real question at hand is, "What quantity of drugs can we afford" and what is the system of barter? Drugs or plant psychotropic abuse is not the real issue, people are. That people need other people is a basic human condition. Without interaction with another human, a person may become psychotic. For example, Howard Hughes, one of the wealthiest men of history, was a nearly total recluse

beset with psychoses and neuroses in abundance. This shows that people do not need just objects and materialism but the human touch. In the movie the "Awakening" Robert De Niro, was suffering from a terrible tremor from the lack of brain dopamine (likened to Parkinson's) but when he danced with a loving caring female his tremors stopped. You could have all the riches in the world and all those things you think you really need to survive and prosper, but there is nothing like a beautiful smile, a handshake, or a hug or a kiss from another individual, or even an intelligent discussion to make you feel like a million bucks!

People provide the real "highs". People need people. However, in today's screwed up, financially unstable (1.4 million bankruptcies 2009), and very scary world, loneliness and alienation are commonplace. Everything would look perfect if we were all living in a vacuum, but instead millions, if their lucky enough not to be homeless, are probably living in glass houses vulnerable to being shattered.

Where love, compassion and friendship are lacking, there is always synthetic chemistry to turn you on to synthetic "highs." While this might be true for many, there are also those that just like to get high through drugs and do it for no special reason except to "feel good". Hey, it's for the party not for the escape. In whatever way happiness is sought, whether through other people, drugs or sugar-coated placebos, the end result is that an individual strives in his own way to achieve happiness. Frank Sinatra had it right in his song- "I did it my way!" However this idea of letting people do their own thing has resulted in billion dollar industry -so called drug rehabilitation with its 11,000 or more treatment centers.

[XII] HAPPINESS: A FUNCTION OF DIFFERENT STROKES FOR DIFFERENT FOLKS

The term happiness is a universally accepted description for pleasure, but despite its universality we must recognize that the concept happiness means "different strokes for different folks". While we as homo *sapiens* are basically hard wired in the same way, there is enough evidence from genetic studies that certain ethnic groups have more or less polymorphisms (gene forms) which can effect protein expressions multiple ways. These gene expressions can be visible (color, skin texture hair etc) or non-visible affecting one's emotions, sensibility, intelligence and even proneness to getting "high". Besides differences because of cultural upbringing, our individuality may be tied to our genome. [50] In fact Barr and Kidd investigated the frequency of the DRD2 A1 allele in 381 unrelated people from 16 different populations. On a global scale the frequency of the A1 allele was found to be dramatically different among the populations studied, from as low as 0.09 to as high as 0.75.

No matter how perfectly organized a society might be, individual differences must still be accounted for in dealings with others. As Margaret Mead pointed out in the introduction

to her 1953 classic *Cultural Patterns and Technical Change* [51]

“ Cultural forms, as human beings have so far developed them, while inclusive enough so that most of the human beings who survive within them can live in terms of their institutions and values, are not sufficiently varied and flexible to protect and express all of the individual personalities- each organized whole- in the society. It is to bridge this gap, between culturally provided solutions for the problems of each individual life and the difficulties which many individuals find in using those solutions, that individual psychotherapy has been developed and is now a recognized part of modern culture.”

Thus, the word happiness takes on many forms, and can only be defined by each of us in our never ending quest to get it. Happiness is individualized. In very simplistic terms, if an infant could even conceptualize what happiness is, it might be its mother’s breast or a bottle of milk.

If you look at a growing child, happiness to this little child might be a toy or a little friend to play with. What is beautiful about children is that their script is not totally formulated, if you believe that premise as presented in *Games People Play* by Eric Berne and Claude Steiner [52]. Have you really taken notice of how kids play? It is beautiful. They shove a little bit, they might push a little bit, and smell a little bit, and they are definitely uninhibited. They’re right out there, right in front. Maybe we could learn something. Just maybe many of us need to lighten up, get out there, let loose, and let others live!

In order for our pursuit of happiness to be successful, we need certain provisions as a bare minimum. These provisions or basic needs are very simple. For example, we all need a little food in our stomachs, although it could be poison if we take too much of it. There is also a need to have a few clothes, especially when the cold wind blows, and an adequate shelter to keep us from freezing or getting wet. Then there is the most important basic need that goes by the name of love. Another hard to define word and is in the eyes of the beholder. It is an individual thing. It has many shapes and forms. It is the subject of everyday life –either having it or not having it or trying to get it. Always achieving or looking for a higher love, sometimes missing it when it is right in front of us. Sometimes all the trying is for naught. Is it destiny or is it just a consequence of our actions. Whatever it is, one thing is clear, for most, it absorbs our spirit, our mood, our well-being, except if we turn it off to protect ourselves. The real question worth pondering is not how to get it, but how to keep it.

And there’s the rub. Many people, including the affluent in material goods and personal relationships, are convinced that even with the apparent fulfillment of their basic needs, something essential is still missing. That essential ingredient is pleasure. And for millions all they really would like is to free their souls and get lost in Rock’ N’ Roll and drift away. In fact,

most of us always want just a little bit more and some are brave enough to get it. Even against all odds! Maybe happiness is in our genes caressed by our environment. [53].

