THE PATHOGENESIS OF ALCOHOLISM

BIOLOGICAL FACTORS

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TABLE 2. Concordance for Alcoholism in Monozygotic and Dizygotic Twins

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Monozygotic</th>
<th>Dizygotic</th>
<th>Heritability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaij (N = 214 pairs)</td>
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<td></td>
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</tr>
<tr>
<td>Interview</td>
<td>0.76</td>
<td>0.61</td>
<td>0.30</td>
</tr>
<tr>
<td>Register</td>
<td>0.81</td>
<td>0.76</td>
<td>0.24</td>
</tr>
<tr>
<td>Partanen et al. (N = 902 pairs)</td>
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</tr>
<tr>
<td>Density</td>
<td>0.61</td>
<td>0.32</td>
<td>0.58</td>
</tr>
<tr>
<td>Amount</td>
<td>0.38</td>
<td>0.11</td>
<td>0.54</td>
</tr>
<tr>
<td>Lack of control</td>
<td>0.35</td>
<td>0.27</td>
<td>0.16</td>
</tr>
<tr>
<td>Jonsson and Nilson (N = 1500 pairs)</td>
<td>45°</td>
<td>35°</td>
<td>0.16</td>
</tr>
<tr>
<td>Loehlin (N = 850 pairs)</td>
<td>0.56</td>
<td>0.24</td>
<td>0.06°</td>
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</tbody>
</table>

* Figures are pairwise concordances (%)

is probandwise concordance, computed as follows: if two twins both independently enter the case rolls (become probands), the pair is counted once for each proband. This figure will always equal or exceed the pairwise concordance. It can be shown (Smith, 1974) that the probandwise concordance, \( r_{pw} \), or \( r_{pt} \), for a dichotomous character equals the intraclass correlation, \( r_{mc} \) or \( r_{md} \), for the same character. Under restrictive assumptions, the quantity \( 2(r_{mc} - r_{md}) \) can be taken as an estimate of the proportion of phenotypic variance represented by genotypic variance, that is, the heritability \( h^2 \).

The figures in Table 2 represent a collapsed form of Kaij's data. He grouped drinking behavior as reported in interviews into five categories, of which the last two—"heavy abusers" and "chronic alcoholics"—are collapsed and called alcoholic. Kaij also grouped temperance board data into five categories, the last two of which have also been grouped together under alcoholism. Probandwise concordance and heritabilities for these dichotomies are computed and the results appear in the table. Since the dichotomized data are more closely to the concept of alcoholism than do the original categorical measures of drinking behavior, we feel that the revised figures serve the purpose better. They give lower heritabilities than Kaij reports for his five-category scales.

Because Kaij carefully documented the case histories of his twins, one can view the data from the standpoint of primary versus secondary alcoholism. He reported no pairs concordant both for depression and alcoholism, and there is only one pair concordant both for depression and alcoholism, and there is only one pair concordant for antisocial personality and alcoholism. Therefore, it seems unlikely that Kaij's results are due to heritable quering as heritable alcoholism.

In 1966 a Finnish research study conducted in the ec survey of every male same-sex. After considerable searching and agreed to participate in appearance, with serological hundred ninety-eight MZ twins investigated using questionnaires. Questionnaire items with a V first factor corresponded to f Density. The second factor w and fourth factors were dece: was Lack of Control over Dr alcoholism were not made, heritabilities for factor scores exceeds \( r_{tr} \) is evidence that t should be an upper bound to the factor's

Jonsson and Nilson (18 twin pairs in Sweden by mean out questionnaires to 7500 p) inquired about five aspects drinker? (b) with what frequent drinking? (c) what average an (more or less than 15 cl)? (d) consumed? and (e) did into closely related to the conception is lose, and results to (1972) mailed a questionnaire to approximately 850 pa. Merit Scholarship Qualifying to tap alcoholism or even alcohol. Nonetheless, Loehlin analyzed concordance. The one item with concept of alcoholism was "the heritability figures for it are about as consistent with single questionnaire items, content and alcoholism, at adolescents will allow. In ge would support a genetic fact
results are due to heritable depression or antisocial personality masquerading as heritable alcoholism.

In 1966 a Finnish research group (Partanen et al., 1966) summarized a study conducted in the early 1960s. They attempted a systematic survey of every male same-sexed twin pair living in Finland in 1958. After considerable searching, 902 living pairs were actually contacted and agreed to participate in the study. Zygosity was determined by appearance, with serological matching used in case of doubt. One hundred ninety-eight MZ twin pairs and 704 DZ twin pairs were investigated using questionnaire and arrest data. A factor analysis of questionnaire items with a Varimax rotation yielded five factors. The first factor corresponded to frequency of alcohol intake and was called Density. The second factor was Amount Drunk per Occasion, the third and fourth factors were deemed uninterpretable, and the fifth factor was Lack of Control over Drinking. Because diagnostic evaluations for alcoholism were not made, the figures given in Table 2 represent heritabilities for factor scores. The fact that the heritability of Amount exceeds $r_{wz}$ is evidence that twin environments are correlated since $r_{wz}$ should be an upper bound to $h^2$ (Loehlin, 1972).

Jönsson and Nilsson (1968) studied alcohol consumption in 1500 twin pairs in Sweden by means of a questionnaire. They actually mailed out questionnaires to 7500 pairs with a 20 percent return rate. They inquired about five aspects of drinking: (a) was the respondent a drinker? (b) with what frequency did the respondent consume distilled spirits? (c) what average amount of spirits was consumed per occasion (more or less than 15 cl)? (d) were large quantities of alcohol frequently consumed? and (e) did intoxication occur? Question (d) seems most closely related to the concept of alcoholism, although the correspondence is loose, and results for that item are given in Table 2. Loehlin (1972) mailed a questionnaire containing some items mentioning drinking to approximately 850 pairs of adolescent twins taking the National Merit Scholarship Qualifying Test. The questionnaire was not designed to tap alcoholism or even alcohol use but rather personality variables. Nonetheless, Loehlin analyzed 12 items mentioning drinking for concordance. The one item which most closely approximates the Jellinek concept of alcoholism was “I have never used alcohol excessively,” and the heritability figures for it are to be found in Table 2. These results are about as consistent with a genetic hypothesis as unreliability of single questionnaire items, uncertainty of relationship between item content and alcoholism, and the low prevalence of alcoholism in adolescents will allow. In general, the twin studies shown in Table 2 would support a genetic factor in alcoholism.

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<tr>
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<tr>
<td>0.36</td>
<td>0.24</td>
<td>0.06</td>
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Sometimes monozygotic twins are reared apart from an early age. When this occurs, constitution formed up to the time of separation and upbringing after separation are obviously better separated than are heredity and environment in twins reared together. It is interesting in this regard to examine the literature on MZ twins reared apart. Lange (1981), in his study of criminal twins, reported a MZ pair reared apart who were concordant for alcoholism, but both were probably antisocial personalities. Newman et al. (1937) reported 19 MZ twin pairs reared apart; no twin was alcoholic. Shields (1968) found a concordant pair among 12 pairs ascertained. Eckert et al. (1980) reported a pair concordant for heavy drinking and another pair discordant for DSM-III alcohol abuse. This latter pair has a narcoleptic twin who abstains because drinking worsens his symptoms; he may be protected from exposure to the critical stressor.

