Alcoholism Research: Delivering on the Promise

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Synopsis

Prospects for research advances in alcoholism are very promising, because of the explosion in the neurosciences and advances in epidemiology and typology of the disorder. For example, the field is now ready for molecular genetics studies of the early onset form of alcoholism that is transmitted from father to son with high penetrance. Leading neuroscientists are being recruited into alcoholism research.

Paradoxically, this time of new hope coincides with challenges to the scientific enterprise, such as the animal rights movement and impatience with the scientific process in the face of the public health emergencies represented by acquired immunodeficiency syndrome (AIDS) and drug abuse.

The emergence of genetically based subtypes of alcoholism suggests that at least two discrete illness processes are involved. Mounting evidence from spinal fluid studies has rekindled interest in a key role for serotonin in the early onset form of alcoholism. One hypothesis now being explored is that genetically low brain serotonin function may be part of the predisposition to this form of alcoholism. It is known that acute alcohol intake transiently increases brain serotonin turnover. Thus, drinking might be viewed as an attempt to correct a deficit, only to produce further serotonin depletion as the drug's effect wears off, setting up a vicious cycle of repeated attempts to self-medicate.

Impulsive, violent, and suicidal behavior as well as alcohol abuse are associated with the low brain serotonin activity. Persons with these problems suffer from circadian rhythm and glucose metabolism disturbances that may also be mediated by serotonin. New pharmacological probes are now available to tease out the mechanisms of altered serotonin function.

The progressively deteriorating course of severe episodic alcoholism in many ways parallels the process of electrically kindled seizures in experimental animals. There is evidence that repeated withdrawal episodes may kindle a worsening course, including phobic disorders, perhaps by triggering a hyper-reactive noradrenalin system.

AS I HAVE just recently assumed the responsibilities of Administrator of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) at this writing, what follows should be taken as a personal statement about my thinking with respect to research prospects in alcoholism. I still have much to learn about developments in this field and am looking forward to working with Dr. Enoch Gordis, Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and his able staff to expand my horizons during the coming months. By making the most of the exciting new research opportunities that are arising, we can deliver on the promise of new hope for persons suffering from this major public health problem.

My own occasional contributions to the alcoholism research literature have stemmed from an interest in the neurobiology of affective and impulse control disorders, and in the intersection between the two. Over the years, I have helped to train younger investigators who are now working in the alcoholism field, among them Dr. Markku Linnoila, Director of NIAAA's Laboratory of Clinical Studies. At the National Institute of Mental Health (NIMH), we have also nurtured lines of research that have potential importance for alcoholism treatment, such as Dr. Steven Paul's explanation of how alcohol's anti-anxiety effects may be mediated through a receptor complex closely linked to that which mediates the action of benzodiazepines. In working with patients, I have come to respect the powerful negative impact that even

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moderate drinking can have on the course and treatment response of patients with recurrent affective disorder. In this regard, I have become increasingly impressed with the essential role that Alcoholics Anonymous and other self-help and group therapy programs play in the recovery process for persons with this often intractable illness. Through my wife Rosemary, a clinical social worker in the Substance Abuse Clinic at Georgetown University School of Medicine, I have gained a new respect for both the devastation wreaked by alcohol on young lives and for what can be done through a vigorous, comprehensive treatment program.

The Promise

We are entering an extraordinarily promising era for research advances in alcoholism. The new opportunities are based on the expansion of our knowledge base in the neurosciences—molecular genetics, molecular biology, neuropharmacology, and brain imaging techniques. As in other clinical fields, the hoped-for progress will depend on fundamental developments in basic research. Although one cannot always predict which clinical problems are going to benefit first from such advances in the basic infrastructure, the potential benefits warrant investment in broad-ranging studies.

For example, the field of molecular genetics is rapidly moving toward the mapping of the entire human genome. Alcoholism represents one of the ripest areas for clinical exploitation of these powerful methodologies, particularly early onset alcoholism, which is transmitted from father to son with high penetrance. The epidemiologic base needed to undertake the necessary clinical studies is now in place. It was such an epidemiologic base that made possible the recent discovery that a gene exists on the short arm of chromosome 11 that predisposes for manic depressive illness among the Pennsylvania Amish (*1*). Another gene locus linked to the disorder has been found on the X chromosome in a group of Israeli families (*2*). While the alcohol field hasn't yet reached this stage, it is similarly poised. All of the indirect data—family history, identical twin and adoption studies, biological markers of vulnerable children—point to the likelihood that a gene or genes linked to the early onset form of alcoholism can eventually be found.

