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Biological Markers: Metabolism and Acute Reactions to Alcohol in Sons of Alcoholics[1]

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SCHUCKIT, M. A. *Biological markers: Metabolism and acute reactions to alcohol in sons of alcoholics.* PHARMAC. BIOCHEM. BEHAV. 13: Suppl. 1, 9–16, 1980.—Substantial evidence has accumulated to indicate that defined aspects of primary alcoholism may be inherited. Family history studies, genetic marker studies, twin studies and adoption studies all contribute to this conclusion. Current studies of possible biological mediators of predisposing factors indicate that men with a family history of alcoholism exhibit higher circulating levels of acetaldehyde after ingestion of ethanol compared to control subjects. Subjects with a family history of alcoholism also respond differently from controls on subjective measures of intoxication and on physiologic measures of ethanol's effects.

Genetic markers Alcoholism Family history Acetaldehyde Intoxication Adoption studies Twin studies

THIS series of investigations is based on the premise that alcoholism is a genetically influenced disorder. It is our goal to attempt to identify some of the possible biological mediators of this genetic propensity.

There are a number of common sense steps which can be taken to maximize the chances of uncovering any such biological mediators. The first is to attempt to make the population under study as homogeneous as possible by using objectively stated definitions, preferably those which have been applied to populations which were then followed up and noted to run a relatively homogeneous course [13]. The definition which best meets the criteria, with all its imperfections, is the life problem approach to alcoholism outlining those alcoholics who have any one of a number of alcohol related life problems including a marital separation or divorce *or* multiple arrests *or* job loss or layoff *or* physical evidence that alcohol has harmed health [30]. Next, recognizing that serious alcohol related difficulties could occur in the midst of other psychiatric disorders, especially the antisocial personality or primary affective disorder, we try to maximize the chances for homogeneity by studying only those individuals with alcoholism occurring in the absence of severe pre-existing psychiatric disorders, i.e. primary alcoholism [27, 28, 30]. These factors are outlined in Fig. 1.

Central to our research on genetic markers for alcoholism is the evidence that alcoholism is indeed a genetically influenced disorder. In the first section below we will briefly review the evidence supporting such genetic factors. This is then followed by a description of the prospective studies presently in progress with sons of alcoholics.

DATA SUPPORTING A GENETIC PROPENSITY IN ALCOHOLISM

The major impact of the studies described here is the consistency of results despite the variety of methodologies using different definitions and populations in different areas of the world [26]. Each type of investigation thus becomes part of a larger picture with no step alone justifying solid conclusions.

The first area of evidence is that it has long been noted that alcoholism runs strongly in families with one-third of alcoholics and only 5–10% of the general population reporting an alcoholic parent [6, 14, 15]. While it is not possible to demonstrate from the family data alone whether this propensity is genetic or environmental (or more likely a combination of the two) the consistency of the findings along with the trend for increasing risks for alcoholism with increasing numbers of relatives who are alcoholic, greater degrees of genetic relationships, and enhanced severity of alcoholism in alcoholic relatives is enough to justify other approaches and investigations.

Animal models have been used to demonstrate that it is possible to breed distinct strains with high or low alcohol drinking preferences. The characteristics of alcohol metabolism (including the level of acetaldehyde) as well as the taste

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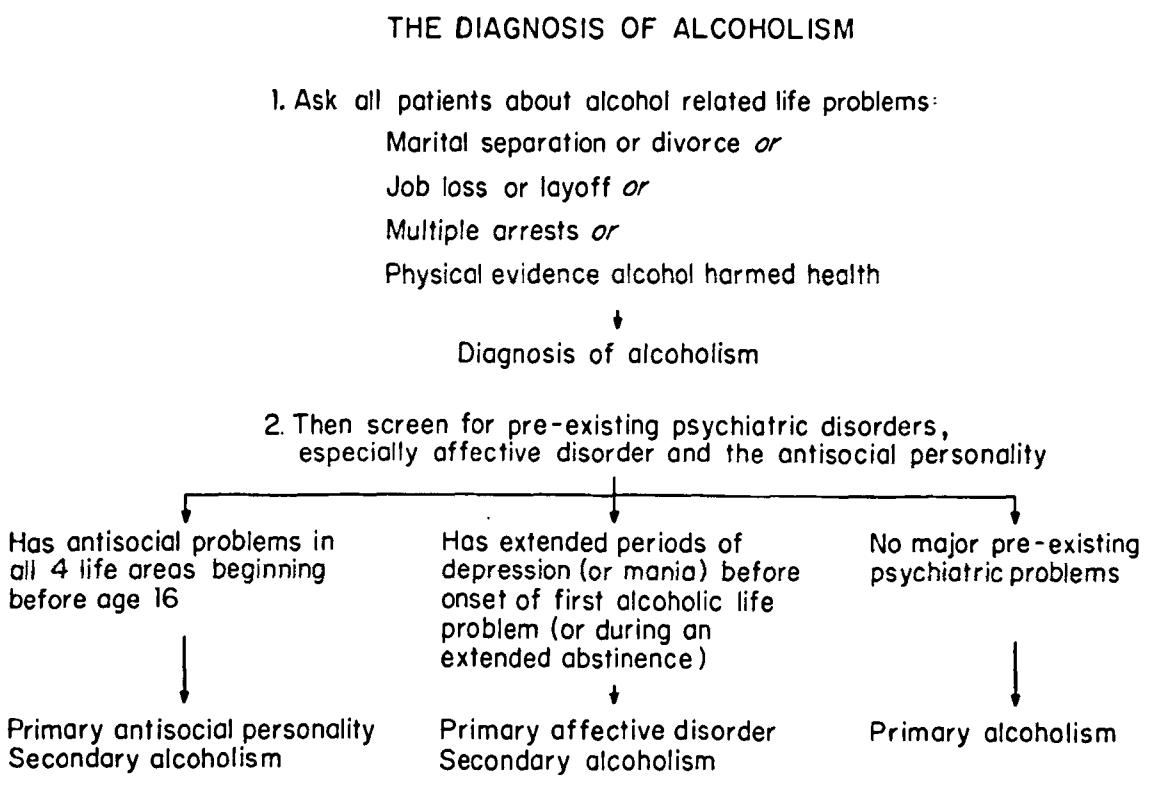