[XIII] CHEMICAL ORIGINS OF PLEASURE: THE ULTIMATE STATE

There is a basic need in man to achieve pleasure states, and some think that drugs provide a means of getting there. For one person it might be a couple of martinis on the rocks, while another might chew coca leaves. We have not yet learned to curtail or control our abuse of various kinds of pleasure states – whether talking about drinking or smoking pot or gambling, watching T.V., having sex or whatever –sooner or later society is going to have to learn to deal with drugs and pleasure in ways other than by sheer emotional reaction. If we take a step backwards in time, Joel Fort in his 1969 book, *The Pleasure Seekers*, [54] carefully documented that people need pleasure and will actively seek it out. However, there are those who believe seeking pleasure is learned and not inborn. We prefer to think about it as the interaction of both our genes and the environment.

Nevertheless, just the idea of pleasure in its purist form excites neurons, dilates blood vessels, speeds the heart, increases blood flow, makes gastric acid flow, raises the pulse, opens up the pupils, increases saliva and all body juices, tingles the spine, depolarizes muscle, piloerects, and causes a bodily explosion resulting in total loss of control filled with euphoric glow or high.

We are all very familiar with the fact that the brain contains *Poppy –like* material, polypeptides known as endorphines which are opiate-like in biological action and may set off a series of reactions which could lead to a euphoric state not so different from that obtained from ingesting, snorting or main lining opium or heroine. Over the last 30 years of research since they were first discovered, endogenous opioids are key in terms of well-being and pain relief. They interact with opiate receptors in the brain and induce dopamine release by inhibiting the substance GABA [33].

The discovery, in the mid 70’s of the opiate-like peptides as well as the earlier findings of opiate receptors in the brain raised interesting questions about the addictive process and the natural innate mechanisms responsible for euphoria. For example what happens chemically when a person has a natural deficiency of these and other brain chemical messengers such as serotonin, and dopamine. Can this sort of deficiency drive some people into seeking another kind of euphorogenic-producing substance to make up for that deficiency? Are imbalances in either the production and/or receptor affinity responsible for certain “abnormal” behavior which we label manic-depressive illness, and/or schizophrenia and /or Reward Deficiency Syndrome? In essence we now believe that certain genes and

their polymorphisms (gene variants) may either under express or over express either enzymes involved in the synthesis and/or destruction of brain chemical messengers and/or their receptors which will influence one's proneness to addiction. These concepts should provide insights into the notion of "pleasure" as a natural entity as far as being possibly mediated via naturally occurring substances. Is this why we have a poppy field growing in our brain?

Andrew Weil and Winfield Rosen were right on when they wrote the book "*From Chocolates to Morphine*" [55]. Did you know that for example, when you drink alcohol, it is converted in the body to a morphine-like substance called TIQ, which was found in the brain and acts biologically via opiate receptors [56]. This substance has also been found in cocoa and chocolates [57]. So the concept of from "chocolates to morphine, is not merely cute but is scientifically correct, albeit the potency of morphine (in terms of getting you high) being much higher than any Godiva bar. It makes you wonder about how many pounds of chocolate are consumed in the United States alone. Over 3.1 billion pounds of **chocolate**, was consumed in 2001 worldwide. To be facetious, if chocolates and morphine have similar pharmacological properties, would society place a ban on the sale of chocolate because of its addictive qualities. Could you imagine an anti- chocolate campaign or a chocolate prohibition!

Moreover, as stated earlier, the brain chemical dopamine influences how people make decisions; both simple and complex decisions, from what to make for dinner to whether to have children. According to a recent publication when making real-life decisions, dopamine has a role in signaling expected pleasure from those possible future events [42] including the desire for chocolates.

All of this provides people with one of their most frustrating paradoxes. On one hand we all seek fulfillment and satisfaction through the attainment of pleasure states –naturally or synthetically induced. On the other hand, while we all have urges, needs, desires, wants and cravings, all of which could be natural, human beings can easily overload their pleasure circuits through abuse, misuse or simple miscalculation. The real question then is - *Where do we draw the line? When should society step in? What should be the punishment for overindulgence?*

With due respect, most of us travel through uncharted territories of pleasure and there are many pitfalls hidden along the way. In terms of our sexuality should society condone same sex marriages, clergy accepting sodomy, while (not condoning) making laws against consenting adult prostitution and pornography. Basically, society does not always condone pleasure if it is not a pleasure that is convenient to current social mores. The long arm of the law often interferes with the pursuit and enjoyment of pleasure, drawing pleasure itself from the process. Would it be better to say "*If it don't kill don't kill it!*" This is a true dilemma when we consider that over one million

people were admitted to a drug rehabilitation treatment facility in 2009 [58].

[XIV] CRIME AT THE GENE

Are genetic factors likely to influence a person to become violent? Many scientists have searched for an answer to this perplexing question. In fact the criminologists of our time have often suggested that murder maybe hard wired into the brain of the serial killer as a form of pleasure.

Advances in our knowledge of the neurobiology of aggression and violence have given rise to rational pharmacological treatments for these behaviors. The main biological systems which are known to be involved are those reward neurotransmitters and include serotonin (5HT), opioid peptides (END), gamma-aminobutyric acid (GABA), and the catecholamines (dopamine [DA], acetylcholine(Ach) and Norepinephrine [NE]).

