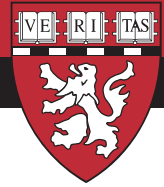


ON THE BRAIN

THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER



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High Society: How Substance Abuse Ravages America and What to Do About It

By Joseph A. Califano, Jr

THERE WAS A TIME IN OUR history—not so long ago—when smoking was cool, when seat belts were for sissies, and when AIDS was seen as a death sentence for gay sex. Today our attitudes are profoundly different—with powerful and beneficial consequences. Smoking has been cut sharply, and so have the related deaths from lung cancer and heart disease. Auto safety measures have curbed the highway death and injury rate. AIDS is recognized as a serious illness rather than a social curse.

In all three cases, we fundamentally changed our attitudes and, as a result, took actions that greatly improved the quality of life for millions of people.

The time has come for a fundamental change in our attitude about the pervasive and pernicious role drug and alcohol abuse play in our society and a revolution in the way we deal with it.

Americans, comprising only four percent of the world's population, consume two-thirds of the world's illegal drugs. The number of illegal drug users, which had dropped from a high of 25.4 million in 1979 to a quarter century low of 12 million in 1992, rose to 20.4 million in 2006. The number of teen illegal drug users, which had dropped from its 1979 high of 3.3 million to a low of 1.1 million in 1992, more than doubled to 2.5 million in 2006.

All the huffing and puffing in the current war on drugs has not been able to blow down the nation's house of substance abuse and addiction:

- 61 million Americans are hooked on cigarettes.
- 16 to 20 million are addicted to alcohol or abuse it regularly.
- More than 15 million abuse prescription drugs.
- 15 million smoke marijuana.

- 2.4 million use cocaine; 600,000 use crack.
- Hundreds of thousands are hooked on heroin.
- More than 750,000 are methamphetamine users.
- 1 million use ecstasy and hallucinogens.
- Almost 2 million of our children have used steroids.
- 4.5 million teens abuse controlled prescription drugs like OxyContin, Ritalin, and Adderall to get high.

The human misery that addiction and abuse cause can't be calculated. The consequences of this epidemic are severe.

Almost a quarter of a trillion dollars of the nation's yearly health-care bill is attributable to substance abuse and addiction.

Alcohol and other drug abuse is involved in most violent and property crimes, with 80 percent of the nation's adult inmates and juvenile arrestees either committing their offenses while high, stealing to buy drugs, violating alcohol or drug laws, having a history of substance abuse/addiction, or sharing some mix of these characteristics.

Seventy percent of abused and neglected children have alcohol or drug abusing parents.

Ninety percent of homeless are alcoholics or alcohol abusers; 60 percent abuse other drugs.

Half of the nation's college students binge drink and/or abuse illegal and prescription drugs. Nearly a quarter of them meet the medical criteria for alcohol and drug abuse and addiction. Cruel courtesy of excessive drinking, each year—700,000 students are injured, 100,000 are raped or sexually assaulted, and 1,700 are killed by alcohol poisoning or alcohol related injuries.

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Joseph A. Califano, Jr., is Chairman and President of The National Center on Addiction and Substance Abuse at Columbia University and a former U.S. Secretary of Health, Education, and Welfare. His book, *High Society: How Substance Abuse Ravages America and What to Do About It*, was published in May of 2007 by Public Affairs/Perseus Books. All proceeds from the sale of this book are being donated to CASA.

Addiction and the Brain

Statistically we have known for some time that teens who abuse alcohol and smoke marijuana are likelier to use drugs like cocaine and heroin. Now biomedical research and the brain imaging work of Dr. Nora Volkow, director of the National Institute on Drug Abuse (NIDA), help explain why teens who play with the fire of cigarettes, alcohol, and marijuana increase the chance they will get burned by the flames of heroin, cocaine, and hallucinogens. All of these substances cause an increase in dopamine levels in the brain. As dopamine levels increase, an individual's feeling of pleasure increases. A growing body of science is finding that all these substances affect dopamine levels in the brain through similar pathways, and dopamine becomes less active in the brains of addicts who use drugs to trigger its release, a condition which in turn reinforces the need for the drug.¹

Studies by scientists in Italy reveal that marijuana affects levels of dopamine in the brain in a manner akin to heroin. Studies in the United States have found that nicotine and alcohol (as well as cocaine) have a similar effect on dopamine

levels through common pathways to the brain.² This may explain why some scientists believe that nicotine makes the brain more accommodating to other drugs.

