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Andrew Bond

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By Andrew Bond

Alcoholism affects some 14 million people in the United States alone. Millions more who are not alcoholics themselves are adversely affected by alcoholics in their lives. In fact, 53 percent of American adults report that at least one of their close relatives has a drinking problem (Congress, 4). Despite its prevalence, alcoholism has remained enigmatic because of its complicated nature. The disease is caused by a complex interaction of genetic and environmental factors, making it difficult to define and to diagnose. Alcohol epitomizes a societal double-edged sword in that it provides a "high" and, thus an escape from the tensions of life but at the same time it exacts a heavy toll from those unable to consume in moderation. The unrestrained consumption of alcohol that is associated with alcoholism and alcohol abuse can lead to health complications, accidents, family problems, job loss, and even death. The recent revolution in genetics has shed new light on alcoholism, but has also revealed the general lack of knowledge of this intricate disease.

Alcoholic Society

According to historian Gregory A. Austin, "The use of alcohol is as old as civilization itself, as are concerns over alcohol abuse (Austin, xiii)." The first recorded evidence of alcoholic beverage production dates back approximately five millennia. This evidence exists in Sumerian documents which cite the production of alcoholic beverages occurring in approximately 3000 B.C. (Austin, 3). The first alcoholic beverages were beer and wine, as hard liquor was not common until the sixteenth century when the distillation process was mastered. What was the purpose of alcohol consumption some 5000 years ago? Some historians have noted that beer and wine were consumed as beverages because they were a safer alternative to the unhealthy water supplies that persisted in many nations until relatively recently. Author Matt Ridley asserts that the wealthy Europeans drank only wine, beer, coffee, and tea until the eighteenth century as it was dangerous to consume water in those times (Ridley, 192). Throughout history there has also been the perception that alcohol has medicinal benefits. It is important to note that the widespread use of pharmaceuticals is a

relatively recent phenomenon and that, for several thousand years, alcohol was an important anesthetic for the pains of life (Austin, xvi).

Nonetheless, the widespread availability of potable water and modern pharmaceuticals has not phased out the consumption of alcohol. Thus, while alcohol may have served as a safe alternative to drinking water long ago, its lastingness for many millennia stems from its ability to produce a "high" for the drinker. Alcohol facilitates relaxation in the drinker and offers a temporary refuge from day-to-day concerns. The ability of alcohol to "take the edge off" and reduce tension has resulted in its designation as a "social lubricant." The ancient Roman expression "*in vino veritas*" meaning "in wine, there is truth," indicates that the Romans clearly understood the potent inhibition-reducing powers of alcohol.

Alcohol, like cocaine or heroin, is a drug. Even so, many cultures do not regard alcohol a drug because it was incorporated into daily life so long ago. According to Ewing and Rouse, "Only the lengthy acquaintanceship of man and alcohol and the integration of alcohol into social and cultural customs prevent this substance from being placed on some dangerous drug list" (Ewing and Rouse, 17). It is important to recognize that alcohol is a poison that is capable of causing bodily harm and even death when ingested is sufficient quantities.

Alcoholism Defined?

Alcoholism remains a difficult disease to define because it is a somewhat subjective condition. Compare alcoholism to another disease, for example, strep throat. A medical practitioner can swab the throat of a person suspected of having strep throat to collect secretions. Those secretions can subsequently be cultured in a laboratory to test for the presence of streptococcal bacteria. If there are streptococcal bacteria present, then the person is diagnosed as having strep throat. Of course, not all diseases can be diagnosed so easily and conclusively, but alcoholism differs because it cannot be linked to a pathogenic microbe, virus, or the uncontrolled growth of a cancerous cell. Furthermore, it is interesting to consider this question: can a person be an alcoholic in the absence of alcohol? It has been proven that alcoholism is the result of complex genetic and environmental factors. Is a genetic predisposition to alcoholism sufficient to qualify a person as an alcoholic? The National Institute on Alcohol Abuse and Alcoholism (NIAAA), the authority on alcoholism in the United Sates, states that there are four major symptoms which characterize alcoholism:

1. **Craving** – A strong need, or urge, to drink
2. **Loss of control** – Not being able to stop drinking once drinking has begun
3. **Physical dependence** – Withdrawal symptoms, such as nausea, sweating, shakiness, and anxiety after stopping drinking
4. **Tolerance** – The need to drink greater amounts of alcohol to get "high"

The NIAAA defines alcoholism solely in terms of a person's interactions with alcohol, thereby disregarding the genetic factors that influence alcoholism. Thus, according to the NIAAA, a person cannot be an alcoholic in the absence of alcohol. The narrowness of this definition is not a reflection of shortsightedness but an indication that the genetics of alcoholism remains largely a mystery at this time. Nevertheless, these criteria for diagnosing alcoholism are not universally accepted. Indeed, there are numerous other definitions of alcoholism and these alternative definitions reflect cultural perceptions towards alcohol consumption. The task of defining alcoholism is further complicated by the notion of alcohol abuse. A person who abuses alcohol experiences problems common to alcoholics but that person does not have a dependency on alcohol. In practice, however, this distinction between an alcoholic and an alcohol abuser can be difficult to distinguish.

