Gene in the Bottle

A controversial alcoholism gene gets a new twist

By BRUCE BOWER

Research into the genetics of alcoholism invariably stirs up spirited controversy. A report issued last year, describing the first evidence that a specific gene creates a susceptibility to at least one type of alcoholism, proved no exception. Critics immediately pointed out flaws in the study, and independent follow-up investigations suggested that the gene plays no role in fostering uncontrollable alcohol consumption.

But the gene will not go away. Its original proponents — who had identified the culprit as one of two genes that occupy a precise spot on chromosome 11 and direct the function of key dopamine receptors on brain cells — now report further evidence linking it to cases of severe alcoholism with medical complications. And another research group suggests that the gene may intensify the severity and medical consequences of alcoholism — rather than cause the disorder — by disturbing normal dopamine transmission. Dopamine, an important chemical messenger in the brain, normally helps to regulate pleasure-seeking behaviors.

"We may have found a gene that modifies, rather than causes alcoholism," says psychiatrist Ernest P. Noble of the University of California, Los Angeles, who co-directed the original study with psychopharmacologist Kenneth Blum of the University of Texas Health Science Center at San Antonio. "We just don't know yet. As research continues, I think we'll find many genes associated with alcoholism."

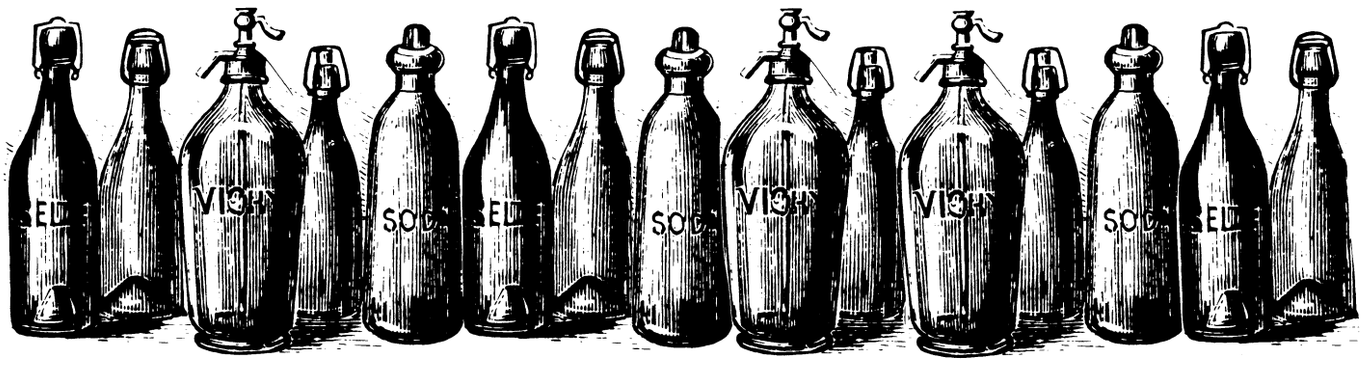
For now, though, the dopamine receptor gene stands alone. Noble's team first reported finding it in DNA from 24 of 35 alcoholics, compared with only seven of 35 nonalcoholics. All DNA samples came from the brain tissue of deceased individuals. The researchers used medical records and reports from family members to determine which individuals met the criteria for alcoholism. Because most of the alcoholics had failed in several rehabilitation efforts and had died of alcohol-related causes, the investigators concluded they had suffered from a severe form of the disorder (SN: 4/21/90, p.246).

Another study, reported last January, raised doubts about the proposed alcoholism gene. These researchers, led by psychiatrist Annabel M. Bolos of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in Bethesda, Md., examined DNA from 40 alcoholics and 127 nonalcoholic controls, including 62 with cystic fibrosis. In both groups, the dopamine receptor gene turned up in about one-third of the volunteers. Bolos and her colleagues contended that psychiatric interviews with the participants, all of whom were living, allowed for more accurate alcoholism diagnoses than those deduced by Noble's group (SN: 1/12/91, p.29).

But Noble and Blum, who have reexamined data from the Bolos study, say the results actually support a link between the dopamine receptor gene and severe alcoholism. According to their analysis, the gene's prevalence increased from 25 percent of the nonalcoholic controls (excluding those with cystic fibrosis, who often die before alcoholism has a chance to develop, according to Noble and Blum) to 30 percent of the 20 alcoholics with no medical complications and 45 percent of the 20 alcoholics with related medical conditions such as liver cirrhosis. Bolos' group excluded alcoholics with the most severe, "acutely active" medical complications, thereby lowering the frequency of the dopamine receptor gene in their study, Noble and Blum maintain in the May 22/29 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

In a commentary accompanying Noble and Blum's argument, Bolos and her colleagues question the revision of their work, noting that a standard alcoholism screening test reveals no difference in symptom severity between alcoholic participants with and without the gene.

Noble and his colleagues continue to pursue the chromosome 11 offender. They have now extended their original genetic investigation to living volunteers: 43 nonalcoholics, 52 with severe alcoholism (dependency symptoms plus medical complications) and 44 with less severe alcoholism (dependency symptoms only). The dopamine receptor gene occurred in 21 percent of the nonalcoholics, 34 percent of those with less severe alcoholism and 63 percent of those with severe alcoholism,



they report in the September ALCOHOL.

The researchers have also conducted a biochemical analysis of 66 of the 70 brain samples from their 1990 study. Samples from individuals diagnosed with alcoholism showed significantly fewer brain-cell binding sites for the dopamine receptor controlled by the chromosome 11 gene, as well as impaired binding function at those sites, the team reports in the July ARCHIVES OF GENERAL PSYCHIATRY. This suggests – but does not firmly establish – that genetically disturbed dopamine activity confers susceptibility to severe alcoholism, they say.