In essence, whatever the substance, the brains of addicts are "rewired," becoming predisposed to cravings.³ Dr. Joseph Frascella of NIDA points out that "in excessive behaviors such as compulsive drug abuse...the brain is changed, reward circuits are disrupted, and the behavior eventually becomes involuntary..."⁴

These statistical and biological findings are underscored by the fact that most addicts are poly-drug abusers. Alcoholics are likely to abuse tranquilizers, sleeping pills, or other psychotropic drugs. Older teens who abuse prescription drugs are often found to be abusing other drugs as well. There are also social elements to the relationship among smoking, drinking, and using illegal and prescription drugs, as well as to poly-drug use, particularly among children and teens. Kids who seek the high from marijuana may also want to look for "better" highs from other drugs. As kids start using drugs, they may tend to hang out and share experiences with others who use different drugs. In a sense, these teens end up encouraging each other to use various drugs.

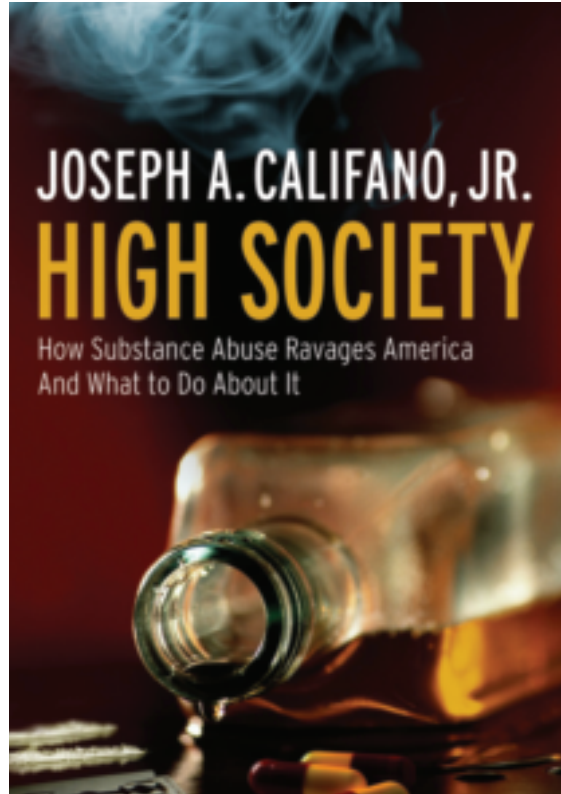
Of special importance is the need to recognize that for many teens, smoking, drinking, or drug use is often a symptom of incipient depression, anxiety or some other (usually undiagnosed) mental illness that hikes the youngster's risk of drug abuse.⁵

Mental health problems go hand in hand with smoking, drinking, and drug use for children and adults, and these problems can lead individuals to self-medicate with a variety of substances. Our current approach to substance abuse does not adequately recognize this.

Mounting a Revolution

We must recognize that substance abuse and addiction is a disease, not a moral failing or easily abandoned self-indulgence. We must recognize that it is a complex disease with neurological, physical, emotional, and spiritual components. We must recognize its impact on the most intractable domestic problems we confront. With such acceptance and recognition, we will appreciate the benefits of a revolution.

In the Health-care System—The National Institutes of Health spend \$13 billion a year on research for cancer, strokes, cardiovascular, and respiratory



diseases, and AIDS, but only one tenth of that amount to study substance abuse and addiction—the largest single cause and exacerbator of this quintet of killers and cripples. It is time for a revolution in health-care: the creation of the National Institute on Addiction, with a budget of at least \$5 billion a year to conduct a “Manhattan Project”-style research initiative identifying the causes and cures of substance abuse and addiction.

Courses in substance abuse and addiction should be a compulsory part of medical school curriculums. Physicians should be trained to diagnose the disease and refer patients for treatment. States and medical societies should establish professional standards for treatment counselors and accreditation systems to certify treatment facilities. Public and private health plans should cover substance abuse treatment and pay doctors to talk to patients.