14.1. Serotonin

A large body of data has emerged linking aggression in humans with low serotonergic function. Yaryura-Tobias et. al. [59] reported higher levels of aggression in adults with low blood levels of serotonin. Linnoila and colleagues [60] reported that impulsive aggression was associated with low levels of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid. Others reported on a Dutch family in which a gene mutation in the monoamine oxidase enzyme (MAOA), resulting in a defect in the breakdown of dopamine, serotonin and norepinephrine, was associated with markedly increased aggressive behaviors in teenagers. [61]. Moreover, Muenlenkamp et. al. [62] has reported that stimulation of the 5-HT_{1A}, 5-HT_{1B} and 5-HT₂ receptors reduces offensive aggression, while defensive aggression is reduced only by stimulation of the 5-HT₂ receptor. In muricidal (murdering) rats, 5-HT was higher in the hypothalamus compared to non-muricidal animals as well as higher levels of 5-HT in the amygdala. The serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) was also found to be higher in the hippocampus of the muricidal rats [63].

14.2. Catecholamines

In animal studies Haller et. al. [64] found that enhancing catecholamine function by treatment with alpha-2 adrenergic receptor antagonists increased aggressive responses to aggressive intruders. Further experiments [65] in rodents revealed that tricyclics and MAO inhibitors, which increased both DA and NE activity, also enhanced aggressive behavior in these animals. In humans, the NE metabolite 3-methoxy-4-hydroxyphenylglycol correlated with a positive history of aggressive behavior [66] and a positive correlation between aggression and blood levels of phenylethylamine was also found in humans [67]. Acute isolation –induced fighting in

mice produced a striking “dose –dependent” increase in K_M and V_{max} for dopamine uptake in mesocortical nerve endings (synaptosomes) but no significant changes for these uptake constraints in nigrostriatal terminals [68]. Moreover, the dopamine metabolite 3-4- dihydroxyphenylacetic acid (DOPAC) was significantly lower in muricidal rats compared to nonmuricidal animals. The hippocampus of muricidal rats showed significantly higher DA levels, as well as higher levels of the NE metabolite homovanillic acid (HVA) [63]. Breese and associates provide evidence to suggest that lack of brain dopamine during development increased the susceptibility for aggression and injurious behavior by influencing D1 dopamine receptor function [69]. Furthermore, work from Comings *et. al.* [70] shows a strong association between aberrant drug seeking behavior and polymorphisms of the D1-dopamine receptor gene.

14.3. Opioid peptides

The role of opioid peptides has also been studied with regard to aggressive behavior and fighting in animals. Beta-endorphin blocked the development of shock –induced fighting, while Naloxone facilitated it but only when shock induced fighting occurred at a low rate. The beta-endorphin induced reduction of fighting behavior was blocked by naloxone, suggesting opiate induced receptor mechanisms in aggressive behavior [71]. Moreover, Comings *et. al.* [72] also associated the enkephalinase gene with low amplitude P300 waves, which has been associated with violent offenders (see P300 wave map in a violent subject presented herein).

14.4. GABA

GABA is found ubiquitously in the central nervous system; its function is reducing neuronal activity. Eichleman [73] concluded that GABA stimulation centrally reduces aggression, but some studies showed a significant percent of patients treated with benzodiazepines becoming more aggressive.

14.5. MAOA: is it a crime gene?

Moreover, research on young people in New Zealand and Australia found a link between the MAOA gene, a person’s environment during childhood and the likelihood of subsequent violent behavior. The gene MAOA stands for monoamine oxidase, and it codes for an enzyme in the brain that is a sort of a clean-up enzyme, and the role of this enzyme is to clear away excess neurotransmitter (especially serotonin) after the brain has responded to a stress. The gene has two forms, a low activity MAOA form which is found in one-third of the human population, and about two-thirds of the human population has a high activity genotype. In the people with the high activity genotype, it’s simply that their neurotransmitter system is more efficient and more quickly returned to a healthy balance after coping with stress, whereas those with the low MAO genotype

might suffer more from stress and have difficulty recovering after a stressful event.

While the gene may not predict violence it does associate with boys that had been victims of maltreatment. In this regard, Terry Moffitt *et al.*, found that those boys who suffered maltreatment, had the low MAOA activity genotype, and were in fact, much more likely to become violent as adults. So 85% of them had a conviction record for a violent crime with New Zealand or Australian Police. In fact they were only 12% of the boys in their city, but they accounted for 44% of the crimes that were committed [74].

These and other genetic findings involving the dopaminergic system, support the concept of polygenic inheritance. It is the total number of polygenes (for example, dopamine D2 receptor gene and the dopamine transporter gene) in combination with one’s environment that will ultimately lead an individual down that violence pathway.

Serial killers as portrayed in the movie MONSTER are a very good example of how child abuse can impact future behavior [74]. More interestingly, as portrayed the monster had great outbursts of violence while under or even after a stressful event. If DNA tested, would she carry the MAOA low activity gene form and maybe other gene forms in a number of neurotransmitter pathways? Thus, albeit, providing an incomplete gene map of violent behavior, it would have been able to potentially predict her risk for such behaviors including murder. Our laboratory has already published on hypodopaminergic genes and pathological aggression. [75, 76].

14.6. Case studies of violent offenders

The above topographical brain map [Figure–1] of a violent substance abusing teenager, is similar for violent substance abuse offenders in treatment at the PATH Medical Clinic over a ten year period. A few such case studies follow:

Case-A

A 52 year –old man guilty of the violent crime of killing his father and mutilating his body was arrested. Following his arrest, The Sheriff’s department requested a BEAM map. This person was found to have the typical bi-temporal abnormalities consistently observed in many violent individuals.