Given the small numbers of MZ twins reared apart and the preponderance of women (none of whom were alcoholic), at most it can be said that no inexplicably discordant pairs have been reported.

The study of genetically related persons reared apart avoids some of the assumptions required in twin studies. If adoptees are assigned by adoption agencies to environments little correlated with biological backgrounds, then prevalence of alcoholism in adopted offspring of alcoholics offers a strong test for genetic factors in alcoholism.

Adoption Studies

Table 3 shows results for all adoptee cohorts of alcoholics reported to date. Many of these studies are Scandinavian, like the twin studies, because of the excellent adoption and census registers in those countries.

Roe (1945) compared 36 adopted children of heavy drinkers with 25 adopted offspring of normal parents. At followup, she found no significant difference in alcoholism between the groups. These results are difficult to explain. The parents called alcoholic were heavy drinkers with repeated job loss and arrests. The adoptees were assessed with a standardized interview by carefully trained raters. The children were placed at an average age of 5.6 and 2.6 years for alcoholic and nonalcoholic biological background groups respectively, so that the children of alcoholics had spent more time in the biological parents' care. Although many had not passed completely through the age of risk (average age was 30), every adoptee was at least 21 at follow-up. The assessments were apparently nonblind with respect to the biological background of the adoptee, and the results could have been affected by this.

### Table 3. Prevalence of Alcoholism

<table>
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<th>Investigator</th>
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<tbody>
<tr>
<td>Roe (N = 61)</td>
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<tr>
<td>Schuckit et al. (N = 69)</td>
</tr>
<tr>
<td>Goodwin et al. (N = 123 men)</td>
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<td>Goodwin et al. (N = 50 men)</td>
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<td>Goodwin et al. (N = 96 women)</td>
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<td>Goodwin et al. (N = 130 women)</td>
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<tr>
<td>Bohman (N = 812 men)</td>
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<tr>
<td>(N = 107 men)</td>
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<tr>
<td>(N = 199 women)</td>
</tr>
<tr>
<td>Cadoret et al. (N = 92)</td>
</tr>
</tbody>
</table>

* Prevalence in half-sibs of alcoholics or alcoholic parental figure.
| Sons of alcoholic biological fathers. |
| Daughters of alcoholic biological parents |

Schuckit et al. (1972) at the Louis hospital. Probands were sibling who might or might not have alcoholism. The probands share a biological parent but often no common genetic relatives. The first-degree relatives of probands in the first-degree relatives used in diagnosing relatives: 3, clearly support a genetic model in which half-siblings have been raised in a nonalcoholic or foster parent than were offspring of alcoholic or fostered children raised in nonalcoholic or fostered alcoholism, without an alcoholic parent. Modeling theory of transmolecular biological parent.
Genetic Factors in Alcoholism

TABLE 3. Prevalence of Alcoholism in Adopted Relatives of Alcoholics (in percentages)

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Adopted relatives of Alcoholics</th>
<th>Nonadopted relatives of Alcoholics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alcohols</td>
<td>Nonalcohols</td>
</tr>
<tr>
<td>Roe (N = 81)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schuckit et al. (N = 69)</td>
<td>50.0*</td>
<td>6.4</td>
</tr>
<tr>
<td>Goodwin et al. (N = 133 men)</td>
<td>25.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Goodwin et al. (N = 50 men)</td>
<td>25.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Goodwin et al. (N = 96 women)</td>
<td>2.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Goodwin et al. (N = 130 women)</td>
<td>2.0</td>
<td>6.4</td>
</tr>
<tr>
<td>Bohan et al. (N = 812 men)</td>
<td></td>
<td>13.6</td>
</tr>
<tr>
<td>(N = 1071 men)</td>
<td>28.6</td>
<td>15.5</td>
</tr>
<tr>
<td>(N = 1993 women)</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Cadoret et al. (N = 92)</td>
<td>53.3</td>
<td>19.5</td>
</tr>
</tbody>
</table>

* Prevalence in half-sibs of alcoholics raised without alcoholic parental figure, versus those with alcoholic parental figure.
  1 Sons of alcoholic biological fathers.
  2 Daughters of an alcoholic biological mother.

Schuckit et al. (1972) examined 69 primary alcoholics from a St. Louis hospital. Probands were selected because each had a living half-sibling who might or might not have been raised with the proband. Thus, the probands share with their half-siblings a common biological parent but often no common familial environment. Probands and all available first-degree relatives were interviewed with a structured interview establishing the diagnosis of the interviewee and inquiring about illness in first-degree relatives of the proband. The same criteria were used in diagnosing relatives as in probands. The results, shown in Table 3, clearly support a genetic interpretation. Sixty-two percent of the alcoholic half-siblings have one or both biological parents alcoholic, versus only 20 percent in the nonalcoholic half-sibs. Since alcoholic half-siblings were raised no more often with an alcoholic biological parent or foster parent than were the nonalcoholic half-siblings, these differences were apparently not due to modeling by an alcoholic parental figure. When Schuckit and his colleagues controlled for genetic load by examining only half-siblings with an alcoholic biological parent, 45 percent of such children raised with an alcoholic parent figure (biological or foster) became alcoholic, as opposed to 50 percent of those raised without an alcoholic parent figure. This difference goes against a modeling theory of transmission. Among half-siblings raised without an alcoholic biological parent, but with (without) an alcoholic parental
figure, the corresponding figures are 14 per cent (8 percent). The difference is small and nonsignificant.

Goodwin, Schulsinger, and their colleagues used the extensive Danish adoption registers in a series of adoption studies on alcoholism. First, Goodwin, Schulsinger, Hermansen, Guze, and Winokur (1973) selected all male adoptees with at least one biological parent hospitalized for alcoholism who were placed in the first six weeks of life with no further contact with biological relatives. To each such adoptee a control was matched for age, sex, and age of placement, whose parents had never been psychiatrically hospitalized. Another matched control was found, at least one of whose parents had been hospitalized, but for something other than alcoholism or schizophrenia. These two control groups finally were pooled. Fifty-five probands and 50 controls were then interviewed with a blind structured interview lasting several hours. Law enforcement records were also searched for information about drinking among the subjects. Alcoholism was diagnosed if heavy drinking occurred with three of the following four symptom groups: (a) trouble with friends or family; (b) job or legal trouble; (c) physical symptoms; or (d) loss of control. The results from Table 3 show the expected excess of alcoholism in those adoptees with a positive biological background for alcoholism.