When such genes are discovered, the awesome power of molecular genetics techniques comes into its own. At a minimum, linked genes can be used as markers for early detection, counseling, and preventive interventions. Genes can be sequenced, cloned, and expressed to discover the proteins they code for. Genes offer shortcuts to understanding and treating the underlying illness process, which may turn out to involve defective enzymes, transmitters, receptors, or other neuronal components. We already have some clues about what some of these components might be. As I will discuss later, emerging evidence linking early onset alcoholism to alterations in brain serotonin systems may be among the leads worth following up in the coming years.

When top scientists from cutting-edge disciplines become interested in an area, it is a sure sign that the field is ripe for discovery. It is no coincidence that neuroscience leaders, such as Dr. Floyd Bloom of the Scripps Institute, have been recruited into alcoholism research in recent years.

A Paradox

Paradoxically, just as a return on our investment in science seems within our grasp, political threats to the research enterprise itself have surfaced. Foremost among these is the radical animal rights movement, which has targeted precisely the kind of biobehavioral research that the ADAMHA institutes must continue to invest in if we are to carry out our mission. I speak here not about the animal welfare community, with whom we share a common concern for the well being of research animals, but about the extremists who would stop all animal research in the name of a misguided sentimentalism.

Unfortunately, rather than attempting to convince the public of their belief that animals and humans are morally equivalent, many animal rights activists seem to have chosen to exploit the public's lack of knowledge about biobehavioral disorders

and the nature of research. They implicitly play upon outdated notions that mental illness and substance abuse somehow stem from uniquely human failings. It is now clear that these serious health problems involve brain mechanisms gone awry, mechanisms that are potentially fathomable, in part, via studies in animals with which we share many biological and behavioral characteristics. Animal rights proponents ignore or seriously distort the scientifically driven medical advances of the past quarter century and appear to discount the possibility of major new discoveries.

Of course, this does not mean that we give scientists carte blanche to use animals frivolously. Animals involved in ADAMHA-supported studies are cared for in the most humane manner possible. Cruelty to any animal is reprehensible and will never, under any circumstances, be permitted. Not only would it be inhumane to the animal subject, it would also be bad science, since any data obtained (especially in behavioral studies) could be confounded by the distress of the animal. By far the great majority of animal studies—90 percent—are conducted in rodents and other lower animals (*3*). For every dog or cat that serves humanity in research, 50 are killed at animal shelters (*4*). Primates are used only when the organ system in other species differs too much from that of humans.

If research on animals were halted, clinical research on brain illnesses would soon be crippled and eventually die. Though animal studies constitute only one-fifth of the ADAMHA research effort, they are the foundation for the entire enterprise. Cut the roots and the tree will die and, with it, its fruits. The major organizations representing persons ill with alcoholism have joined with their counterparts representing other illnesses and the health professional community in voicing support for continued use of animals in research.

Yet another challenge to research comes from political pressure to solve problems quickly. It is the responsibility of our scientific leadership to explain to our political leaders why we can only push science so fast. Sometimes short-term solutions to problems may damage the acquisition of long-term knowledge upon which real solutions ultimately depend. Simply delivering more services when we are not yet sure which interventions work best, and under what circumstances, may not be in the best interest of the public health—especially if it means curtailing research investments that could lead to the development of better treatments in the long run. For example, during the polio epidemic of the early 1950s, there were very strong pressures to spend large sums to perfect portable iron lungs. In retrospect, it turned out to have been a very wise decision to instead invest the bulk of March of Dimes money in basic biological research.

Today, we face similarly pivotal issues in substance abuse research policy. In some quarters, our research effort is branded "ivory tower," unresponsive to pressing public health needs. In fact, we really do have information gaps. We need to close them as quickly as we can in the face of a public health emergency. Yet, as we have seen with AIDS, even when we expedite a promising new discovery from the test tube into clinical trials, it still may seem too slow to people who do not understand the scientific process.