FIG. 1. An overview of the diagnosis of alcoholism, separating individuals into primary and secondary disorders. Reprinted with permission from Schuckit, M. A. *Drug and Alcohol Abuse: A Clinical Guide to Diagnosis and Treatment*. New York: Plenum Press, 1979.

discrimination ability and caloric preferences parallel the intake patterns in different groups. These results indicate the possibility that drinking patterns (not necessarily alcoholism) might be genetically influenced in humans as well [11].

Studies of *genetic markers* attempt to establish a link between alcoholism and a trait already known to be genetic. These can include a wide variety of traits ranging from blood groups to color blindness to any of a variety of blood proteins. One series of investigations, begun in Chile, reported that alcoholics more often were color blind than non-alcoholics [7,14]. However, while an association was found within given families, these studies have not been uniformly replicated and other investigations raise the possibility that the deficiency in color vision may be temporary and revert to normal after a period of abstinence [12,14]. In another series of investigations, Hill *et al.* compared alcoholics and their non-alcoholic first degree relatives on 11 serological markers, demonstrating a lower prevalence of the S antigen in the non-alcoholic relatives and linkage in repulsion between the D gene of the Rh system, along with an association between alcoholism and DSS phenotype for complement C3, a serum protein [16]. Another association with markers has been reported between blood group A and alcoholism [22], a finding which was not corroborated by Achte [1]. In an interesting approach, Peeples compared alcoholics and controls on the genetically influenced trait of tasting phenylthiocarbamide (PTC), finding a higher incidence of lack of tasting in alcoholics [25]. In summary, while not the major topic for discussion here, genetic marker studies represent an interesting approach to attempting to increase our knowledge of possible genetic factors in alcoholism. While findings have been relatively inconsistent from population to population, this could represent the possibility that there are different biologically influenced factors raising the risk for alcoholism in different population groups.

One impressive area of evidence for a genetic propensity in alcoholism comes from studies of *twins* in that such studies at least in part, control for gross environment. The twin studies have asked two separate but possibly related questions. The Finnish investigation carried out by Partanen *et al.* began with individuals in a twin register and looked for differences or similarities in drinking patterns and alcohol related problems between monozygotic (i.e. identical) twin pairs and the level of similarity within same sex dizygotic (i.e. fraternal) twin pairs [24]. Partanen's work sheds little light on the genetics of alcoholism itself but did indicate a level of heritability for the frequency and amount of drinking. Kaij *et al.* [19] asked a separate question by looking at a group of alcoholics, with results showing a concordance rate less than 30% in dizygotic twins versus 60% in monozygotic twin pairs—a significant difference.

The *adoption* studies carry the question to a logical next step, addressing the issue of the drinking behavior in children of alcoholics separated from their parent during childhood and raised by non-alcoholics [3,14]. This problem has been approached through a half-sibling method done in the United States and a classical adoption study done in Den-

mark. The most often quoted adoption study, done by Goodwin *et al.*, followed the adult incidence of primary alcoholism in two groups of men studied in their mid thirties—individuals in one group had a biological alcoholic parent and individuals in the other group, adopted through the same agency, had no evidence of alcoholism in their parents [14,15]. The alcoholism rate in the family history negative group was 5%, while the sons of alcoholics had a 20% risk of becoming alcoholic. The rates did not increase if the subject was raised by an alcoholic adoptive parent.

In summary, the data coming from family, twin, and adoption type studies carried out by different investigators using different methodologies in different countries all consistently point to a probable genetic influence in alcoholism. These studies, however, can not be considered conclusive. It is still possible that *in utero* environment or interactions between the infant and parents during the first six weeks of life explain the familial nature of the disorder. However, the data are impressive enough to justify speculations on how a genetic influence might be mediated.

AN OVERVIEW OF POSSIBLE BIOLOGICAL MEDIATORS

The decision regarding which of the myriad number of potential factors are worthy of investigation must be a practical one based on a balance between those factors which are most likely to be important and those that are the most readily testable. Speculations about the types of factors which must be considered include (but aren't limited to) five general categories, which are modified from a list presented by Omenn [23]. Considering the possibility that alcoholism is a polygenic, multifactorial disorder, the chances of developing alcoholism may be mediated by a combination of these and other factors.

Individuals at high risk for the development of alcoholism might inherit a different *acute response* to doses of alcohol. This could give a more pleasant or intense intoxication with the result that people might seek out alcohol, or, on the other hand, give a lowered level of response to alcohol so that individuals must drink more alcohol in order to get the same "high" as their neighbors. It is also possible that the genetic factors might help protect non-alcoholics from developing significant alcohol related problems through giving an adverse reaction to low doses of ethanol by producing irritability, skin flushing, nausea, etc. [9,37].