Goodwin et al. (1974) then compared a subset of brothers who shared an alcoholic biological parent, one being adopted while the others were not. Twenty adoptees and 30 nonadopted brothers were studied. They found approximately the same rate of alcoholism in adopted and nonadopted sons of alcoholics (Table 3).

Goodwin et al. (1977a) next repeated their work with daughters of alcoholics. Using the same selection and assessment procedures as with adopted men, they examined 49 adopted daughters of alcoholics and 47 adopted daughters of normal parents. This time the result did not generalize. This may be because the total amount of alcoholism found was small, making comparison difficult, or it may represent the state of nature. This might imply that the transmission of alcoholism in women is familial but not genetic. Goodwin et al. (1977b) studied sisters who shared an alcoholic biological parent and of whom one was adopted while the others were not. The results are given in Table 3 for completeness. The numbers examined, only 49 adopted and 81 nonadopted daughters, leads to such small numbers of alcoholics (one vs. two) that no conclusions of any kind can be drawn.

Collectively, the studies of Goodwin, Schulsinger, and their colleagues represent a major step forward in unraveling the etiology of alcoholism. Their results for men indicate that alcoholism often "breeds true" even after the interposition of adoption. The results for women indicate that alcoholism is not transmitted through a genetic line.

Bohman (1978) studied a sample of 723 adopted and 723 not adopted men. He found that the men of the adoptive group showed a higher rate of alcoholism than those of the nonadopted group. The results, shown in Table 3, indicate that adopted men are at greater risk for alcoholism than nonadopted men. The results also show that adopted women are at greater risk for alcoholism than nonadopted women. The results of these studies are consistent with the hypothesis that alcoholism is transmitted by a genetic factor.
are 14 percent (8 percent). The sir colleagues used the extensive adoption studies on alcoholism, nsen, Guze, and Winokur (1973) one biological parent hospitalized the first six weeks of life with no es. To each such adoptee a control of placement, whose parents had ed. Another matched control was ts had been hospitalized, but for schizophrenia. These two control e probands and 50 controls were red interview lasting several hours.

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dwin, Schulinger, and their col- ar in unraveling the etiology of icate that alcoholism often "breeds true" even after the interposition of surrogate parents, and that the risk of alcoholism is about the same whether the high-risk child is raised with an alcoholic or not.

Bolman (1978) studied all adoptees born in Sweden between 1930 and 1949. Because he studied only offspring of alcoholic, noncriminal parents, secondary alcoholism among his adoptees is much reduced relative to other studies. He found 89 adopted sons of primary alcoholics and 723 adopted sons of nonalcoholic, noncriminal fathers. He also studied 42 adopted sons of alcoholic noncriminal mothers and 1029 adopted sons of nonalcoholic noncriminal mothers. Last, he examined records of 197 adopted daughters of alcoholic noncriminal parents. The results, shown in Table 3, are clear-cut. They follow the pattern of the Goodwin and Schulinger studies in which the effect of having an alcoholic parent shows up to the sons but cannot be discerned in the daughters. However, the number of daughters in the Bolman study does not leave much room for complaint of small sample size. There seems to be no excess of alcoholism in the adopted-away daughters of alcoholics.

Bolman conducted a control study to rule out possibilities that age of placement or social status of placement for example, might account for the excess of alcoholism in offspring of alcoholics. He selected 50 sons and 50 daughters of the severest alcoholic fathers and 42 sons and 50 daughters of alcoholic mothers. He selected for each of these probands a control, matched for sex, age, age at placement, occupation of adoptive parents, and ages of biological and adoptive parents at birth of the adoptee. The match was successful in every respect except that probands' children were placed three months later than controls.

The results are qualitatively identical to those derived from the entire population of adoptees. The males show transmission of alcoholism down the genetic line but the females do not. In the latter case, 3 percent of women with alcoholic parents were alcoholic, which is identical to the prevalence in daughters with nonalcoholic, noncriminal parents.

Cadoret et al. (1980) recently reported on a series of Iowa adoptees. Ninety-two men adopted at birth and their parents were to be interviewed, and blind interviews of 87 adoptive parental pairs and 60 adoptees were obtained. Adoptees were divided into those with a positive first- or second-degree relative with alcoholism (N = 15), and those without such a background (N = 77). For each adopted child of an alcoholic, there was a control adoptee matched on age, sex, time spent in foster care, and age of biological mother at the birth of the child. Diagnoses of relatives were based on adoption agency records of
interviews with the biological mother and her parents and on information obtained from other social agencies. Medical, psychiatric, and prison records were obtained whenever possible for the adoptees. Diagnoses of the adoptees in adulthood (all were 18 or older) were based on the interviews with the adoptee and/or his adoptive parents. St. Louis group diagnostic criteria were applied blindly with respect to the biological background of the adoptee.

Table 3 gives the essential result. (These figures were not published in the original report and are provided here.) As in the Goodwin and Schulzinger and the Bohman studies, there does seem to be transmission down the biological line. A logistic regression analysis predicting adoptee alcoholism by biological and environmental background variables was computed. Results showed that having a first-degree relative (parent or sibling) or second-degree relative (mainly grandparent) alcoholic predicted adult alcoholism in the adoptees. The finding that alcoholism in second-degree relatives predicted adoptee alcoholism is particularly striking. Environmental variables added no predictability over that afforded by knowledge of biological background. In particular, and in agreement with the results of Goodwin and Schulzinger, having an alcoholic adoptive relative in the home did not increase the risk of alcoholism in the adoptee, either among those with a positive alcoholic biological background or among those without such a background.

Taken together, the adoption studies and the twin studies constitute practically irrefutable evidence of a genetic factor predisposing to alcoholism. However, several cautions are appropriate. First, the situation is not at all clear for the daughters of alcoholics. It seems likely that the transmission of alcoholism in women is different from the process in men. Second, the relationships between parental and filial status are not so clearcut as to invite a simple Mendelian explanation, that is, a single dominant gene which always leads to alcoholism. This shows up, too, in the twin studies, where the concordance rate among MZ twins is nowhere near 100 percent. Third, children having nonalcoholic parents seem to have a slightly (though nonsignificantly) higher risk for alcoholism when exposed to an alcoholic surrogate parent than when not so exposed (Schuckit et al., 1972). Succinctly put, there is a lot of unexplained alcoholism left.

Attempts have been made to apply biological characteristics of known genetic origin to map the transmitted alcoholism-predisposing factor onto the genome. Collectively, these are called association and linkage studies. It seems that, having established that something is transmitted genetically to some alcoholics, such analyses might clarify what is transmitted.

Association and Linkage

Cruz-Coke and his colleagues; number of reports favoring alcoholism. An X-linked recessive alcoholism allele should be 1 to 2 alkoholgen allele. First, Cruz; high proportion of cirrhosis the Ishihara plates detected on 400 male and 400 and 12 women had cirrhosis eight percent of cirrhotic men color-blind. These figures confirm cirrhotic men and women a replication with 450 patient (H-R-R) plates. These tests are in detail in Kalmus, 1965. It Laennec's portal type, which et al. (1966) studied 24 males with the H-R them after their acute cirrhosis since color vision pigments chiefly in liver, the defects fact found that 78 percent o normal at second testing. Th (1964, 1965). Since all of their study also fails to replicate an increase of color defect.