Only through professionalizing the treatment system will we be able to bring it fully into the medical care system, which, in turn, is key to obtaining parity of coverage.

In the Justice System—Our nation’s prison system is as anachronistic as the debtor prisons in Charles Dickens’ day. Prosecutors, courts, and prisons must seize the opportunity to reclaim hundreds of thousands of addicts by using the criminal justice system to offer effective treatment for all who need it and incentives for them to achieve and maintain sobriety. Successfully treating and training inmates could deliver the greatest reduction in criminal activity in the nation’s history. Experts estimate that the number of crimes committed by a drug addict range from 89 to 191 annually.

In the Social Service System—Parental substance abuse accounts for \$23 billion in the nation’s child welfare spending, and most domestic violence involves alcohol or other drugs. The time has come for a complete overhaul of family court, adoption, and foster care systems in order to better deal with alcohol and drug abusing parents and partners.

The only way we will rehabilitate our nation’s homeless population is by investing in substance abuse and mental health treatment.

In the Education System—Schools, from elementary through college, should include age appropriate education about all substance abuse involving tobacco, alcohol, prescription, and illegal drugs as they do about other health matters from hygiene to STDs.

Prevention should be “laser beamed” on children. Sixteen years of research at The National Center on Addiction and Substance Abuse finds that a child who gets through age 21 without smoking, using illegal drugs, or abusing alcohol is virtually certain never to do so.

It is time to end the denial and stamp out the stigma associated with substance abuse and addiction, and to finally commit the energy and resources to confront a plague that has maimed and killed more Americans than all our wars, natural catastrophes, and traffic accidents combined.

In his monumental study of history, the brilliant British historian Arnold Toynbee found that the great civilizations were destroyed not by an external enemy, but from within. “Civilizations,” he said, “die from suicide, not by murder.” Of all the internal dangers our nation faces, none possess a greater threat to our children and families and none is complicit in more domestic ills than substance abuse and addiction.

This is our enemy within.

The judgment of history will be harsh if we fail to defeat that enemy—and deservedly so, when the stakes are our children and there is so much we can do to help them. ♥

Endnotes

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Another Drug in the Toolbox to Treat Alcohol Addiction

IT'S A WELL-KNOWN FACT: drinkers smoke and smokers drink. In fact, the National Institute on Alcohol Abuse and Alcoholism says that more than 80 percent of alcoholics are also smokers.

While the exact reason for this relationship remains unknown, there are certain biological, chemical, and social linkages. Alcohol and nicotine both stimulate the release of the neurotransmitter dopamine in the brain's mesolimbic pathway (one of the four major dopamine pathways that is involved in producing pleasurable feelings and is associated with reward and desire). The release of this neurotransmitter increases the pleasurable effects of both. Therefore, nicotine increases the urge to drink, and vice versa. A 2004 Duke University Medical Center study found that even small



amounts of alcohol can boost the pleasurable effects of nicotine, inducing people to smoke more when drinking alcoholic beverages. The Duke researchers say their findings provide a physiological explanation for the common observation that people smoke more in bars.

Scientists recently found another link between nicotine and alcohol. Researchers at the University of California, San Francisco found that varenicline, a drug that is used for smoking cessation, can also help curb heavy drinking. Psychiatrist Kevin P. Hill,

MD, MHS, of McLean Hospital and Harvard Medical School, calls the findings, reported in the Proceedings of the National Academy of Sciences last year, "exciting because they support the notion of a common pathway for addiction."

A little 'bang' of dopamine

Sold under the brand name Chantix, varenicline is a partial nicotine receptor agonist. The drug binds to and activates nicotine receptors in the brain, but it only has a partial effect on the receptors. Clinically, the drug activates nicotine receptors to give a desired response and reduce overstimulation of the receptors.

"The partial agonist effect is important," says Hill, a clinical fellow in psychiatry at HMS. "Effective medications for addiction need to provide a little 'bang' and this provides just enough dopamine to do that, but it also reduces the reinforcing effects of smoking."