The difference between those predisposed and those not predisposed to alcoholism may lie with more *subacute* reactions to the drug. One example could be a differential level of development of tolerance to alcohol in high and low risk individuals leading those with rapid development of tolerance to take more and more of the drug over time. This could be tied to an alteration in vulnerability to physical dependence to ethanol.

Another possibility rests with a differential vulnerability to *chronic* exposure. Here, the individual predisposed towards alcoholism could in fact be carrying a higher risk towards being identified as a case through an enhanced risk for organ damage such as Wernicke-Korsakov's disease or cirrhosis [2]. Another aspect of differential vulnerability to chronic effects of the drug could mediate the time course and severity of physical dependence.

A predisposition towards alcoholism could also be mediated by differences in *metabolism* of alcohol. It may be that metabolism of alcohol, perhaps affected by altered forms of alcohol dehydrogenase (ADH) or aldehyde dehydrogenase (ALDH), could affect the level of intoxication, the length of the drug effects, the manifestations of alcohol on central nervous system neurotransmitters, or the amount of acetaldehyde which develops after exposure to alcohol. Depending on the final level of this toxic substance (ie: acetaldehyde), the altered metabolism could *help* explain why some people don't become alcoholic because their levels of acetaldehyde are quite high and produce adverse reactions. Or, acetaldehyde, if present at lower levels, could change the quality of the intoxication or have no immediate effect but over a long period of time be responsible for differences in organ vulnerability.

Finally, the inherited factors could be mediated by *psychological* parameters. This could include the inheritance of certain personality characteristics which, even in the absence of evidence of an "alcoholic personality," could mediate a higher or lower general propensity towards alcoholism through such factors as general level of anxiety, level of impulsiveness, etc.

This list is not exhaustive and is given to stimulate speculation and to lay the groundwork for the series of studies that we are presently carrying out. It was with these thoughts in mind that we have begun our efforts in prospective studies of alcoholism.

THE PROSPECTIVE INVESTIGATIONS

Once primary alcoholism has been defined and the major research areas outlined, the relevant subject population must be chosen. One approach is to observe people at high risk for the future development of alcoholism, perhaps selecting them based on their family history of this disorder. This obviates the difficulties of interpreting whether a difference noted between a *bona fide* alcoholic and a control reflects the original cause of the alcoholism or was a result of the many years of heavy drinking. Ideally, these would be men (because men have a higher rate of alcoholism than women) in the 21–25 age range (i.e. old enough to drink, young enough to have probably not demonstrated their alcoholism, yet old enough to develop their alcoholism within the next 5 to 15 years), who have one or more primary alcoholic close relatives [35].

This population has been studied in two locales. A questionnaire was sent to a randomly selected sample of young men in this category at the University of Washington in Seattle and the University of California, San Diego. The instrument covered demography, drinking pattern, alcohol problem history (including those items necessary for the diagnosis of alcoholism), personal history of other major psychiatric disorders (especially the antisocial personality and affective disorder to rule out secondary alcoholics), and family history of alcoholism and other psychiatric disorders for first degree family members. All young men meeting the criteria for primary alcoholism were excluded from future testing as they, obviously, could no longer be considered at high risk for the future development of alcoholism and any abnormality in biological reactions could be explained by their past drinking patterns. For the remaining individuals, all those who reported enough alcohol related problems in a first degree relative to justify a label of primary alcoholism were placed in the "high risk" category. For each potentially high risk subject, a matched control was chosen based on demography and alcohol quantity and frequency pattern as defined by Cahalan and Cisin [4] but who had no alcoholic close relatives. The major data of importance rests with the

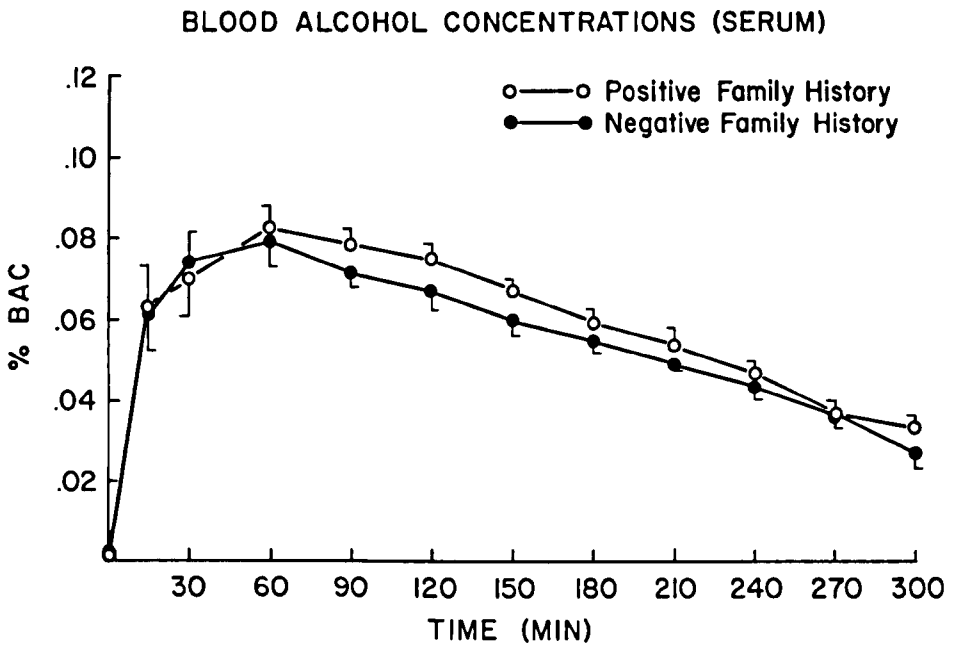

FIG. 2. Serum blood alcohol concentrations over 300 min for family history positive and negative individuals. From Schuckit, M. A., D. Engstrom, R. Albert and J. Duby. Differences in muscle tension between relatives of alcoholics and controls. Submitted for publication.

comparisons between subjects and matched controls when they were brought into the laboratory for testing.