Case-B

A 32 –year –old man who attended a prestigious Ivy League school who played football for the school’s varsity team. One night after graduating from college, shot his lover in a fit of jealous rage. The man was arrested and spent three years in jail for the shooting. Following his release a beam map showed the

typical bi-temporal abnormalities, including low voltage p300. Blood test revealed low tyrosine levels.

Case-C

A 28-year old woman with a history of opiate dependence with comorbid alcohol and cocaine use had violent outbursts and rage. As a child she was involved in a skiing accident and, also

during childhood, she experienced mood swings. Ongoing analysis of the electrical status of her brain via the beam technique revealed temporal lobe abnormalities.

We are providing BEAM representation of a normal vs abnormal brain depicted in **Figure-1**.

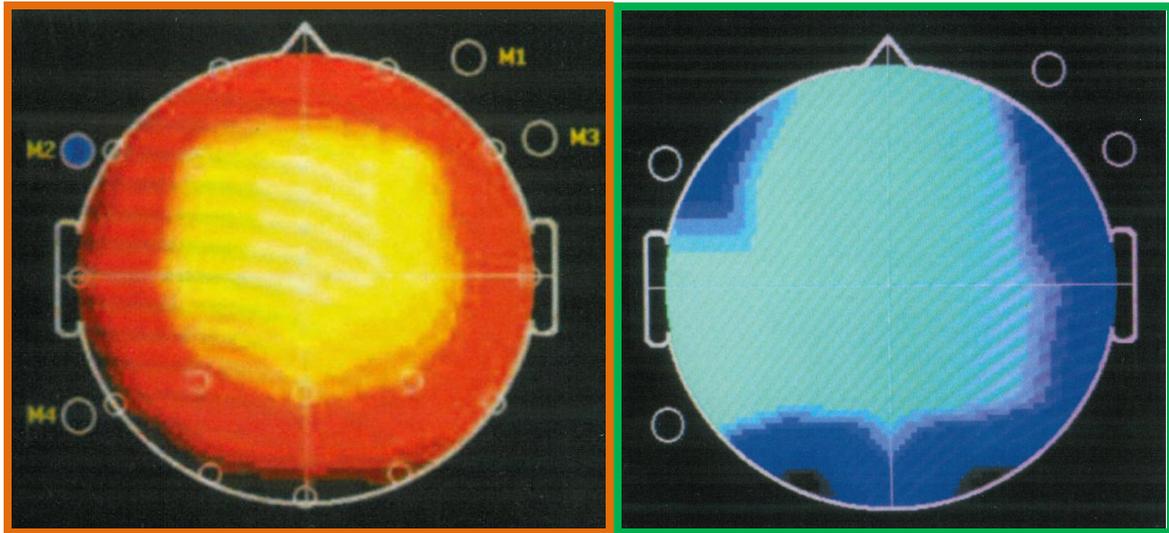


Fig: 1. BEAM image of a healthy brain (Left). The even and symmetrical dispersion of red and yellow indicate a balance in brain chemicals and behavior. **BEAM image of a violent subject's brain** (Right). The large intense area of light blue indicates a severe GABA deficiency, manifesting in the GABA deficient symptoms of rage and violent behavior (with permission from Eric R Braverman, MD –*The Edge Effect*).

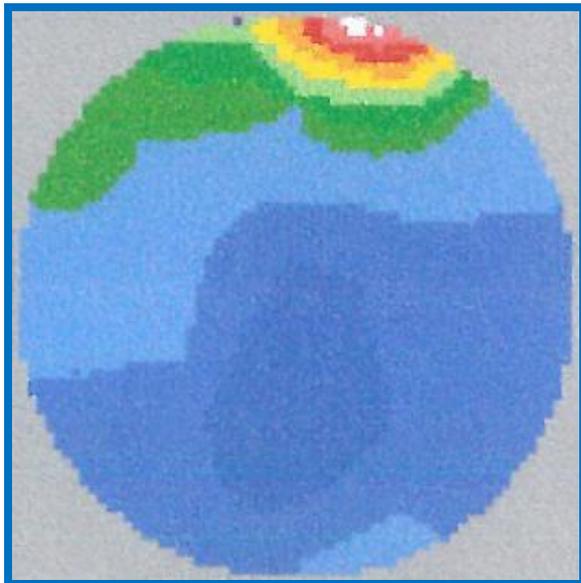


Fig: 2. This BEAM image shows a large amount of light blue, indicating a severe GABA deficiency, manifesting in a GABA deficient symptoms of rage and violent behavior

Figure-2 represents the BEAM of a violent person putatively showing abnormalities in the GABA system. This BEAM representing possible GABA deficiency may result in excessive DA release especially in the amygdale leading to rage and violence.

One major problem is to recognize that when we consider the pathological violence phenotype it may be represented by some combination of a number of behavioral tendencies. In this regard, when we consider reward dependence behaviors an emerging concept called “REWARD DEFICIENCY SYNDROME (RDS)” may help define this complex array of behaviors [36, 77, 78]. RDS broadly defines a common genetic tendency whereby the individual may be predisposed to a number of addictive, impulsive and compulsive behavioral tendencies. It appears that this phenotype is so heterogeneous that it may be not useful. However, the need for homogeneity in the affected phenotype is important not only for population-based association studies but also for linkage analysis. Thus we consider that under the RDS concept there is a remarkable list of behavioral tendencies including: dependence on alcohol, psychostimulants (cocaine), opiates, marijuana, nicotine (smoking), carbohydrates (sugar binging), pathological gambling, sex addiction and even Attention Deficit

Hyperactivity (ADHD), and aggression and violence, having the same genetic defects under one rubric [36].