Varenicline acts on nicotine receptors in the ventral tegmental area, or VTA, a cluster of neurons in the center of the brain that play an important role in the brain's reward circuit. For 25 years, scientists have known that alcohol and nicotine activate receptors on neurons in the VTA, which causes the release of dopamine and creates the "feel good" sensation smokers and drinkers get from these substances. In addition to nicotine and alcohol, dopamine release occurs with the use of most addictive drugs, including cocaine and morphine.

In the UCSF study, laboratory rats had access to alcohol every other day for a period ranging from two to four months. The rats steadily increased their alcohol intake each day it was available, an indication of alcohol dependence. Intermittent access to alcohol is thought to produce stress as a result of the days when alcohol was not present and the animals were in withdrawal. This models the early stages of alcohol dependence in people during which abstaining for a day or more induces the sensation of withdrawal, which then leads drinkers to consume more and eventually leading some to addiction.

The researchers found that varenicline curbed the animals' drinking and, even when the drug was stopped, the animals returned to their previous level of drinking, but no higher.

Early reports suggested that varenicline might be more effective in heavy drinkers. Hill, however, says it is dangerous to extrapolate animal findings to humans. "This study supports testing varenicline in patients who drink," he adds, "but it's hard to make a leap to what subtype of drinkers it might benefit."

Hill, who has used varenicline clinically to treat smokers, says the drug can cause a "fair amount" of nausea in anywhere from 30 percent to 40 percent of patients. In addition, the FDA, in February, issued an advisory saying that varenicline can also increase neuropsychiatric symptoms such as depression. Physicians and patients, therefore, must weigh risks versus benefits when contemplating the use of varenicline. He adds, however, that many smokers do well once they get past the tolerability issues.

A common addiction pathway

Perhaps the most promising aspect of the varenicline research is that it reinforces the notion of a common pathway in addiction. In general, Hill says, drugs that help curb one form of addiction may be promising for others. For example, varenicline has been proven successful in smoking cessation programs, but it is also being used in cocaine dependence trials.

"This research," he says, "supports the idea that there is a common pathway for dopamine and suggests that if varenicline works well for one addiction, it may work well for another addiction."

That is good news for researchers who study addiction and doctors who treat problem drinkers. Currently, there are only three drugs FDA-approved for the treatment of alcohol dependence. Disulfiram, or antabuse, was the first medication approved for the treatment of alcohol abuse. It works by causing a severe adverse reaction when someone taking the drug drinks alcohol. Naltrexone (brand names Revia and Depade) work by blocking in the brain the "high" that people experience when they drink or take drugs like heroin or cocaine. Acomprosat (Campral) is the most recently approved drug treatment for alcohol dependence. This drug reduces the physical distress and emotional discomfort people usually experience when they quit drinking.

"The pharmaceutical industry and academia are working feverishly on medications to treat addiction," says Hill. "Varenicline is promising as a treatment for smoking cessation, so the idea that it could potentially help with drinking is significant. There are limited tools available to treat addiction,

so any study that suggests another drug for the toolbox [to treat addiction] provides hope for patients and clinicians."

Hill says there are at least 50 trials ongoing with varenicline, according to the Web site www.clinicaltrials.org, including studies examining its effectiveness in treating alcohol dependence, cocaine addiction, and smoking. ♥



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Mutations Determine Role of Brain Tumor Gene

SHOCK WAVES REVERBERATED throughout the political—and non-political—world when news broke that Sen. Edward M. Kennedy, the long-standing senator from Massachusetts, had brain cancer.

Kennedy was diagnosed with malignant glioma, cancer of the structural cells that surround and support the neurons that conduct much of the brain's actual work. While doctors have not specified which type of glioma Kennedy has, the most aggressive form of the disease, called glioblastoma, is almost always fatal, with limited treatment options.

"Brain tumor pathogenesis is still very poorly understood and we are far from able to treat them effectively," says Azad Bonni, MD, PhD, an associate professor of pathology at Harvard Medical School who studies brain tumors. "It's a quite devastating disease."

Jekyll and Hyde

Bonni led a research team that recently discovered that a key gene involved in glioblastoma, one believed for years to be a villain in cancer, might actually play a Jekyll-and-Hyde role. In a study published in *Genes and Development*, the researchers found that STAT3 is an oncogene (a gene that promotes tumor growth) in some tumors, while, surprisingly, in others it acts as a tumor suppressor. The findings, says Bonni, lay the foundation for more personalized approaches to treatment based on a tumor's genetic makeup.