Until this time, no one has measured color blindness alcoholism. However, the association would be consistent with the vision defects of vision defects (protonymically) caused by genes of alcoholism were transmitted vision loci. Then such an attempt to be transmitted to advanced this theory as an unreported new data on familial defect in fathers was highly.

However, that color bin
and her parents and on infancies. Medical, psychiatric, and ever possible for the adoptees. e (all were 18 or older) were tee and/or his adoptive parents. e applied blindly with respect to cee.

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Association and Linkage Studies

Cruz-Coke and his colleagues in Santiago, Chile have published a number of reports favoring an X-linked recessive gene mechanism for alcoholism. An X-linked recessive gene would explain the much lower rate of alcoholism in women, since the proportion of men to women affected should be as g^2 where g is the gene frequency of the alcohogenic allele. First, Cruz-Coke (1964) reported that an inordinately high proportion of cirrhotics were color-blind (type unspecified), using the Ishihara plates to detect defective color vision. His results were based on 400 male and 400 female hospital patients, of whom 58 men and 12 women had cirrhosis of the liver (type unspecified). Twenty-eight percent of cirrhotic men and 33 percent of cirrhotic women were color-blind. These figures compared with 6 percent and 2 percent in noncirrhotic men and women, respectively. Cruz-Coke (1965) reported a replication with 450 patients of each sex using the Harry-Rand-Ritter (H-R-R) plates. These tests and all others to be mentioned are discussed in detail in Kalmus, 1965). In the latter study, the cirrhotics were of the Laennec's portal type, which occurs predominantly in alcoholics. Fialkow et al. (1966) studied 24 male and 22 female Laennec's cirrhotics, tested them initially with the H-R-R and Ishihara plates and then retested them after their acute cirrhotic symptoms had subsided. Reasoning that since color vision pigments are synthesized using an enzyme found chiefly in liver, the defect would disappear on reexamination, they in fact found that 78 percent of all retested color anomalous patients were normal at second testing. They therefore could not replicate Cruz-Coke (1964, 1965). Since all of the Fialkow et al. patients were alcoholics, their study also fails to replicate Cruz-Coke and Varela's (1965) finding of an increase of color defects in 100 male alcoholics.

Until this time, no one had actually suggested that the association between color blindness and alcoholism indicated X-linkage for alcoholism. However, the association, if not simply a sequel of liver damage, would be consistent with linkage because all three varieties of color vision defects (protanomaly, deutanomaly, tritanomaly) are most frequently caused by genes on the X chromosome (Kalmus, 1965). If alcoholism were transmitted as a sex-linked recessive near the color vision loci, then such an association once established in a parent would tend to be transmitted to progeny. Cruz-Coke and Varela (1966) advanced this theory as an explanation for the association. They also reported new data on families of 20 alcoholics, in which a color vision defect in fathers was highly correlated with defects in daughters.

However, that color blindness is transmitted in a sex-linked fashion
is well known. In order to establish that alcoholism is transmitted as a sex-linked recessive near the color vision loci, it is necessary to do two things. First, pedigrees must be provided showing the proper proportions of father–son, father–daughter, mother–son, and mother–daughter transmission of alcoholism consistent with a particular genetic hypothesis. Second, either extended pedigrees (several generations) or large sibships which are informative for linkage (in that one knows from which parent transmission of each character occurred) must be examined and must show a much greater than chance association between affectational status and the marker allele. In all succeeding reports (Mardones, 1972; Reid et al., 1968; Sassoon et al., 1970; Smith, 1972; Swinson, 1972; Thulin, 1972; Varela et al., 1969), not one pedigree or sibship suggesting linked loci has been published. The available evidence is as consistent with a pleiotropic effect of a cirrhosis-predisposing gene as it is with X-linkage for alcoholism. Moreover, the type of color blindness reported here has shifted from protanomaly and deutanomaly to tritanomaly (detected with the Farnsworth-Munsell 100-Hue Test), suggesting inconsistent findings among even the Chilean studies.

Other investigators have studied serological markers in alcoholism. Nordmoe (1959) classified 5637 Colorado State Hospital patients for ABO and Rh and found an excess of blood group A in 939 alcoholics (p < .004). This relationship held for both sexes. The basis of the diagnosis of nonalcoholics and the actual percent of type A alcoholics and nonalcoholics are not given.

Camps and Dodd (1967) reported an increase of nonsecretors of ABH blood group substances in saliva among alcoholics. Three hundred eighteen alcoholic patients and 323 randomly chosen individuals were tested. Thirty-two percent of alcoholics and 23 percent of controls were nonsecretors. The tendency not to secrete was considerably stronger among blood type A than among blood type O alcoholics. Camps et al. (1969) noted, however, that this did not lead to an excess of alcoholics with blood type A as one would expect. Camps (1972) interpreted this as indicating that alcohol abuse affects secretion of blood group substances and that the original finding was therefore unrelated to linkage.

In 1975 Hill et al. reported on 35 families containing 48 alcoholics and 46 nonalcoholics. Diagnoses were based on a structured interview and St. Louis group criteria. The sib pair method of Penrose (1953) was used to detect linkage in the sibships. The D gene of the Rh system was described as significantly linked in repulsion to alcoholism, but the relationship was not especially strong. But this interpretation of the data was probably not appropriately made from the contingency tables available. Moreover, the Penrose method counts all possible sib pairs from a sibship as independent. This assumption is incorrect. Findings of this study indicate with nonalcoholism and with alcoholism, did not survive. To our knowledge, this finding has been reported.

Winokur (1973) has posited bipolar depression, one of probands as alcoholism. If this is correct, some primary affective depression spectrum method to detect nonalcoholism in bipolar disease and between haptoglobin C and <.005) in 14 sibships. With many other investigators and

On the whole, the association sensitive to methadone studies as have the other six find a sizeable subgroup of a would be a major step forward even when not uniformly in direction for future research have a heritable predisposition even for the observed correlation in the review.