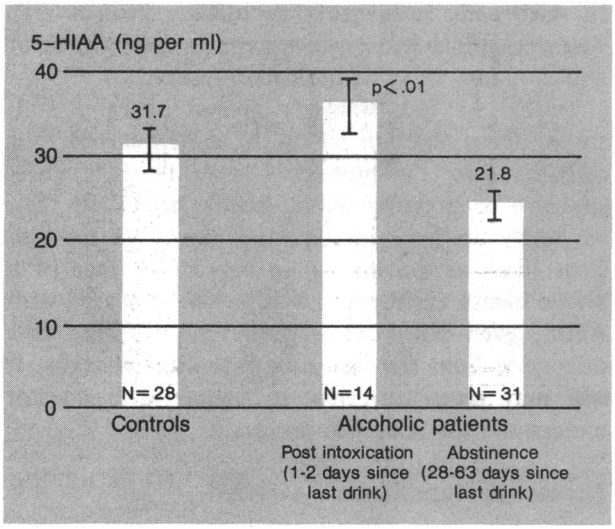
Serotonin Hypothesis Revisited

One outgrowth of my early research on the pathophysiology of depression has been an interest in the relationship between the neurotransmitter serotonin and impulse control problems. A hypothesis I helped to formulate a decade ago concerning a role for serotonin in alcoholism continues to influence some clinical investigations. In the late 1970s, our group at NIMH (*5*) assessed brain function and personality characteristics of sailors in treatment for alcoholism at the National Naval Medical Center. Spinal fluid samples were assayed for levels of 5-HIAA (5-Hydroxyindoleacetic acid), a byproduct of the metabolic breakdown of serotonin that provides an indirect window into turnover of the neurotransmitter in brain. We found that upon admission when still intoxicated, the alcoholic sailors' 5-HIAA levels were relatively higher than a control population's. After 4 weeks of abstinence, their 5-HIAA levels had dropped significantly below those of nonalcoholic controls with similar personality profiles (fig. 1).

On the basis of this and animal research findings, we speculated that (*5*) (fig. 2)

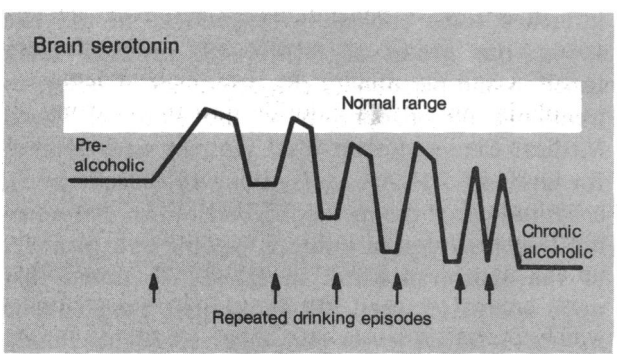
> . . . the pathophysiology of alcoholism might involve preexisting low brain serotonin levels that are increased transiently by alcohol consumption, but that brain serotonin levels gradually undergo increments of further depletion as a consequence of repeated drinking. This alcohol-produced depletion would aggravate the postulated preexisting serotonin deficit, setting up a "vicious cycle" in which the alcoholic repeatedly seeks to pharmacologically modify a central indoleamine deficit.

Figure 1. 5-HIAA in the CSF of type 2 alcoholic patients immediately after intoxication and during abstinence



NOTE: 5-HIAA = 5-Hydroxyindoleacetic acid; CSF = cerebrospinal fluid; ng per ml = nanograms per milliliter
SOURCE: Reference 5.

Figure 2. Alcohol and central serotonin: a possible "vicious cycle"



SOURCE: Reference 5.

A year later, we found that depressed patients with a history of alcoholism in first or second degree relatives had significantly lower 5-HIAA levels than depressed patients without family histories of alcoholism (*6*) (fig. 3).