While there are poly genes involved, there is close similarity in terms of all of these substances and behaviors induce pre-synaptic dopamine release at the NAc. The common genetic basis may yield more of chance of obtaining homogeneity than if the so called affected probands appeared to be so diverse in their behavioral tendencies (more heterogeneous). In our opinion it would be very difficult to separate alcohol from other drugs as well as other addictive, compulsive and impulsive tendencies such as pathological violence [79]. We as scientists are pressed to answer the very complicated question concerning whether or not genes can be blamed for violence amongst school age killers. “Are some kids simply born bad?” The short answer is yes, as we see from the data presented herein, genes play a role in aggressive and violent behavior. It is our opinion that criminals and or even terrorists may share common gene polymorphisms. Studies at the University Of Wisconsin and others using identical twins raised in different families, who had parallel lives, showed that about half of human behavior (including aggression, sexuality, mental function, eating disorder, alcoholism and drug abuse or generalized RDS) can be accounted for by DNA [80]. Genome –wide scans have shown significant heritability of many genes involved in addictive behaviors [81]. The driving nature in behavior is that very few elements of behavior depend upon a single gene: a complex of genes (polygenic), often across chromosomes, drives most of our heredity-based actions.

Certainly abnormal functioning of these brain systems can be due to specific genetic factors as well as abuse of various psychoactive substances, particularly alcohol and stimulants. In this regard, it has been shown that these individuals may have a reduced number of dopamine D2 receptors [82, 83] associated with the dopamine D2 receptor gene polymorphisms [84, 85] and a high number of dopamine transporter sites [86].

Understanding the interaction of these components and the current literature, has led to some degree of success in the management of aggressive and violent behaviors (the limbic psychotic trigger reaction.), using selective serotonin re-uptake inhibitors (SSRIs), lithium carbonate, beta-adrenergic blockers, anticonvulsants, anxiolytics, typical and atypical neuroleptics, and novel agents such as anti-androgens and serenics (agonists which act on 5-HT1A and 5-HT1B receptors) [87]. The most parsimonious approach may be the utilization of serotonergic and dopaminergic agonist therapy [88, 89]. However, information derived from DNA studies will provide better targeting.

[XV] ARE WE MAKING LAWS AGAINST NATURE?

If indeed we are pleasure –seekers and our brain producers naturally occurring substances with potential euphorogenic

properties, then it should follow that people will seek out natural ways to “turn on”. Many of us are acquainted with others who seem always bored, or unhappy or sad and nothing seems to turn them on except when they turn to psychoactive chemicals for brief glimpses of paradise. These people turn on to the same phenomenon as the diver who dives 100 feet into the depths of the sea, the skydiver speeding toward the ground, or the daredevil jumping his motorcycle over a river. In every case the resultant effect is one characterized as being pleasurable, filled with gratification of the senses or mind.

While we are cognizant of the need to safe guard our citizens against real harm can we be so bold as to make laws against nature. Are there laws against the sea diver, skydiver, daredevil, soccer player, boxer, teenagers and lovers seeking out love? If not, then why are there laws against the user of psychoactive chemicals? Certainly, there must be laws to protect society, but how to explain other laws which “protect” against not only consenting individuals but victimless crimes?

People will incur costs to punish defectors [90]; punishment, even at personal cost, activates neural reward systems [91]. Instead of activating medial prefrontal cortex, which is engaged in judgments of self in relation to others, Princeton undergraduate students viewing pictures of homeless people and drug addicts preferentially activated insula and amygdala, limbic regions involved in the emotions of disgust [92] and fear [93], respectively. In these extreme forms of prejudice the neural signature implies that the objects of social rejection were perceived as less than fully human [94].

For years we have heard from eastern philosophers concerning the search for natural highs as a way of life instead of seeking unnatural highs through psychoactive chemicals. Research on the subject might reveal one day in the future that when we “meditate” we do indeed ‘medicate’, a statement predicated on the potential of endorphin-dopamine interactions. In other words; is the Nirvana of life endorphin induced inhibition of GABA brain activity and thus an extraordinary release of neuronal dopamine at the reward site and its subsequent interaction with D2 receptors leading to an orgasmic high? Thus, if this is what is happening under states of meditation, then mediators are getting high, like those in the drug culture, but using “natural” means and methods.

Most recently Jung et al [95] found that meditation as mind-body training is associated with lower stress, higher positive affect and higher plasma DA levels when comparing the meditation group with the control group. Thus, mind-body training may influence stress, positive affect and the sympathetic nervous system including DA activity. These findings should be confirmed by analyzing cerebral spinal fluid to prevent brain and peripheral admixture. This finding takes on even greater importance when coupled with our recent findings of KB220Z induction of an increased alpha increased low beta bands as observed in protracted abstinent psychostimulant abusers using qEEG analysis [96].