Another report in the same issue indicates that the cerebral havoc wreaked by this gene may jack up the severity of alcoholism, rather than light the fuse of alcohol abuse. Geneticist Abbas Parsian and his co-workers at Washington University School of Medicine in St. Louis found that 13 of 32 alcoholics (41 percent) carried the dopamine receptor gene, compared with three of 25 nonalcoholics (12 percent). And among alcoholics with serious, related medical problems, six of 10 carried the gene.

However, when the same researchers performed genetic analyses of 80 individuals in 17 families with numerous cases of alcoholism, they uncovered no increased susceptibility to either mild or severe alcoholism among those carrying the dopamine receptor gene.

Since the critical gene clearly stands out among unrelated severe alcoholics with medical complications, but does not congregate in family members afflicted by alcoholism, the St. Louis scientists conclude that it probably plays a secondary role of fanning the flames of uncontrolled alcohol consumption. The gene may also speed the progression of alcohol-related diseases such as liver cirrhosis, they say.

This intriguing possibility calls for larger genetic studies that carefully partition alcoholics according to the severity of their medical problems, asserts P. Michael Conneally, a geneticist at Indiana University in Indianapolis.

Conneally's plea may not go unheeded. He and seven other investigators, based at six research centers, now direct the largest-ever study on the genetics of alcoholism. Participants in the NIAAA-financed study include 600 alcoholics and thousands of their family members. Project investigators hope to determine whether certain genes produce a specific vulnerability to alcoholism or a general susceptibility to all sorts of compulsive behaviors.

Noble suspects the dopamine receptor gene will fall into the latter category, working in concert with several genes to promote the full spectrum of substance use and abuse.

"If the good Lord didn't have alcohol around, we'd still have this gene, and we'd still get a charge out of certain pleasurable behaviors that sometimes become compulsive," Noble says.

The recent emphasis on combing through chromosomes for offending genes linked to alcoholism cannot deny evidence of vigorous environmental influences on compulsive alcohol use, he adds. These include expectations about alcohol's effects, as well as conditioned emotional and situational cues that trigger a craving for alcohol (SN: 8/6/88, p.88).

"The environment is a tremendously powerful agent in producing alcoholism," Noble remarks. "But genes are easier to study." □

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were borderline, and involved only crude measures of exposure, such as the proximity of subjects' homes to neighborhood distribution lines.

A valid study must reliably distinguish exposed from unexposed individuals, or at least sort them according to exposure. Yet people are constantly exposed to power-frequency fields, at highly variable levels, as shown by the studies with personal dosimeters.

The implication of the dosimeter findings is not that alarm clocks, electric trains, computer terminals, etc., might be hazardous, but rather that *nothing* can be concluded reliably from the epidemiologic evidence about a possible connection between power-frequency fields and health.

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Neandertal: Evolution ...

"Neandertals' Disappearing Act" (SN: 6/8/91, p.360) is a well-written overview of this very contentious issue. However, I feel a few points were overlooked.

First, showing the Qafzeh 6 and Amud 1 fossils face-front obscures some important morphological contrasts, such as the greater Neandertal midfacial prognathism (protruding jaw) and the greater basicranial flexion of the Qafzeh hominids.

Second, most vertebrate paleontologists agree that without genetic data from the fossils themselves, the only way to infer evolutionary relationships among fossil specimens is from a cladistic analysis of their morphological characteristics. Wolpoff's and Arensburg's contention that the Skhul/Qafzeh and Tabun/Amud/Kebara/Shanidar fossils represent a single, undifferentiable group probably reflects their emphasis on sorting these fossils by shared primitive characteristics rather than uniquely derived characteristics.

Third, the "Neandertals as an extinct race" argument ignores the profound nature of the functional anatomical contrasts among them. Erik Trinkaus has for years documented numerous contrasts that set these fossils apart from each other in terms of bone growth, locomotor patterns, probable nutritional requirements and differences in longevity.

Fourth, Bruce Bower's article – and the whole "origins of modern humans/fate of the Neandertals" debate – overlooks the role that competition must have played in any evolutionary relationships between early modern humans and Neandertals. If and when they overlapped chronologically, it is likely that individuals of both morphotypes would have competed with each other for access to resources and for reproductive opportunities, either as members of distinct groups or as individuals within mixed Neandertal and robust modern human populations.

Neither Neandertals nor early modern humans necessarily enjoyed any great subsistence advantage over the other. To what, then, should we ascribe their obvious morphological contrasts? The time has come to investigate the role of different reproductive strategies and life-history parameters in the evolutionary trajectories of these hominids. That Neandertals no longer live in the world today need reflect nothing more than a small difference in reproductive success sustained by early modern humans for a few critical millennia.

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... and etymology

We at work were wondering why you spelled Neandertal without the "h." We thought (and our dictionary confirmed) that it was spelled Neanderthal.

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We thought so, too, until we decided to look into it after noting that many anthropologists drop the "h." Our survey of anthropological organizations and journals turned up several that consistently omit the "h," and a few fence-sitters that vary the spelling depending on individual researchers' preferences, but none with a policy of inserting the "h."

The Leakey Foundation – adamant about dropping the "h" – notes in the spring 1991 ANTHROQUEST that the first Neandertal skeleton was discovered in 1856 in a German quarry called Neander Thal (pronounced "tal"). Around the turn of the century, according to the ANTHROQUEST article, Germans dropped the silent "h" in this and many other Old German words to reconcile spelling with pronunciation.

"Unfortunately," the article states, "Anglophones moved to adopt this change about as rapidly as the glaciers retreated after the last Ice Age." – the editors