Among other groups of sailors studied at the Bethesda Naval Hospital, those who had a history of impulsive-aggressive behavior problems also had low levels of 5-HIAA. Swedish investigators had earlier observed that depressed patients who attempted suicide were similarly deficient in the metabolite. Over the past decade, an odyssey of studies in Sweden, Finland, and the United States has added impulsive murderers and other impulsive, violent criminals, borderline personalities, arsonists, and violent suicides to the low 5-HIAA list. A profile has emerged of an antisocial personality characterized by low harm avoidance, high novelty seeking and low reward dependence—prone to alcohol abuse and linked to low brain serotonin activity.

Studies in animals provide added support. Drugs or diets that deplete brain serotonin increase shock-induced fighting and mouse-killing behavior in rats. This effect can, in turn, be attenuated by drugs that inhibit reuptake of the transmitter from the synapse or otherwise enhance serotonin function.

All of this converging evidence dovetails with the genetically based subtypes of alcoholism characterized by C. Robert Cloninger of Washington University in adoption studies (*7*). In a recent review (*8*) of serotonin links to impulsivity, violence, and alcoholism, NIAAA investigator Alec Roy and colleagues built a convincing case for a serotonin-type II alcoholism connection. Type II alcoholism affects sons of alcoholics, requires no environmental triggers for expression of the gene, and is characterized by early onset in young adulthood, antisocial personality traits, craving for alcohol as a euphoriant, episodic binges, brawls, and arrests. Type 1 alcoholism—the more common form—affects both sexes, typically in mid-life, is linked to life stresses, anxious personality traits, and is marked by rapid development of tolerance, gradually increasing dependence, and less clear-cut genetic loading, at least in males. Mechanistically, this latter type probably relates more to the benzodiazepine/GABA receptor (gamma-aminobutyric acid receptor) complex. Thus, at least two discrete illness processes may be involved in what we call alcoholism.

Persons who fit the type II personality constellation have a tendency to develop low blood sugar during glucose tolerance testing and are also prone to disturbances of the sleep-wake cycle. Animal studies have shown that both glucose metabolism and circadian rhythm functions are regulated by the suprachiasmatic nucleus of the hypothalamus, which turns out to be densely innervated by serotonin neurons.

Perhaps it is more than a coincidence that Seasonal Affective Disorder (SAD) patients—who suffer disordered circadian rhythms as well as intense carbohydrate cravings with impulsive eating and drinking in winter—tend to have family histories of alcoholism (*9*). Indeed, my wife has observed a seasonal pattern of alcoholism in her work at Georgetown University, where they have had some experience treating the winter intensification

of alcohol abuse with the same high intensity, full spectrum lights used to treat winter depression. Among all neurotransmitters studied, serotonin deficits appear most likely to be involved in the pathophysiology of SAD, providing further rationale for the possible efficacy of light treatment in other serotonin-related disorders, such as alcoholism.

New research tools are now available to reexamine the serotonin hypothesis. These include specific pharmacological probes or challenge drugs, such as the serotonin receptor agonist MCPP (m-chlorophenylpiperazine) and the selective serotonin reuptake blocker fluoxetine. Preliminary studies suggest that such serotonin-stimulating substances can reduce alcohol consumption and also decrease the cognitive and memory deficits associated with alcohol. Another challenge strategy might involve administering a serotonin precursor substance such as tryptophan and examining effects on cortisol output as a way of gauging the integrity of neurohormone systems regulated by serotonin.

Kindling a Worsening Course

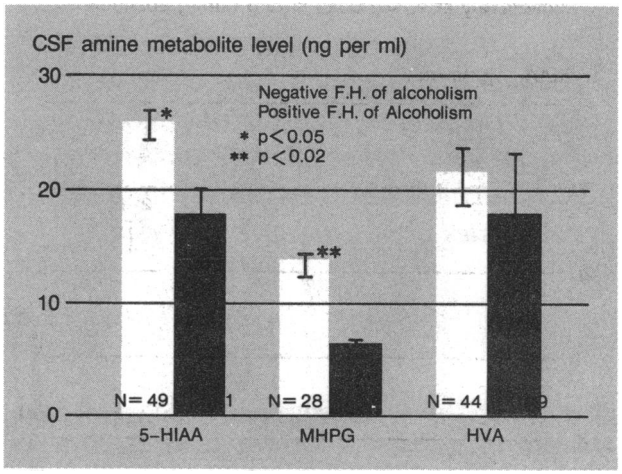
Another decade-old NIMH hypothesis about alcoholism now gaining currency proposes that the characteristic downhill course of the illness is "kindled" by repeated withdrawal episodes—a course that is analogous to that of electrically kindled seizures (*10*). Symptoms of tremor, shakes, seizures and delirium tremens become increasingly worse with each withdrawal experience, presumably because of a progressive deterioration in neuronal responses.