In a related issue, the drug war to some has been considered harmful. In the US, in the past marijuana laws have contributed to a huge increase in the prison population, with vast racial disparities. Recently, the U.S. attorney general has signaled out legitimate medical use of marijuana for special-law enforcement attention and abuse. Our president Obama has suggested non-prosecution of marijuana users. A Time Magazine cover story (November 4, 2002) reported that most Americans do not want marijuana legalized, but do not want users to go to jail either. Public fear of legalization is understandable; it could bring high –powered corporate promotions, as with tobacco-including campaigns to target young people.

Many believe that U.S. society needs but does not have a middle –ground for activities that individual adults can do personally without breaking the law, yet which are officially discouraged and cannot be commercially promoted. Such a middle ground will become increasingly necessary as technology progresses. The potential FDA approval of a Cannabis Tincture, atomizer, is one such example. So we should be thinking about it now!

On the other hand there appears to be a compelling interest on the part of the legal authorities in opiate use or misuse as a means to achieve pleasure states. Evidently, the law focuses on opiates because people utilizing these substances are compelled to lie, cheat, steal and commit other crimes to obtain adequate supplies and in doing so hurt other members of society. When other members of society are effected, the state should make laws against this potential hazard. However, if heroin or other psychoactive agents (or drugs that mimic heroin's effect are easily available at little or no cost to the seeker, the actual damage against other members of society would become very minimal (there would be no money in it) thus there would be no compelling interest for the state and no laws would be necessary. This may be true if we lived in a vacuum and people were interested in loving and caring for people rather than money. That is why any legalization must be carefully considered on a global basis. This is clouded by the hundreds of millions being genetically predisposed to drug seeking behavior [97].

In the words of Harris and Fiske:

“...Even reactions as immediate as disgust to a dirty, unkempt homeless person or an IV-drug-injector can be altered if one plays the role of a soup-kitchen volunteer attempting to feed the hungry, or a social worker leading someone on the path away from drug-addiction” [98].

Ponder this, if drugs induce pleasure states, and if pleasure states are natural, then how responsible or guilty are those people when they turn to artificial forms of euphoria producing substances? In the same way how guilty are we for our sexual deviance if it does not involve hurting others? Are our laws

really adequate for dealing with this human reality? Are we making laws against drugs or against Nature (pleasure)? These are the kinds of questions that need to be explored seriously by the physician, by the research scientist by the legal profession, by the courts and by the social biologist.

[XVI] EPIGENETICS A NEW TARGET FOR THERAPEUTICS

Epigenetics encompasses those heritable changes in genome function, occurring without DNA sequence alteration, that involve (a) transference of gene expression patterns over cell generations, (b) alteration of gene expression during cell differentiation, and (c) environment-induced alterations of gene expression. Despite the maintenance of these changes over the cells' lives and even over multiple generations, there are no alterations to the underlying DNA sequence, instead non-genetic factors induce the genes to “express themselves” differently” (up-regulated/down regulated /no change) [99]. As the putative interface in gene-environment interactions, transgenerational epigenetic inheritance is present in widely differing species. [100,102, 93]. Adverse foetal and early life conditions that disturb normal brain development are associated with neuropsychiatric disorders and epigenetic consequences emerging to early expression [103,104]. This early life adversity effecting adolescent and adult behaviour reflects the putative epigenetic mechanisms through which early life environmental influences determine life-long susceptibility to chronic disease states [105, 107]. Specific expression of a disorder (e.g. psychosis) integrates the relationship between adverse events during childhood and the disease state with epigenetic processes. These processes involve the stress regulating functions of the hypothalamic-pituitary-adrenal axis and the neurobehavioral mechanisms through which specific types of childhood trauma may lead to specific types of (e.g. psychotic) experiences [108]. Despite its complexity, the application of treatment drugs that modify the genome, emphasise the necessity for epigenome targeting. Examples are DNA methyl transferase inhibitors and histone deacetylase inhibitors for disorder-related deficits [101,109].

When the action of one gene is modified by the actions of one or several other, “modifier”, genes, epistasis occurs. These modifier genes have their phenotype expressed while hypostatic genes have altered/suppressed phenotypes. This difference is an important determinant of disorder propensity. [110] Genetic epistasis offers plausible mechanisms for the etiopathogenesis of neurobehavioral attributes, such as neuropathological impulsiveness, that contribute to neuropsychiatric disorders [110]. Measurable endophenotypes, both as neuropsychiatric concepts and biomarkers, indicate a point on the pathway from gene to disorder. When linked to an expressed abnormality, it is reflected in clinically unaffected relatives, vulnerability polymorphisms, and the cognitive-emotional domains [111]. Taken together, the relative contributions of endophenotypes

and epistasis in the mediation of epigenetic phenomena may prove essential to diagnosis, intervention and prognosis [112].

[XVII] THE IMPACT OF EPIGENETIC BIONANOTECHNOLOGY ON DELIVERY OF ACTIVE MOLECULES

Bionanotechnology is the key functional technology of the 21st century. The possibility to exploit the structures and processes of biomolecules for novel applications in materials, biosensors, bioelectronics and medical applications has created the rapidly growing field of nanobiotechnology. At the nano level, atoms demonstrate extreme diversity and uniqueness. The term “Bionanotechnology” is a fusion of biology and nanotechnology based on the principles and chemical pathways of living organisms, and refers to the functional applications of biomolecules in nanotechnology. Guided by studying the structure and function of the natural nano-molecules found in living cells bionanotechnology encompasses the study, creation, and illumination of the connections between structural molecular biology, genetics, nutrition.