Our next decision was whether we were interested more in drinking going on over a period of time or in the reaction to a single bolus of ethanol. We chose the latter because this would simplify our investigations into the metabolism of alcohol. Each of these steps was somewhat arbitrary but in this first blush approach, it was necessary to recognize that not all questions can be answered.

The basic paradigm, therefore, was to bring subjects into the laboratory at 7:00 a.m. after an overnight fast. Individuals were then attached to a polygraph to measure their physiological responses to acute doses of alcohol including muscle tension and level of facial flushing. These measurements are related to the hypothesis that individuals with a negative family history for alcoholism might show greater adverse effects of low doses of alcohol as a possible protective mechanism against alcoholism. In order to study the metabolism of alcohol, an indwelling venous catheter was inserted so that blood could be drawn every 15 to 30 minutes. The procedure was performed a minimum of half an hour before testing with the requirement that all physiological measures have to return to baseline after the venipuncture before alcohol is given.

At the baseline period just before the administration of alcohol, blood was drawn, baseline polygraph measure were taken, and the subjects were administered a series of paper and pencil tests measuring mood (e.g. the Profile of Mood State or POMS) [21], level of somatic feelings as used by Wolff and Eckman (e.g. subjective feeling of flushing, nausea, hot burning stomach, lightheadedness, etc.) [9,37] and a 43 item scale rating various levels of intoxication as developed by Judd *et al.*—the Subjective High Assessment Scale (SHAS) [18]. Subjects were then administered 0.75 ml of 95% ethanol per kilogram given as a 20% solution in room temperature sugar-free 7-Up—the temperature and carbonated vehicle were chosen to maximize the rate of absorption [29]. Subjects were then monitored with breathylizer readings every 15 minutes and blood was drawn for measurement of blood alcohol and acetaldehyde levels every 30 minutes. The paper and pencil tests were administered every 30 minutes over the subsequent 3 to 5 hours. The experimenters were blind as to whether a subject or a control individual is being tested.

The results from this study can be broken down into two areas:

The Metabolism of Ethanol

The Seattle study revealed significant differences between the "high" risk and "low" risk groups on their metabolism of alcohol [29]. While there were no significant differentials in the blood alcohol level (Fig. 2) family history positive subjects demonstrated significantly higher levels of acetaldehyde at all data points from 15 minutes onward as shown in Fig. 3. This elevation was much lower than that seen in a disulfiram reaction [20]. Interestingly enough, the data included a trend for approximately one-third of the family history positive men to have very high levels of acetaldehyde, one-third to show moderate levels, and one-third to show levels indistinguishable from that of controls.

These results suffered from a number of methodological problems in the processing of the acetaldehyde samples as discussed by Eriksson [10]. When the basic procedure was repeated utilizing subjects in San Diego, blood was immediately deproteinized and thiourea added and fresh samples were analyzed. Results to date on 15 pairs of nonalcoholic young men with alcoholic family histories compared to controls indicate a replication of the significantly increased acetaldehyde levels in the group with positive