Models of Transmission

Two models for the trigenic recessive gene and the multi-locus evidence for X-linked reviewed. Sex differences in been reported for Santiago, 83 percent of men and 0.7 percent of women. A sample (N = 1976) alcoholic (1966) model requires alcohol per year, because alcoholics of increase seems very high could be expected to hold o
alcoholism is transmitted as a single gene, it is necessary to do two things: showing the proper proportion of son, and mother—daughter with a particular genetic hypothesis (several generations) or large kage (in that one knows from actual occurrence) must be examined again chance association between these. In all succeeding reports 

ssoon et al., 1970; Smith, 1972; et al., 1969), not one pedigree or published. The available evidence of a cirrhosis-predisposing gene. Moreover, the type of color in protanomaly and deutanomaly (Munsell 100-Hue Test), even the Chilean studies.

zological markers in alcoholism. Ado State Hospital patients for blood group A in 939 alcoholics or both sexes. The basis of the percent of type A alcoholics and 

1 an increase of nonsecretors of among alcoholics. Three hundred randomly chosen individuals were and 23 percent of controls were secre was considerably stronger of type O alcoholics. Camps et al. 

to lead to an excess of alcoholics. Camps (1972) interpreted this secretion of blood group sub 

as therefore unrelated to linkage. families containing 48 alcoholics 

based on a structured interview 

air method of Penrose (1953) was The D gene of the Rh system was repulsion to alcoholism, but the g. But this interpretation of the data from the contingency tables, though counts all possible sib pairs from a sibship as independent when calculating the significance test; this assumption is incorrect, biasing the test in unknown ways. Other findings of this study indicating an association of the r homozygote with nonalcoholism and of the third component of comple ment, C3, with alcoholism, did not survive an attempted replication by Winokur et al. (1976). To our knowledge, no attempt to replicate the Rh linkage finding has been reported.

Winokur (1973) has posited the existence of three types of primary unipolar depression, one of them appearing in relatives of depressed probands as alcoholism. If his concept of “depression spectrum disease” is correct, some primary alcoholism might be the manifestation of a depression spectrum genotype. Tanna et al. (1977) used the sib pair method to detect linkage between C3 (p < .01) and depression spectrum disease and between haptoglobin and depression spectrum disease (p < .005) in 14 sibships. Winokur’s conception has not been adopted by many other investigators and awaits further validation.

On the whole, the association and linkage studies have not been as insensitive to methodological variations and to changes in population studied as have the other studies reviewed here. On the other hand, to find a sizeable subgroup of alcoholics with clear Mendelian transmission would be a major step forward, and these investigations are important even when not uniformly successful. Linkage studies point out a logical direction for future research. Since it is established that some alcoholics have a heritable predisposition, to perform more studies (at least on men) demonstrating the role of unspecified genetic factors is not especially helpful. Instead, consideration of models which might account for the observed correlations is in order. These will be examined later in the review.

Models of Transmission

Two models for the transmission of alcoholism are the X-linked recessive gene and the multifactorial or diathesis-stress model. Some of the evidence for X-linked recessive transmission has already been reviewed. Sex differences in prevalence according to the ratio g:g2 have been reported for Santiago, Chile by Marconi et al. (1955), who found 8.3 percent of men and 0.7 percent of women in a general population sample (N = 1976) alcoholic. Unfortunately, the Cruz-Coke and Varela (1966) model requires alcoholism in men to be increasing by 1 percent per year, because alcoholic men have a fertility disadvantage. This rate of increase seems very high, and it is doubtful that this mechanism could be expected to hold outside Chile.
Winokur (1967) pointed out that the Amark data do not support X-linked recessive transmission because the proportion of affected brothers of alcoholic men is only about 20 percent, which does not approach the 50 percent predicted by this model. As a matter of fact, no one has reported 50 percent affected brothers of alcoholic probands.

Spalt (1979) reported a proband series seen at Washington University (N = 154). These were consecutively evaluated patients. He found 44.7 percent of men and 15 percent of women alcoholic according to St. Louis group criteria. The incidence in women is approximately the square of that in men. Family histories suggested more alcoholic maternal grandfathers of male alcoholics than of female alcoholics. These findings are in line with expectation on an X-linked recessive model. However, the number of histories gathered (N = 37) and the extreme difficulty of ascertaining grandparents from their descendants makes one cautious in interpreting these results. Moreover, psychiatric outpatients are not a random population sample for estimating sex differences in prevalence, since female alcoholics probably are less often treated than males (Gomberg, 1976).

Kaj and Dock (1975) directly tested sex-linked transmission by examining grandchildren of alcoholics in the Malmö, Sweden area temperance register. Seventy-five men born from 1870 to 1887 were chosen from the register, and all grandchildren in the population register were ascertained through the temperance register. X-linked transmission requires that the sons of the daughters of a male alcoholic be at higher risk than the sons of his sons. The point prevalence in 1973 for sons of sons was 20.6 percent versus 17.9 percent among sons of daughters, which goes against the hypothesis. Of course, brothers in sibships are not independent observations, and it is desirable to examine the data by sibships. When sibships which have at least one registered male member are counted, the proportion among sons with sons was 22.2 percent versus 26.2 percent for daughters with sons. This difference is not significant.

The presence of assortative mating between alcoholics complicates transmission studies. The proportion of alcoholic offspring in a sample of families ascertained through just one affected parent will be higher under assortative mating than under random mating. The exact incidence depends on the extent of assortative mating and on the phenotype distribution in the heterozygote. Correcting the X-linked recessive model for assortative mating is complicated and to our knowledge has never been attempted for alcoholism.

Although sex-linked recessive transmission may not hold generally, multifactorial transmission theory attempts to explain sex differences in rates of alcoholism in a w nongenetic factors. The multi disease state but a liability to (Falconer, 1965). Customarily distributed and may compricences. Every person whose parent was a patient of a transmission liability distribution for relat for the general population, s the threshold. Quantitative correlation between selected population prevalence and the threshold. Quantitative correlation between selected population prevalence and the threshold. The correlation coefficient is based on a sex-different multifactorial model. There are women such that if any pē person falls ill. Conceptual between male relative and proband, male relative and f i female proband. The st tetrachoric correlation between parent-transmitter pair. Hypot sometimes is translated into tually distinct parameters. (prevalence in men), K_m^p (p threshold in men, m (threshold in women), and r_mf, r_fm, and r_f. The first second the relative's. Seve distinguished. One of these particularly interesting because tending) factors in alcoholism in both men and women. All differential stress and opp the rearing environment. It

Clearly, this model is uncor if most of familial influence More as an illustration:
The Amark data do not support the proportion of affected at 20 percent, which does not his model. As a matter of fact, brothers of alcoholic probands, enes seen at Washington Univerly evaluated patients. He number of women alcoholic according in women is approximately ories suggested more alcoholic less than of female alcoholics. nation on an X-linked recessive ries gathered (N = 37) and the parents from their descendents se results. Moreover, psychiatric sample for estimating sex alcoholics probably are less often
d sex-linked transmission by s in the Malmo, Sweden area born from 1870 to 1887 were andchildren in the population temperance register. X-linked he daughters of a male alcoholic sons. The point prevalence in versus 17.9 percent among sons s of course, brothers in ons, and it is desirable to examine nch have at least one registered rion among sons with sons was laughters with sons. This differ-
g between alcoholics complications of alcoholic offspring in a sample e affected parent will be higher random mating. The exact in
cise mating and on the phenotype recting the X-linked recessive ated and to our knowledge has
mission may not hold generally, mpts to explain sex differences
in rates of alcoholism in a way that takes account of both genetic and nongenetic factors. The multifactorial model assumes that it is not the disease state but a liability to develop the disease which is transmitted (Falconer, 1965). Customary, this liability is assumed to be normally distributed and may comprise both genetic and familial cultural influences. Every person whose liability exceeds a threshold value falls ill. The presence of transmitted factors is indicated if the mean of the liability distribution for relatives of affected individuals lies above that for the general population, so that more relatives of probands lie above the threshold. Quantitative methods may be used to estimate the correlation between selected classes of relatives in liability, given the population prevalence and the prevalence in probands' relatives. Reich et al. (1973) estimated the correlation in liability for alcoholism at .38.