There is now evidence that repeated withdrawals may eventually trigger panic attacks and other anxiety disorders. The results of one recent study suggest that repeated withdrawals may eventually result in a hyperreactive noradrenalin system (*11*). It found that with successive withdrawals, the responsibity of noradrenalin (alpha 2) autoreceptors became blunted. Some of the investigators in this group are proposing a longitudinal, multicenter study "to determine the clinical significance of withdrawal-induced kindling and other central nervous system damage" (*12*).

Blocking Alcohol's Reinforcing Effects

To deal with highly reinforced drinking behavior in vulnerable persons, we need to understand the cellular mechanisms for the initial effects of alcohol. As I noted earlier, Dr. Steven Paul and

Figure 3. CSF monoamine metabolites in depressive subgroups



NOTE: CSF = cerebrospinal fluid; FH = family history; ng per ml = nanograms per milliliter; 5-HIAA = 5-Hydroxyindoleacetic acid; MHPG = 3-methoxy-4-hydroxyphenylglycol; HVA = homovanillic acid.
SOURCE: Reference 6.

colleagues at NIMH have been studying the intimate workings of the brain's benzodiazepine system. A recent outgrowth of this work has been the discovery of a way to selectively block the intoxicating, reinforcing effects of alcohol in rats (*13*). The investigators have demonstrated that alcohol acts on the GABA-benzodiazepine-barbiturate receptor complex much like the benzodiazepines, stimulating uptake of chloride into the neuron. By injecting an "inverse agonist" which binds to and occupies the receptor (but which is without pharmacological effects of its own), they were able to block alcohol's ability to stimulate this chloride uptake and its attendant behavioral effects. Thus, they prevented that aspect of alcohol's effects which probably contribute most to repeating the behavior—the initial, mildly intoxicated calming effect.

The findings help to explain the anti-anxiety, sedative-hypnotic, and anesthetic properties of alcohol and may provide valuable insights into the mechanisms of alcohol tolerance and dependence. They also may lead to the development of medications that could be used to treat alcoholism in much the same way that naloxone and naltrexone are used in the treatment of opiate addiction.

Alcohol and Depression

As I noted earlier, in my clinical work with affective disorder patients, I have become increasingly impressed with the profound negative effect alcohol can have on the course of an affective disorder and with the profound interference the

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drug can present to effective pharmacological management of patients. I feel we need to do a lot more to educate physicians about alcoholism and alcohol abuse. From my own experience, it seems especially important to educate professionals who work with affective illness about alcohol abuse. By the same token, people in the alcohol field need to educate their colleagues about the affective disorders. This is important because, although the two disorders overlap considerably, treatment approaches are quite specialized. There is now an array of effective treatments for depression. Issues of comorbidity with affective illness are still underappreciated, because the treatment systems for alcoholism and depression have tended to operate so independently of one another.

Borrowing new treatments from the other field may also prove fruitful. For instance, the previous discussion of alcohol and kindling may prove to be more than academic. We know there are many manic depressive patients for whom the anticonvulsant drug carbamazepine seems to be effective because of its antikindling properties. Perhaps anticonvulsants might be useful as an adjunctive treatment for certain patterns of episodic drinking.

Again, these remarks are simply some initial thoughts, examples of new alcoholism research opportunities offered us by the neuroscience revolution, drawn from my own research and clinical background. As ADAMHA Administrator, I expect to learn about the full range of biological and behavioral research in this exciting field. Indeed, the alcohol treatment and research communities are themselves showing an increased interest in each other's work—an encouraging development that will certainly benefit persons with this disorder.

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