Can science help?

The uncertainty in defining and diagnosing alcoholism could be eliminated if there was a test that could diagnose suspected alcoholics. Recent scientific advances have led to more quantitative methods that can sometimes be useful for inferring alcoholism. Blood can be tested for gamma-glutamyltransferase, an enzyme that is present in elevated levels in the case of liver injury (Congress, 432). This test, however, has not been proven accurate enough for use in a clinical setting and it is not understood why heavy drinking increases the level of gamma-glutamyltransferase. Another test measures the level of carbohydrate-deficient transferrin (CDT) in the bloodstream. A person who consumes more than five drinks per day for two to three weeks generally shows elevated levels of CDT in the bloodstream and thus, the test can be useful for detecting the long-term drinking patterns that are common to alcoholics. It is still not clear exactly why CDT is present in higher levels in alcoholics but there is speculation that ethanol and/or acetaldehyde (a product of ethanol metabolism) interferes with anabolic pathways resulting in elevated CDT levels (Musshoff, 463). This test also has the serious drawback in that it cannot detect alcoholism in women, those with liver disease, and binge drinkers (Congress, 432). The absence of a reliable laboratory test means that most diagnoses are made by health care professionals using tests and questionnaires.

Genetics of Alcoholism

People have long suspected that genetics influences alcoholism. Certain populations, such as East Asians and Native Americans, have traditionally been known to have problems dealing with alcohol consumption. The higher frequency of alcoholism in certain families was recognized long before there was an understanding of genes, DNA, and patterns of inheritance. The long-standing speculation that alcoholism is a heritable disease has been confirmed through advances in genetics research. This does not mean that scientists have located the "alcoholism gene" – alcoholism is a complex disease that is the consequence of many different genetic

and environmental factors. Early research was critical in establishing that there is, indeed, a genetic component of alcoholism. More advanced research is helping to pinpoint specific genes that may contribute to this multifaceted disease.

Establishing the Link

The most useful source of general information for understanding the genetics of alcoholism has come from twin studies. Twin studies are particularly practical for determining the overall effect of genetics on alcoholism although they yield no information on specific genes that influence the disease. The heritability of alcoholism is calculated through comparisons of monozygotic twins (identical) and dizygotic twins (fraternal) because monozygotic twins are genetically identical (at least theoretically) whereas dizygotic twins are only fifty percent identical (Congress, 169). Researchers examine the prevalence of alcoholism in monozygotic twins and compare it to the prevalence of alcoholism in dizygotic twins. Early twin studies estimated the genetic component of alcoholism to be approximately fifty percent in men but significantly lower in women (Congress, 170). This inability of early twin studies to establish a genetic link to alcoholism in women was likely due to insufficient samples of women in early studies. Since 1992, several studies with larger samples sizes have indicated that the level of heritability in men and women is approximately equal and that there is no evidence of genetic factors operating in only one sex (Congress, 170). Despite the prevalence of twin studies, there remains no agreed-upon level of genetic influence in alcoholism. The NIAAA reports that the range of heritability for alcoholism is between forty and sixty percent (Gordis, 2).

Gene Hunting

In 1989, the Collaborative Studies on Genetics of Alcoholism (COGA), funded by the NIAAA, set out to obtain more quantitative information by determining the actual genes responsible for alcoholism. The research effort was expected to discover a few genes responsible for alcoholism but early research indicated that the search would not be so easy. According to Robert Karp, PhD, the program director for genetics at NIAAA, "The end stage of alcoholism looks fairly similar, but there are many different ways to get there, so there are probably many different genetic causes (Elliot, 1)." Thus, it has been difficult for researchers to pinpoint specific genetic causes of this complex disease. Linkage studies have yielded some information about the location of genes that are involved in alcoholism. In linkage studies, researchers monitor genetic markers throughout the entire genome to determine how these markers are inherited in relation to the inheritance of alcoholism. Thus, a marker that is close to a gene that affects alcoholism is likely to be inherited along with the disease more often than is statistically probable. Linkage studies have allowed researchers to recognize areas of on chromosomes that are likely to contain genes that are involved in alcoholism.