Cloninger et al. (1978) discuss a model for alcoholism that directly incorporates a sex-difference parameter. They consider the following multifactorial model. There is one threshold for men and another for women such that if any person's liability exceeds the threshold, that person falls ill. Conceptually, transmission can occur in four ways: between male relative and male proband, female relative and male proband, male relative and female proband, or between female relative and female proband. The strength of transmission is measured by the tetrachoric correlation between liabilities of members of the transmitter-transmitter pair. Hypotheses about the nature of transmission can sometimes be translated into predictions about the identity of conceptually distinct parameters. The full model has six parameters: $K_{pm}$ (prevalence in men), $K_{mf}$ (prevalence in women), which are determined by $T_m$ (threshold in men, in standard deviations from the mean) and $T_f$ (threshold in women), and the four correlations for transmission $r_{mnm}$, $r_{mfn}$, $r_{fmm}$, and $r_{ffm}$. The first subscript indicates the proband's sex, the second the relative's. Several special multifactorial models may be distinguished. One of these models, the environmental model, is particularly interesting because it specifies that the familial (genetic and rearing) factors in alcoholism are identical in kind and importance in both men and women. All sex differences in prevalence are due to differential stress and opportunities to become alcoholic after leaving the rearing environment. In that case

$$t_{mf} = r_{pm} \left(\frac{r_{mnm} + r_{ffm}}{2}\right)$$

Clearly, this model is uncomplicated from a geneticist's point of view, if most of familial influence is genetic.

More as an illustration of method than as asserted hypothesis,
Cloninger et al. (1978) tested goodness of fit of three multifactorial models to the Pitts and Winokur data. Parameters were estimated by minimum chi-square. There was distinctly better fit to the environmental model than to the other models examined.

If these results are replicable and general, then it seems one can give an account of the sex differences in alcoholism. Women inherit just as great a tendency to alcoholism as do men, and in the same way. Genetic factors are augmented by same-sexed cultural transmission (modeling). The interaction of genes and environment create a diathesis of about equal magnitude in men and women. However, men are exposed to more opportunities and pressures to drink heavily than are women. Heavier exposure to alcohol over time then leads to alcoholism. This view is supported by findings by Robins, who reported that of those who drink heavily, a like proportion of men and women become alcoholic (Robins et al., 1962).

Of course, the hypothesis cannot be accepted on the strength of present evidence alone. The sample of alcoholics used in Pitts and Winokur (1956) may not represent the universe of primary alcoholics to which one would like to generalize. Female alcoholics may have a smaller likelihood of becoming probands (ascertainment bias). Uninterviewed relatives may not have the same risk of alcoholism as interviewed relatives. Unreliable diagnostic procedures for detecting nonalcoholism radically bias prevalence estimates and therefore bias the calculations for the multifactorial model (Shrout and Fleiss, 1980).

However, the most serious problem with the method is that when applied to intact families it cannot separate genetic from environmental models of transmission; Cloninger et al. (1978) make this clear. It would seem that these methods could profitably be applied to nonintact families, for example, adoptees. Presumably a suitably chosen sample of adoptees has familial cultural factors approximately uncorrelated with genetic background, and the estimated correlations should take on different values according to different genetic models. Sex-linked transmission at a single major locus should generate correlations differing from those for polygenic transmission.

The multifactorial model can be modified to take account of assortative mating (Rice et al., 1978), and this may be a distinct aid to future research on transmission.

What Is Transmitted Genetically to Account for Development of Alcoholism

Many hypotheses have been proposed for genetic factors operating in the individual to cause alcoholism. In a recent review of etiological

Genetic Factors in Alcoholism

...
of fit of three multifactorial parameters were estimated by a better fit to the environmental general, then it seems one can in alcoholism. Women inherit do men, and in the same way, sex-sees cultural transmission environment create a diathesis in men. However, men are sure to drink heavily than are r time then leads to alcoholism. Robins, who reported that of en of men and women become accepted on the strength of alcoholics used in Pitts and universe of primary alcoholics Female alcoholics may have a s (ascertainment bias). Uninterest of alcoholism as interviewed for detecting nonalcoholism therefore bias the calculations (Fleiss, 1980).

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Account for Development

sed for genetic factors operating in a recent review of etiological genetic factors in alcoholism, Goodwin (1979) suggested several innate variations in alcohol response which could predispose to alcohol intake or avoidance of alcohol. Some of these factors are (1) adverse reactions to alcohol including cutaneous flushing to alcohol, which has been described in Japanese subjects and which could lead to physiological intolerance of alcohol; (2) innate factors which allow large quantities of alcohol to be ingested, a lack of intolerance; (3) innate differences in the way alcohol affects the psyche, leading to more euphoria or other potentially positive reinforcing of drinking behavior. Obviously there are many possible physiological mechanisms (under genetic control) which could be described under headings above. The flushing response described in the Japanese appears to be primarily under genetic control rather than a product of dietary or cultural differences (Seto et al., 1978). However, it is not clear that flushing is necessarily a factor which "protects" against the development of alcoholism.

Recent work by Schuckit and Raynes (1979) has shown a possible familial factor in the metabolism of alcohol. Nonalcoholic male relatives of alcoholics were found to produce higher levels of blood acetaldehyde to a standard oral dose of alcohol when compared to an age- and sex-matched control group. Such a difference could represent a genetic factor, although how it could act as a factor in the development of alcoholism is not at all clear. Although it is obvious that many metabolic or physiological processes associated with alcohol are under genetic control, it will be difficult to determine which of them is etiologically involved in alcoholism.

Another possible genetic etiological factor in alcoholism is that of personality. We have already mentioned the association of significant alcoholism with antisocial personality. A recent review of the concept of the alcoholic personality (Barnes, 1979) has reported evidence for a prealcoholic personality as distinct from the type of personality traits found in alcoholics who present themselves for treatment. Individuals who later became alcoholic were more likely to be impulsive, nonconforming, and gregarious, as well as more undercontrolled and rebellious when compared to controls. Several European authors have found higher incidence of psychopathy in alcoholic individuals (only some of these personality disorder individuals would be called antisocial in our current nomenclature) (Amare, 1951; Bleuler, 1955a). In the Amare study, traits of anxiety, uneasiness, and depression characterized those psychopaths who suffered from alcoholism.