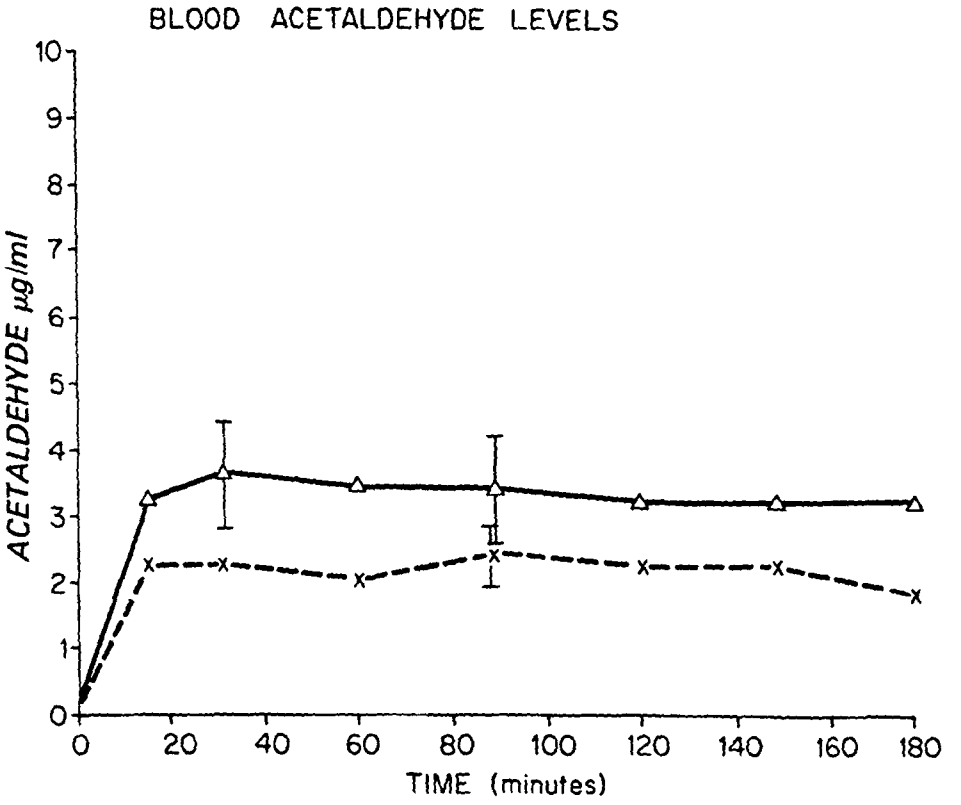

FIG. 3. Acetaldehyde concentrations in micrograms/ml after an ethanol load of 0.75 ml/kg in young men with alcoholic relatives and controls. Reprinted with permission from Schuckit, M. A. and V. Rayses. Ethanol ingestion: differences in blood acetaldehyde concentrations in relatives of alcoholics and controls. *Science* 203: 54–55, 1979. Copyright 1979 by the American Association for the Advancement of Science.

family histories [32]. We are presently attempting to refine the methodology further and apply it to a larger sample.

It is important to note that in both the San Diego and Seattle samples family history positive and negative groups did not differ significantly on the amount of time elapsed until peak blood alcohol concentration (BAC) was reached, the magnitude of the peak BAC, or the rate of disappearance of alcohol from the blood [33]. Thus, the differences in acetaldehyde between subjects and controls do not seem to reflect gross differences in absorption, distribution, or rate of ethanol metabolism.

Investigations are now underway in an attempt to determine the possible mechanisms for the elevated acetaldehyde levels. We are in the process of refining an assay method for isolating and measuring alcohol dehydrogenase (ADH) in the serum. Activity levels for this ADH are close to zero before alcohol administration, peak in the serum shortly after the blood alcohol peaks, and then tend to disappear over the five hour testing period. To date the pH optimum, the effect of thiourea on the reaction, and electrophoretic properties of the ADH do not appear to be different for family history positive and negative individuals. All samples thus far processed (10 pairs of subjects and controls) evidenced that appears to be a normal ADH and one which does not resemble the atypical form outlined by von Wartburg [36].

The elevated acetaldehyde levels, of course, could be related to a difference between family history positive subjects and family history negative controls on the enzyme responsible for the oxidation of acetaldehyde, aldehyde dehydrogenase (ALDH). This possibility is highlighted by the finding that ALDH activity in liver biopsy specimens showed alcoholics to demonstrate reduced enzyme activity [17]. We are presently attempting to isolate aldehyde dehydrogenase from the blood in order to replicate these findings in our subject-control pairs.

At the very least, if replicated, the different levels of acetaldehyde might serve as a biological marker for those individuals with high risk for alcoholism. On the other hand, the elevated acetaldehyde levels could explain a propensity towards alcoholism through the production of higher levels of catecholamine condensation products of the tetrahydroisoquinoline variety (TIQ) which might mediate actual addiction [8], a theory bolstered by the finding of one TIQ, salsolinol, in the urine of alcoholics [5]. Finally, the higher acetaldehyde levels might predispose higher risk individuals towards more organ damage in the presence of alcohol and thus increase their chances of becoming labelled as an alcoholic. The true importance of these findings will await replication and the determination of whether a 5 to 10 year follow-up of these subjects demonstrates that the acetaldehyde levels either alone or in combination with the family histories predict which individuals will in fact become primary alcoholics.

Acute Reactions to Ethanol

Another interesting finding in the Seattle study was the

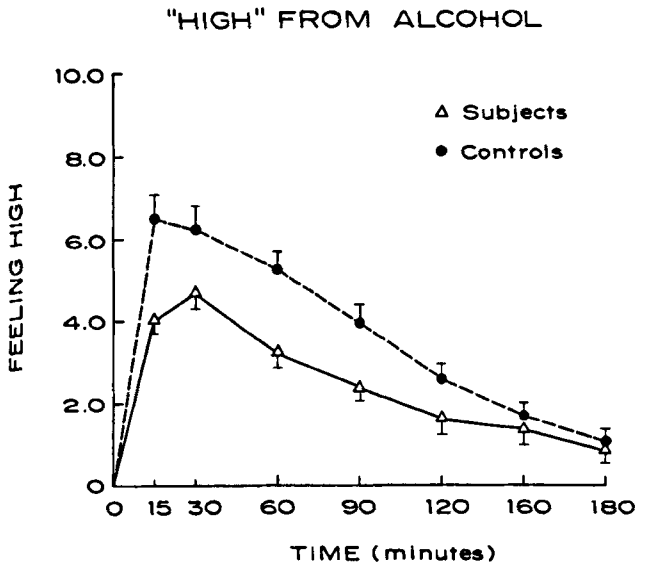

FIG. 4. Subjective levels of intoxication after 0.75 ml of ethanol per kilogram in young men with alcoholic relatives and controls. From [34].

difference between the family history positive groups and the controls on their *subjective* report of intoxication [34]. Despite nonsignificant differences in levels of blood alcohol the "high risk" individuals reported significantly lower levels of subjective intoxication as measured by the SHAS and global ratings. A similar trend was noted in the San Diego study. The majority of items on the SHAS demonstrated that family history positive subjects related a less intense subjective reaction to alcohol on a host of measures when compared to controls as shown in Fig. 4.