A COGA-sponsored study in 1998 determined that there were likely to be genes influencing alcoholism on chromosomes one and seven and possibly a gene on chromosome two (Congress, 174). However, this sample was limited in that it consisted of 987 individuals who were mostly Caucasian-Americans. Another study, conducted by the NIAAA, utilized 152 participants from a Southwestern American Indian tribe. This study found evidence for genetic susceptibility to alcoholism on chromosome eleven (Congress, 174). The fact that these two studies discovered different regions of genetic susceptibility is evidence of complexity of the disease. While it might appear surprising that only a few chromosomal regions were cited as perspective areas of heritability for this genetically complex disease, each of these small chromosomal areas contain hundreds of genes, all of which could be involved in alcoholism (Congress, 174). Additionally, it is probable that new regions of genetic influence will be discovered if further linkage studies are conducted on larger populations which contain more ethnic (and genetic) diversity.

Alternate Starting Point

Researchers have shed further light on the genetics of alcoholism by identifying the enzymes responsible for ethanol metabolism and subsequently locating the genes responsible for those enzymes. The major enzymes in alcohol metabolism are alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Alcohol dehydrogenase catalyzes the reaction of ethanol to acetaldehyde. The aldehyde dehydrogenase then converts acetaldehyde to acetate. Researchers noticed that certain groups of people, particularly East Asians, have difficulty consuming alcoholic beverages so they decided to investigate the ADH and ALDH enzymes in these groups. These studies suggested that certain alleles of the ADH and ALDH genes that are prevalent in the East Asian populations may actually protect against alcoholism. What is the mechanism for this protection?

The ADH2*2 and ADH3* variants of the ADH gene encode a high-activity alcohol dehydrogenase enzyme (McKusick). It appears that it is the high activity of these ADH alleles that protects against alcoholism. When ethanol is ingested, it is quickly converted to acetaldehyde. The enzymes encoded for by ADH2*2 and ADH3* catalyze the conversion of ethanol to acetaldehyde at an unusually high rate, creating an accumulation of this acetaldehyde intermediate. Acetaldehyde is toxic and its accumulation creates unpleasant effects such as such as dizziness and nausea. The story of the ALDH2*2 allele is different than that of the ADH2*2 and ADH3* alleles. The ALDH2*2 allele codes for a low-activity version of the aldehyde dehydrogenase enzyme which converts acetaldehyde to acetate at an abnormally slow rate (McKusick). The reduced capacity of the enzyme to convert acetaldehyde to acetate results in a buildup of acetaldehyde, leading to the unpleasant effects mentioned above. Thus, phenotypes that contain any one of the three aforementioned alleles experience an accumulation of acetaldehyde that makes even moderate alcohol consumption unpleasant.

These alleles make the consumption of alcohol unpleasant and this prevents the individual from consuming large quantities of alcohol. Not surprisingly, individuals with these genotypes do not become alcoholics and these alleles effectively afford protection from the disease of alcoholism. It appears that these protective genes would provide a selective advantage against alcoholism. However, some might argue that these genes are not advantageous. Alcohol is widely consumed for its calming and stress-relieving properties and person who is unable to consume alcohol cannot enjoy these effects of alcohol. It is difficult to decide where the advantage really stands. Do the soothing effects of alcohol outweigh the risks of alcoholism? The answer to that question determines the selective value of ADH and ALDH alleles.

Looking Forward

The consumption of alcoholic beverages will not end anytime in the near future. Previous attempts by authorities to outlaw drinking (i.e., Prohibition) were largely unsuccessful and hugely unpopular. At the same time, the dangers of drinking have been well-understood for thousands of years and this understanding has not curtailed consumption. Therefore, it seems unlikely that any further discoveries will bring a halt to drinking. The public has been showered with hundreds of studies documenting the extreme dangers of smoking cigarettes, yet significant numbers of people choose to begin smoking every single day, indicating that general education is not effective in curbing dangerous habits. In the future, however, scientist may be able to identify complex combinations of genes that lead to increased susceptibility to alcoholism. Genetic testing could then be employed to determine an individual's risk of becoming an alcoholic. Ideally, the availability of this information would compel individuals at risk to avoid alcohol consumption. The current reality, however, is that alcoholism remains a mystery and, while there has been recent progress in researching this disease, much remains to be done. The completion of the sequencing of the entire human genome has laid the groundwork for major advances in understanding the genetics of alcoholism. It appears probable that much will be learned about alcoholism in the coming years. Thus, the major issue will shift from obtaining information about alcoholism to applying this information to the prevention and treatment of this disease.

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