Almost all brain tumors originate in astrocytes, star-shaped glial cells that, among other functions, play a role in the repair and scarring process in the brain, or the neural stem cells that generate astrocytes. Bonni, a neuroscientist and neurologist, became interested in investigating the genetic makeup of glioblastomas by examining whether STAT3 and other genes that control astrocyte formation during normal development play a role in these tumors.

"Could something be happening during the development of these cells that contributes to the pathogenesis of glioblastoma?" he asks. "Could specific features of the tumors arise depending on

where the tumor cells come from, whether neural stem cells or astrocytes?"

Bonni and his colleagues used previously published data to examine two genes whose mutated forms are associated with glioblastoma to see if they affect STAT3 function in astrocytes. In mouse models, they found that the mutation of one of these genes, EGFR (epidermal growth factor receptor), causes STAT3 to act as an oncogene, but when the other gene, PTEN (phosphatase and tensin homolog), is mutated, STAT3 acts as a tumor suppressor.

"EGFR, in its normal state, is a transmembrane receptor, usually performing its functions at the cell surface," says Bonni. "However, when it's mutated, we find it in the cell's nucleus, interacting with STAT3 and turning it into an oncogene. STAT3 itself is not mutated or damaged. It's the process of regulating STAT3 that gets damaged."

On the other hand, PTEN is itself a tumor suppressor that normally prevents cells from turning into tumor cells by promoting apoptosis, or programmed cell death, or by inhibiting cell proliferation. When PTEN becomes deficient in astrocytes, full-fledged tumors do not form because STAT3, which is also normally tumor suppressive, stands in the way. As more PTEN becomes disabled, STAT3 function is inhibited, leading to the development of tumors.

"Because of the long-held belief in the scientific community that STAT3 is an oncogene, it took [us] a long time to convince people that STAT3 could also be a tumor suppressor," says Bonni. "It took some very persistent investigators in my lab to get the job done. As a result, we're convinced of the data."

Bonni says that brain tumors typically stratify into distinct groups. You have either PTEN deficiency or EGFRvIII (the mutant form of EGFR), but occasionally both occur simultaneously. This suggests that there are circumstances when STAT3 is either an oncogene or a tumor suppressor.

The problem, however, is determining in what capacity the gene works in whom. "You could make the argument that by looking for gene alterations—clues for PTEN deficiency or EGFRvIII expression—in tumors following surgical removal, you could figure this out. No one is doing this but, theoretically, you could," he says.

Laying the groundwork for personalized medicine

Bonni's findings lay the groundwork for personalized medicine. That is, by knowing which way STAT3 works, patients could be given a STAT3 inhibitor if they have the oncogenic form or an activator to enhance its tumor suppression properties.

"Our research," says Bonni, "tells us it's important to know which patients will respond to which approach. If you give a STAT3 inhibitor to someone in whom STAT3 is a tumor suppressor, it will have the opposite of its intended effect."

Bonni says that some effort is being put into developing STAT3 inhibitors, but the work is not going to happen overnight. Researchers are currently trying to develop small-molecule compounds that modulate STAT3 activity to either inhibit or activate the protein in certain genetic environments.

In a recent study published in the *Journal of Neuroscience*, Bonni and his colleagues examined STAT3 and validated their previous findings that it works with PTEN deficiency in human glioblastoma cells. The study shows that scientists are able to prohibit tumor cell proliferation by activating

STAT3 in human tumor cells that are PTEN-deficient in culture. He calls this a "positive step" toward validating their findings in human subjects.

Better odds

While glioblastomas are relatively uncommon, they account for nearly half of all primary brain tumors. Most brain tumors do not metastasize and spread to other parts of the body; however, glioblastomas spread rapidly throughout the brain, taking up substantial space, squeezing other tissue in the brain, and impairing its function. The tumors are resistant to chemotherapy and other conventional therapies, so most efforts focus on relieving symptoms and improving patients' neurological function. Median survival is about 12 months; eight percent of patients survive two years.

In addition to glioblastoma, STAT3 has been implicated in both breast and prostate cancer. Bonni says his findings may translate to these and other cancers, as well. ♥



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