Deviant personality traits antecedent to alcoholism have been reported from two adoption studies which were positive for transmission of alcoholism. Goodwin et al. (1975) reported that childhood hyperactivity, shyness, school truancy, hot temper, disobedience, and aggressiveness
occurred at higher incidence in their 14 adopted alcoholics. Cadoret and Gath (1978) reported a higher incidence of childhood and adolescent conduct disorder in adoptees who as adults were alcoholic (but were not antisocial personalities as adults).

Some of the personality traits described above have been reported to have a genetic factor: childhood hyperactivity in adoption studies (Cunningham et al., 1975; Cadoret and Gath, 1980); shyness and social insecurity in separated twin studies (Shields, 1973); and several deviant childhood temperament types in adoptees (Cadoret et al., 1975).

On the basis of these reported associations between biological background, childhood and adolescent behavior, and adult alcoholism, we would predict that personality variables (other than antisocial) may be potent factors in the etiology of alcoholism.

ACKNOWLEDGMENTS

The authors wish to acknowledge the assistance provided by Dr. Thomas Bouchard, Ms. Colleen Cain, and Dr. Norman Garmezy in the conception and completion of this review.

REFERENCES


adopted alcoholics. Cadoret et al. (1970) and Cadoret et al. (1980) have been reported to have been reactivity in adoption studies (cadaret et al., 1980); shyness and social development (cadaret et al., 1973); and several deviations (cadaret et al., 1975).

The associations between biological shyness and adult alcoholism (other than antisocial) may be a possible source of this association.


CHAPTER 3
Acute Pharmacology on the Central Nervous System

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INTRODUCTION

The mechanisms by which the nervous system are both the site of evidence and, however, suggest effects of this chemical on membrane (Hunt, 1975). There is a depression of the
CHAPTER 2

Genetic Factors in Alcoholism

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and

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Alcohol abuse and alcohol dependence, as defined in the new Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-III; American Psychiatric Association, 1980) is a common disorder when compared to the major psychoses. The lifetime prevalence in the United States of the former disorders, traditionally grouped under the rubric “alcoholism,” is estimated to lie between 5 and 15 percent for men and 1 and 5 percent for women (Cahalan, 1970). Work on genetic factors in alcoholism proceeded in Europe during the 1930s, but it was not until the 1950s that such research began in earnest in the United States, followed by many studies in the last two decades.

This chapter reviews research on genetic factors in the etiology of
alcoholism. The review covers studies establishing the familial nature of alcoholism, studies attempting to separate genetic from nongenetic factors, and studies examining possible modes of transmission of alcoholism or of predispositions to it.

COMMON METHODOLOGICAL PROBLEMS IN RESEARCH ON GENETIC FACTORS IN ALCOHOLISM

Diagnosis

The definition of alcoholism has varied from study to study, but there is a broad consensus that alcoholism consists of some combination of the following features: (a) excessive intake of alcohol, (b) social consequences of alcohol use or misuse, and (c) physical sequelae of alcohol use or its cessation. Some investigators would add a fourth criterion, (d) inability to control drinking or craving for alcohol. Collectively these criteria were advanced by Jellinek (1960) and they appear in DSM-III. It is clear that differences in criteria defining alcoholism may lead to study of different populations and to different conclusions about the importance of genetic factors in the disorder.

The reliability of diagnostic procedures is seldom discussed in the genetic literature on alcoholism. The replicability of individual findings obviously depends on reliable diagnoses as well as on clear criteria. The Jellinek definition of alcoholism which has been used in most studies from the 1950s onward was embodied in the St. Louis group criteria for alcoholism (Feighner et al., 1972). High reliability was reported for diagnoses made according to these criteria (Helzer et al., 1977). A modification of these criteria, the Research Diagnostic Criteria (Spitzer et al., 1978), has excellent reliability (six-month test–retest R = .94 for lifetime prevalence of alcoholism; Andreasen et al., 1981). Spitzer and Fleiss (1974) showed average reliability (coefficient kappa) of hospital staff diagnoses of .71, which is adequate if not outstanding. There is, therefore, some reason to think that diagnoses made according to Jellinek criteria are reasonably reliable.

Blindness of diagnostic assessment is another often neglected factor in genetic studies of alcoholism. The investigator who assesses family members without being blind to proband diagnosis runs the risk of biasing the outcome of the study. Of course, the use of nonblind diagnoses does not guarantee that bias will creep in, but blind diagnosis practically assures that it will not.

Genetic Factors in Alcoholism

Nosology

Alcoholism is a common personality (Cadoret, 1976) factors predispose to antisocial (Slater and Cowie, 1971), depression or of depression may be not. Winokur et al. (1971) did those with preexisting occurring in the context of further work, this "primary" alcoholism (i.e., a psychiatric disorder) where factors can be demonstrated not to be open to the criticism.

Age of Onset

Onset of alcoholism between members have of the number who will have. Family members could be in of recollection would negate the risk period might be long enough, and it seems estimating morbid risks. So adjusted for ages of related different investigators have different risk periods make different risk periods make seldom published in a way compute age-corrected figures with a different risk stand as reported, noting periods where appropriate.

Sex Differences

One of the most striking in prevalence. Although so: converging (Gomberg, 1976...
Genetic Factors in Alcoholism

Nosology

Alcoholism is a common sequel of depression and of antisocial personality (Cadoret, 1976). Since there is good evidence that genetic factors predispose to antisocial behavior (Crowe, 1974) and to depression (Slater and Cowie, 1971), the genetic transmission of antisocial personality or of depression may cause alcoholism to seem “genetic” when it is not. Winokur et al. (1971) showed that alcoholics without preexisting depression or antisocial personality had more alcoholic relatives than did those with preexisting disorders. Although the study of alcoholism occurring in the context of another disorder (“secondary” alcoholism) deserves further work, this review will focus on the transmission of “primary” alcoholism (i.e., alcoholism in individuals with no preexisting psychiatric disorder) whenever the distinction can be made. If genetic factors can be demonstrated in primary alcoholism, these results will not be open to the criticism just mentioned.

Age of Onset

Onset of alcoholism before age 15 is uncommon, while onset in late life is nearly as rare (Amor, 1951). If a family is ascertained (diagnosed) before its members have passed through the risk period, a misestimation of the number who will eventually become alcoholic is likely to occur. Family members could be interviewed late in life, but then inaccuracies of recollection would negate the advantage. Moreover, those who died during the risk period might have developed alcoholism had they lived long enough, and it seems desirable to take account of these facts in estimating morbid risks. Some investigators have used morbid risks adjusted for ages of relatives while others have not. The fact that different investigators have computed these adjusted figures using different risk periods makes comparison of studies difficult. Data is seldom published in a way that makes it possible for the reader to compute age-corrected figures from uncorrected ones, or to recompute figures with a different risk period. We have let morbid risk figures stand as reported, noting age corrections and their associated risk periods where appropriate.