We are presently attempting to expand these findings by utilizing more objective measures of the effects of ethanol—recognizing that these may not correlate closely with subjective reports [31]. As part of this paradigm electromyogram (EMG) readings were made using a frontalis electrode placement with silver-silverchloride electrodes applied over Beckman electrode gel. The EMG gave input into a single channel BFS system (Biofeedback System Muscle Action Quantifier). At baseline (before alcohol), 15 min after alcohol intake, 60 min, and every 30 min thereafter readings were taken over a 2 min period (as two discrete one min recordings which were then averaged) while the subjects had their eyes closed and were resting (resting readings), and again while filling out an adjective checklist of their present feeling state (active reading). EMG levels were observed from a digital quantifier displaying results in integrated peak-to-peak microvolts (μV).

At baseline, family history positive and negative subjects did not differ significantly on EMG readings. As can be seen from Fig. 5, the percent change in EMG scores from baseline for subjects and controls during active conditions (while filling out the questionnaire) were quite similar. However, Fig. 6 demonstrates that at rest, controls showed no significant change in EMG scores during rising blood alcohol levels, while family history positive subjects demonstrated a decrease in EMG from baseline at 15 minutes, becoming signif-

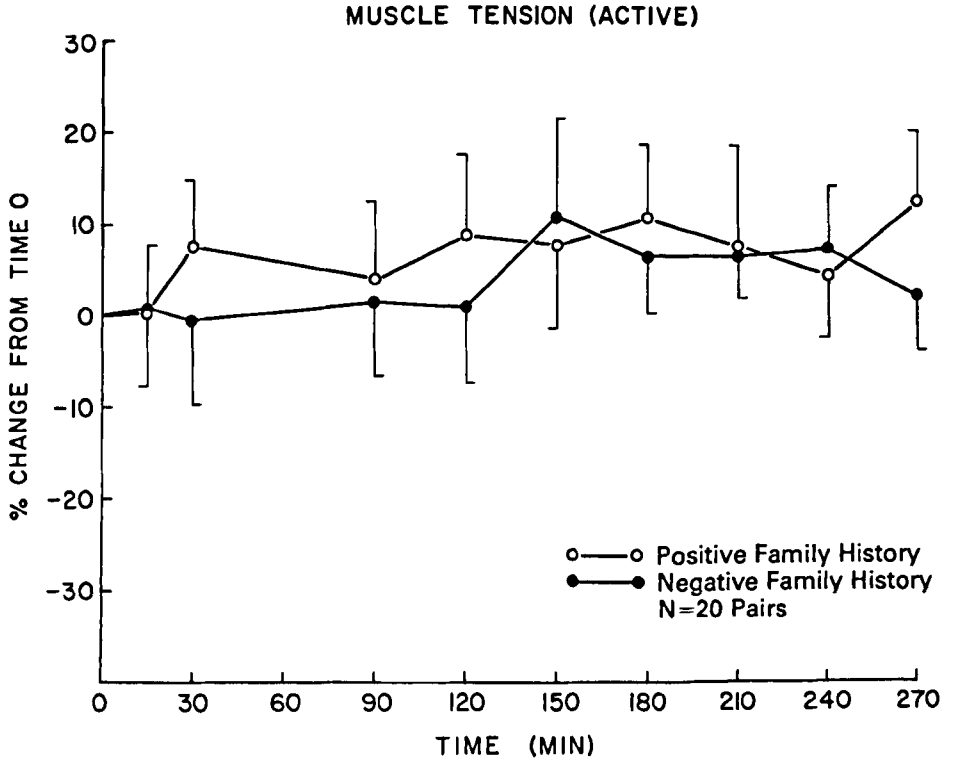

FIG. 5. Percent change from baseline muscle tension scores as measured during a mental task after 0.75 ml of ethanol per kilogram in family history positive and negative young men. From Schuckit, M. S., D. Engstrom, R. Albert and J. Duby. Differences in muscle tension between relatives of alcoholics and controls. Submitted for publication.