Bionanotechnology of “biomimetic membranes” describes the current state of research and development in biomimetic membranes for bionanotechnology applications. The application areas in bionanotechnology range from novel nanosensors, to novel methods for sorting and delivering bio-active molecules, to novel drug delivery systems. The success of these applications relies on a good understanding of the interaction and incorporation of macromolecules in membranes and the fundamental properties of the membrane itself.

The biological and physical sciences share a common interest in small structures (ranging from 1 nm to 1 mm). Development of nano-science around new materials and tools (largely from the physical sciences) and new phenomena (largely from the biological sciences) are happening. The physical sciences offer tools for synthesis and fabrication of devices for measuring the characteristics of cells and sub-cellular components, and of materials useful in cell and molecular biology; biology offers a window into the most sophisticated collection of functional nanostructures that exists.

The present situation of biomaterials which are currently in use are vastly different from those of a decade ago. Although implantable medical devices are still immensely important, medical technologies now encompass a range of drug and nano delivery systems, tissue engineering, cell therapies, organ printing and cell patterning, nanotechnology based imaging and diagnostic systems and microelectronic devices. These technologies still encompass metals, ceramics and synthetic polymers, but also biopolymers; self assembled systems, nanoparticles, carbon nanotubes and quantum dots. These changes imply that our original concepts of biomaterials and our expectations of their performance may have to change. It may be concluded that many substances which were not

regarded as biomaterials and may now be considered as traditional structural biomaterials. Hence, substances have been engineered and developed to perform functions within health care where it is directly controlled by interactions with cells and tissue components. These include engineered tissues, cells, organs and even viruses.

Conventional imaging paradigms rely on the detection of anatomical changes in disease that are preceded by molecular genetic changes that go otherwise undetected. With the advent of molecular imaging (such as qEEG, fMRI and PET) it will be possible to detect these changes prior to the manifestation of disease. Molecular imaging is the amalgamation of molecular biology and imaging technology that was spawned by parallel advances in the two fields. Fundamental to this technique is the ability to directly image biological processes that precede the anatomical changes detected by conventional imaging techniques. The two main strategies for imaging of biologic processes are direct and indirect imaging techniques. Direct techniques use molecules that have specific affinities for targets of interest that can be radiolabeled or otherwise detected on imaging. Indirect imaging uses reporter genes that are coexpressed with therapeutic proteins or other proteins of interest to image vector-transfected cells. This is important in gene therapy already accomplished with cDNA directed D2 receptors in alcohol –preferring and cocaine self administration [37, 38]. Optical imaging and nanotechnology paradigms will also prove to be important additions to the imaging arsenal. These principles take on even more importance when one considers the need to provide the human organism with safe compounds at significantly lower dosage to reduce adverse effects and cost [113-116].

[XVIII] CONCLUSION

While it is true that Homo sapiens in evolutionary terms are changing very slowly it is also true that certain genetic traits such as genes that regulate pleasure seeking may be the exception. At this juncture we do not know whether the DRD2 A1 allele is an older gene allele or is it newer than the DRD2 A2 allele. Understanding this will help explain the nature of humans relationship with pleasure seeking and even possible its benefit to survival. Certainly carriers of the DRD2 A1 allele are more aggressive than carriers of the DRD2 A2 allele [79].

In conclusion, we must ask; Who are the people that could just say NO? In this regard it is noteworthy that almost half of the US population has indulged in illegal drug practices. Why do millions have this innate drive in face of the danger of putting themselves in harms-way? Why are millions paying the price of their indiscretions in our jails, in hospitals, in wheel chairs or lying dead in our cemeteries. What price must we pay for pleasure seeking or just plain getting “HIGH”?

While it is true that imaging studies of the brains of people addicted to drugs have helped to clarify the mechanisms of drug addiction we must reflect on the question of how we address

legally the natural pursuit of pleasure seeking. Moreover these studies and the initial work of Blum and Noble [13] and others have also helped to change the public's view of drug addiction, from that of a moral violation or character flaw to an understanding that pathological changes to brain structure make it very difficult for addicts to give up their addictions.

The frontal orbital cortex abnormalities of addicts create a feeling of need or craving that addicts know is irrational but cannot prevent. Prefrontal abnormalities also make it difficult to override compulsions to take drugs by exercising cognitive control. The main areas affected are the orbitofrontal cortex, which maintains attention to goals, and the anterior cingulate cortex, that mediates the capacity to monitor and select action plans. Both areas receive stimulation from dopamine centers lower in the brain.

A steady influx of dopamine makes it difficult for addicts to shift their attention away from the goal of attaining drugs. It also fastens their attention to the motivational value of drugs, even though these drugs have long stopped providing pleasure. While the release of dopamine may result in ultimate pleasure states its real importance or relevance is that of sought-after goals. Addicts have a hard time turning their attention -- and their actions -- away from the goal of acquiring and consuming drugs. They are caught in a spiral of physical brain changes and the psychological consequences of those changes, leading to further changes.

What is needed is a little understanding from those in power. Should we need to lighten up, look the other way as long as no one gets hurt? Easily said but not easily done. We need a holistic approach to the process of life that mirrors the intuitive forces unleashed in more primitive societies, before civilization took upon itself the role of arbitrator and rule-maker over the seeking of pleasure states.