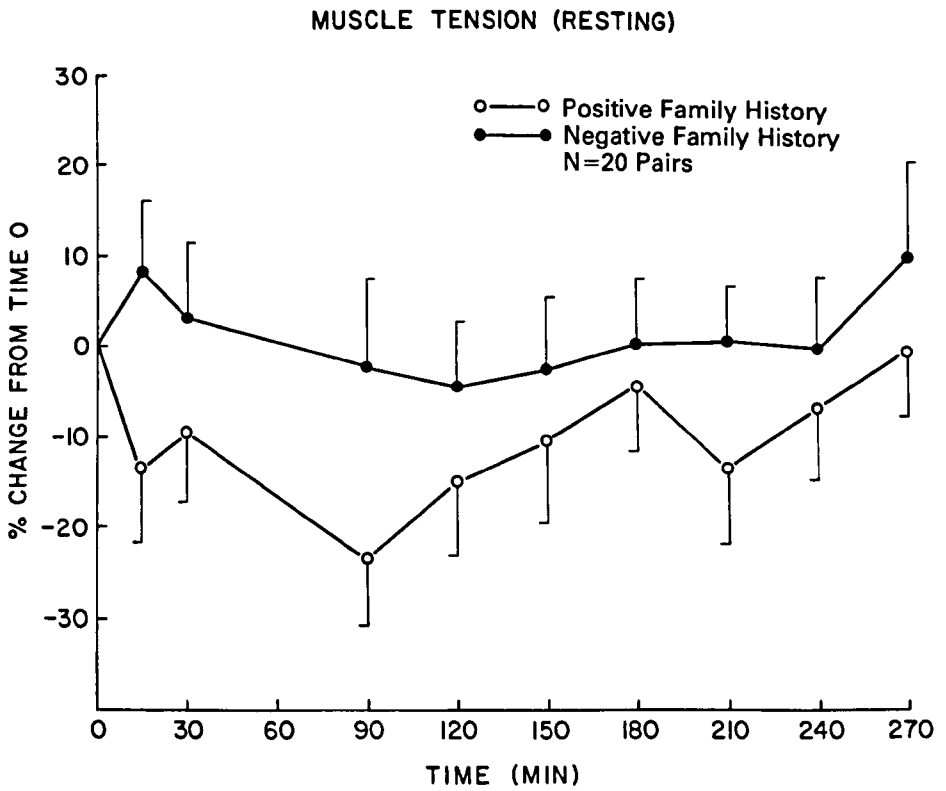

FIG. 6. Percent change from baseline muscle tension scores as measured during resting condition after 0.75 ml of ethanol per kilogram in family history positive and negative young men. From Schuckit, M. S., D. Engstrom, R. Albert and J. Duby. Differences in muscle tension between relatives of alcoholics and controls. Submitted for publication.

icant at 90 minutes ($t=13.42, p<0.002$). Between 90 and 180 minutes family history positive subjects demonstrated a significant increase in EMG scores which then continued to return towards baseline ($t=-2.02, p<0.01$). Looking at between group differences, scores were significantly lower for family history positive subjects than for family history negative controls at 15 minutes ($t=-2.28, p<0.025$). It is not certain whether the differences represent the role of expectancy or the actual effects of ethanol (the former made less likely in light of the fact that subjects and controls were matched on alcohol intake patterns), however the results are consistent with the possibility that an enhanced reaction to alcohol's ability to reduce muscle tensions, or an elevated expectation of such an effect, might be one mechanism responsible for an elevated risk for alcoholism in the relatives of alcoholics.

SUMMARY AND CONCLUSIONS

The best data to date are consistent with the hypothesis that carefully defined primary alcoholism is a genetically influenced disorder. It is probable that multiple genes (each of which might raise or lower an individual's risk for alcoholism) interact with multiple environmental factors (with similar positive and negative effects) to determine whether an individual will demonstrate the disorder.

Based on this premise, we are in the process of carrying out a series of investigations attempting to test a variety of possible biological mediators in young men at elevated risk for the future development of alcoholism. To date we have established the possibility that family history positive young men given alcohol demonstrate a twofold increased level of acetaldehyde than controls using two different samples with blood analyzed by two different methods. However, even though blood samples from family history positive and negative subjects to which alcohol was added and acetaldehyde determined showed no differences, we have yet to prove definitively whether the higher observed acetaldehyde levels were a direct result of enzymatic action in the liver or represents a difference between family history positive and negative individuals in the rate of artifactually produced acetaldehyde in blood samples. At the very least the finding may indicate a "marker" for high risk for alcoholism and at the best may represent one of a variety of possible mechanisms whereby an individual's risk for alcoholism may become heightened. The studies on ADH and ALDH may help to clarify the reasons for the differences.

Both subject samples have also demonstrated a tendency for family history positive young men to report less intoxication after a standard alcohol load. More objective measures of intoxication included a greater reduction in EMG levels at rest for the higher risk individuals when compared to controls.

If these findings are replicated it may be that some individuals have a heightened risk for alcoholism due to greater reinforcing properties of alcohol regarding tension reduction, others through a decreased subjective sensitivity to the drug, and yet others through a greater risk for organ damage or THQ formation as mediated by higher levels of acetal-

dehyde. It is also possible that these factors act in concert where low subjective sensitivity combined with a greater feeling of relaxation makes some people more likely to take higher levels of alcohol which in turn results in even higher acetaldehyde levels than would be expected from controls with all of the resulting chemical changes and organ pathology.

These findings and their interpretations, however, must be considered heuristic. What is most important is not whether the specific factors related here are "real" but that young men at elevated risk for the future development of alcoholism can be compared to adequate controls in attempting to study possible biological mediators of a genetic propensity to this serious disorder.