In his book "The Origin of Consciousness in the Breakdown of the Bicameral Mind", Julian Jaynes inferred that the sense of self-awareness emerged about four millennia ago when the experiences from the right hemisphere blended with linguistic and other related properties of the left hemisphere. The consequences of these insights are consonant with the authors' observations and portend remarkable possibilities. Perhaps the most compelling congruence with Jaynes's insights is in the field of genetics. It has been shown that single point mutations on genes can produce permanent changes in speech production. There is now evidence that point mutations can diffuse within decades throughout entire populations [117]. As Marcel Kuijsten writes in his recent re-examination of Jaynes' work:

"...reflexive rejection of novel concepts is the antithesis of discovery. Science is the pursuit of the unknowns and open-mindedness to contentious concepts...is the optimal environment for discovery" [117]

The complexity of modern society brings down technological barriers between our inner strivings and those elusive pleasure states which seem always to dance just beyond our reach. We

need to get in touch with our own identities, grasp the meanings of symbols which lie beyond our current language and mathematics, and once again confront ourselves in the unconscious and nearly forgotten well-springs of our origin. Rather than allow ourselves to become castaways of a genetic legacy which passes us by on the way to some ultimate and unknown fulfillment, it is time for us to pause, to listen to the voices of our primitive past while going beyond to the pleasure states which comprise our ultimate destiny whether god induced or just nature's way [118].

We all have the right to life. However, does that give us the right to take away the life of others, especially, if we only have 120 years to live? Does that give us the right to take away our choices in life? Does that right include getting high, smoking, having sex or just having fun? It does not include bombing the world trade center, or the holocaust or any other human induced tragedy including the killing of new borne girls or clitoral castration.

As to the questions posed herein related to evolutionary genetics and more importantly gene selection we refer to the work of David Comings emeritus Chairman of the department of Medical Genetics, City of Hope National Medical Center, Duarte, California writing in his popular book: "The Gene Bomb" [119]. In one important scenario Comings suggests that while it may be true that genetic adaptations are very slow there may be some exceptions like the Tibetan altitude gene [4].

Let us assume that the a mutant gene called X causes addiction, and that individuals with this X gene drop out of school earlier and start having children earlier than individuals who do not carry the mutant gene. Let us also assume that the average age at birth of the first child of mutant carriers is 20 years, while for those not carrying the mutation it is 25 years. As a result, the mutant form of the gene will reproduce faster, namely every 20 years, while the normal form of the gene will reproduce every 25 years. The ratio of 25/20 is 1.25. Figure-3 illustrates the results of using one of the equations [119] that calculates the rate at which the frequency of a gene with such a selective advantage will increase over succeeding generations.

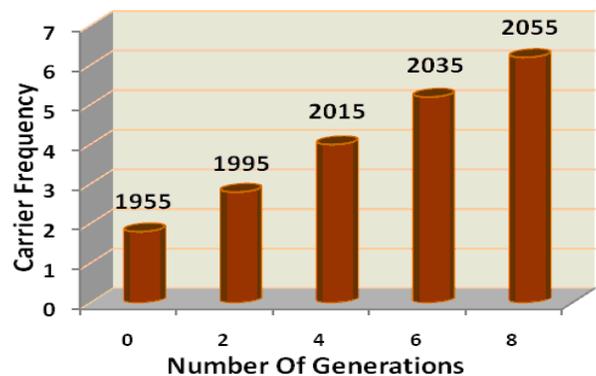


Fig: 3. The rate at which a RD gene that has a 1:25 -fold selective advantage will increase in frequency from generation to generation

While we must caution against our hypothesis due to many caveats such the complexity of polygenic inheritance rather than one gene –one phenotype including the number of children, number of siblings, number of genes involved, different selective pressures and mathematical considerations, we propose that the carrier frequency of such a gene could double from, for example, from 1995 to 2015 and could have increased 150% from 1955 to 1995. While this gene X may seem to not have any selective benefit one must consider the fact that having low D2 receptors in our current society may confer certain competitive advantages leading (e.g. enhanced aggression, novelty seeking, risk taking) to greater survival.

If this is so then it not unlikely that carrying for example, the DRDD2 A1 allele enhanced prevalence could be responsible in part for the remarkable increase in RDS globally. In fact it has been shown that the onset of sexual intercourse significantly increases in A1 carriers of the DRD2 gene [120].

Attempts to understand the “High Mind” have eluded the best neuroscientists in the world. In approximately one-third of America, Dopamine is a key genetically induced deficient neurotransmitter resulting in aberrant craving behavior and excessive pleasure seeking. Is it parsimonious that finding ways to enhance dopamine D2 density instead of blocking dopaminergic function may be the best strategy to unlock the elusive addiction riddle and attenuate abuse?

Perhaps for some the answer lies in a leaf, alkaloids found in herbs and plants. PERHAPS THE ANSWER HAS BEEN THER ALL ALONG! We ask are we dealing ourselves enough “Dopamine for Dinner” [121].

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The following people claim a potential conflict of financial interest based on ownership and relationship to LifeGen, Inc patented products: Kenneth Blum, B.W .Downs, Margaret Madigan, Roger Waite, Eric Braverman, John Giordano, and Gwen Bauer, No other author claims any financial conflict of interest.

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