ACKNOWLEDGEMENT

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REFERENCES

1. Achte, K. Korreloituvatko ABO-veriryhmat ja alkoholismi (Correlation of ABO blood groups with alcoholism). *Duodecim* **74**: 20–25, 1958.
2. Blass, J. P. and G. E. Gibson. Abnormality of a thiamine-requiring enzyme in patients with Wernicke-Korsakoff syndrome. *New Eng. J. Med.* **297**: 1367–1370, 1977.
3. Bohman, M. Some genetic aspects of alcoholism and criminality. *Archs gen. Psychiat.* **35**: 267–276, 1978.
4. Cahalan, D. and I. H. Cisin. American drinking practices: summary of findings from a national probability sample. *Q. Jl Stud. Alcohol* **29**: 130–151, 1968.
5. Collins, M. A., W. P. Nijm, G. F. Borge, G. Teas and C. Goldfarb. Dopamine-related tetrahydroisoquinolines: significant urinary excretion by alcoholics after alcohol consumption. *Science* **206**: 1184–1186, 1979.
6. Cotton, N. S. The familial incidence of alcoholism. *J. Stud. Alcohol* **40**: 89–116, 1979.
7. Cruz-Coke, R. and A. Varela. Inheritance of alcoholism: its association with colour-blindness. *Lancet* December 10: 1282–1284, 1966.
8. Davis, V. E. and M. J. Walsh. Alcohol, amines, and alkaloids: a possible biochemical basis for alcohol addiction. *Science* **167**: 1005–1007, 1970.
9. Ekman, G. Effects of alcohol intake on subjective and objective variables over a five-hour period. *Psychopharmacologia* **4**: 28–38, 1963.
10. Eriksson, C. J. P. Elevated blood acetaldehyde levels in alcoholics and their relatives: a reevaluation. *Science* **207**: 1383–1384, 1980.
11. Ericksson, K. Alcohol imbition and behavior: a comparative genetic approach. In: *Psychopharmacogenetics*, edited by B. E. Eleftheriou. New York: Plenum Press, 1975, pp. 127–168.
12. Fialkow, P. J. and M. C. Thuline. Lack of association between cirrhosis of the liver and the common types of color blindness. *New Engl. J. Med.* **275**: 584–587, 1966.
13. Goodwin, D. and S. D. Guze. *Psychiatric Diagnosis*. New York: Oxford University Press, 1979.
14. Goodwin, D. *Is Alcoholism Hereditary?* New York: Oxford University Press, 1976.
15. Goodwin, D. Is alcoholism hereditary? *Archs gen. Psychiat.* **25**: 545–549, 1971.
16. Hill, S. Y., D. W. Goodwin, R. Cadoret, C. K. Osterland and S. M. Doner. Association and linkage between alcoholism and eleven serological markers. *J. Stud. Alcohol* **36**: 981–992, 1975.
17. Jenkins, W. J. and T. J. Peters. Selectively reduced hepatic ALDH in alcoholics. *Lancet* **1**: 628–629, 1980.
18. Judd, L. L., B. Hubbard, D. S. Janowsky, L. Y. Huey and P. A. Attewell. The effect of lithium carbonate on affect, mood, and personality of normal subjects. *Archs gen. Psychiat.* **34**: 364–351, 1977.
19. Kaij, L. *Studies on the Etiology and Sequels of Abuse of Alcohol*. Department of Psychiatry, University of Lund, 1960.
20. Kitson, T. M. The disulfiram-ethanol reaction. *J. Stud. Alcohol* **38**: 96–113, 1977.
21. McNair, D. M., M. Lorr and L. F. Droppleman. *Profile of Mood States* (Manual). San Diego: Educational and Industrial Testing Service, 1971.
22. Nordmo, S. H. Blood groups in schizophrenia, alcoholism and mental deficiency. *Am. J. Psychiat.* **116**: 460–464, 1959.
23. Omenn, G. S. Alcoholism: a pharmacogenetic disorder. In: *Recent Developments in Genetics and Psychopharmacology*, edited by J. Mendlewicz. Brussels, Basel: Karger, 1975, pp. 12–22.
24. Partanen, J., K. Bruun and T. Markkanon. *Inheritance of Drinking Behavior*. Helsinki: Kekuskirjopoino-Centraltryckeriet, 1966.
25. Peeples, E. E. Taste sensitivity to phenylthiocarbamide in alcoholics. Master's thesis. Stetson University, Deland, Florida, 1962.
26. Robins, L. N. Sturdy childhood predictors of adult antisocial behavior: replications from longitudinal studies. *Psychol. Med.* **8**: 611–622, 1978.
27. Schuckit, M. A. Alcoholism and sociopathy—diagnositc confusion. *Q. Jl Stud. Alcohol* **34**: 157–164, 1973.
28. Schuckit, M. A. Alcoholism and affective disorder: diagnostic confusion. In: *Alcoholism and Affective Disorders*, edited by D. W. Goodwin and C. K. Erickson. New York: Spectrum Press, 1979, pp. 9–19.
29. Schuckit, M. A. and V. Rayses. Ethanol ingestion: differences in blood acetaldehyde concentrations in relatives of alcoholics and controls. *Science* **203**: 54–55, 1979.
30. Schuckit, M. A. *Drug and Alcohol Abuse: A Clinical Guide to Diagnosis and Treatment*. New York: Plenum Press, 1979.
31. Schuckit, M. A. Differences in muscle tension between relatives of alcoholics and controls. Submitted to *J Stud. Alcohol*, 1980.
32. Schuckit, M. A. Response to: Elevated blood acetaldehyde levels in alcoholics and their relatives: a reevaluation. *Science* **207**: 1384, 1980.
33. Schuckit, M. A. Alcohol absorption rate in men at high risk for the future development of alcoholism. *Alcoholism: Clin. Exp. Res.*, 1980, in press.
34. Schuckit, M. A. Self-rating of alcohol intoxication by young men with and without family histories of alcoholism. *J. Stud. Alcohol* **41**: 242–249, 1980.
35. Schuckit, M. A. Alcoholism and genetics: possible biological mediators. *Biol. Psychiat.* **15**: 437–447, 1980.
36. von Wartburg, J. P. The metabolism of alcohol in normals and alcoholics: enzymes. In: *Biology of Alcoholism, Vol. 1*, edited by B. Kissin and H. Begleiter. New York: Plenum Press, 1971, pp. 63–102.
37. Wolff, P. H. Ethnic differences in alcohol sensitivity. *Science* **175**: 449–450, 1972.