Sex Differences

One of the most striking facts about alcoholism is the sex difference in prevalence. Although some researchers believe that the rates are converging (Gomberg, 1976), there is no question that study rates of
alcoholism invariably show more men than women affected. Any genetic
toelm theory of alcoholism must account for this fact. Most alcoholism research
has not fully met this challenge, because female probands, study of
whom might clarify matters, are hard to gather in numbers large
eough to permit statistical treatment. Much less is known about the
toelm causes of alcoholism in women than in men, and clinical observations
indicate that the etiologies are not completely parallel. Female alcoholics
have a later age of onset than male alcoholics (Winokur and Clayton,
1968), and they are much more likely to have a primary affective
disorder or affective symptoms (Schuckit et al., 1969).

These methodological issues recur in the literature on the genetics
of alcoholism. This literature may be divided into family studies, twin
studies, adoption studies, and association and linkage studies. Family
studies without suitable comparison group data present grave difficulties
in interpretation and will not be reviewed. Cotton (1979) has published
an excellent review of English-language family studies on alcoholism,
including a number of the studies reviewed here as well as others which
lack comparison data.

Family Studies

Morbid risk figures for the family studies to be reviewed are
presented in Table 1 for comparison. It is clear that rates differ widely
from study to study.

Amark (1951) studied consecutively admitted men at the Karolinska
Clinic in Stockholm \( N = 103 \). He personally interviewed each proband,
inquiring about alcoholism among first-degree relatives. Amark
reported age-corrected morbid risk (MR) figures separately by sex of
proband. Amark's probands were older than those of most studies, the
modal and median age decade being 40–50. Since Amark used 20 to 40
as the risk period for developing alcoholism, most of the siblings can be
expected to have passed through the risk period, and almost all parents
would have done so.

Amark's results are shown in Table 1. Comparison figures are
taken from Fremming's (1947) computation or morbid risk in the
general population of Denmark. The comparison speaks for itself.

Bleuler (1955a,b) compared American and Swiss alcoholics. His
American probands, seen at the Payne Whitney Clinic, were highly
educated but severe and long-standing alcoholics. The Swiss cases were
of lower social standing and had even longer illness than the Americans.
Both proband cohorts consisted solely of primary alcoholics. Bleuler
inquired about alcohol abuse and its consequences in relatives both of
American and of Swiss alcoholics, using probands' information to

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjoerke (N = 119)</td>
<td>Fathers</td>
<td>4.9</td>
</tr>
<tr>
<td>Amark (N = 103)</td>
<td>Mothers</td>
<td>26.3</td>
</tr>
<tr>
<td>Olhava and Frenken (N = 560)</td>
<td>Parents</td>
<td>3.5</td>
</tr>
<tr>
<td>Jacobson and Cowdry (N = 128 men)</td>
<td>Silde</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*Note: Figures are in percentages.*
TABLE 1. Morbid Risk Alcoholism in First-degree Relatives of Alcoholics and Controls (in percentages)

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Fathers</th>
<th>Mothers</th>
<th>Brothers</th>
<th>Sisters</th>
<th>Total</th>
<th>Parents</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugger (N = 119)</td>
<td>29.8†</td>
<td></td>
<td></td>
<td>11.0†</td>
<td>10.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amark (N = 103)</td>
<td>26.3</td>
<td>6.5†</td>
<td>21.1</td>
<td>0</td>
<td>11.8</td>
<td></td>
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<tr>
<td>Ottman and Friedman (N = 500)</td>
<td></td>
<td>27.6‡</td>
<td></td>
<td></td>
<td>14.0‡</td>
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<tr>
<td>Jackson and Connor (N = 218)</td>
<td>4.9</td>
<td>0.8</td>
<td></td>
<td></td>
<td>4.8</td>
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<tr>
<td>(N = 24 women)</td>
<td></td>
<td></td>
<td>0.2</td>
<td></td>
<td>4.0‡</td>
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<td></td>
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<tr>
<td>Bleuler (N = 57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.9</td>
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<tr>
<td>Bleuler (N = 50)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Gregory (N = 56)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Pitts and Winokur (N = 62)</td>
<td>16.1</td>
<td>1.5</td>
<td></td>
<td></td>
<td>7.0‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hassall (N = 40)</td>
<td>2.5</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Parker (N = 56)</td>
<td></td>
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</table>

* Parents or siblings, not reported by sex.
† Includes half-siblings.
‡ Includes children who have entered risk period.
establish diagnoses in relatives. His comparison group was a personally interviewed group of Swiss surgical cases from that part of Switzerland highest in rate of alcoholism. In addition to the high rates of alcoholism in relatives of alcoholics reported in Table 1, Bleuler found that 8 of 46 spouses (17 percent) were alcoholic. It is likely that some of these marriages represent assortative mating. This complicates genetic research and is discussed below.

A host of investigators have used similar designs but less sophisticated assessments to obtain data on alcoholism among alcoholics' relatives. Brugger (1933) used very severe alcoholic probands and a control group of more than 1300 physically ill patients. Oltman and Friedman (1958) studied 500 alcoholics under age 50 with a questionnaire, as did Jackson and Connor (1953) in comparing 1000 alcoholics (return rate 20 percent) with financial supporters of the Washington State Temperance Association (return rate 8 percent). In the latter study, the fault in choice of comparison group is grievous. Gregory (1959) found 56 alcoholics in a consecutive series of 1000 patients seen at Ontario Hospital; in the table we have compared the rate of alcoholism in their relatives with that of psychopath's relatives because they are the group next most afflicted with alcoholism and therefore constitute a stringent comparison. Hassall (1968) interviewed 40 alcoholic men under age 50. Controls were matched on sex, age, and social class and were physically ill hospital patients. Parker (1972) sent a questionnaire to 56 female alcoholics and compared them to his personal acquaintances on paternal heavy drinking. Except for Kassall, whose alcoholics were young and mildly ill, every investigator found an excess of alcoholism in relatives of alcoholics.

The chief problem with these studies is the nonblind assessments and the reliance on probands for most information on alcoholism in the relatives. Research has consistently indicated that informants report less alcoholism in their relatives than do the relatives when themselves interviewed (Andresen et al., submitted for publication; Guze et al., 1968; Rimmer and Chambers, 1959). Reports about relatives (called the family history method) are much less sensitive in case detection than are direct interviews of relatives (called the family study method). Therefore, the figures reported by all these investigators are probably underestimates. However, by the same token, so are the comparison figures (except for those of the Amark study). The estimate of the difference between alcoholic and control relatives should be biased downward; therefore, the comparison of rates militates against finding significantly higher familial incidence of alcoholism among alcoholics than in the comparison group. Nonetheless, much higher rates in alcoholics' families emerge, a familial disorder.

Pitts and Winokur (1964) reviewed using a blind family available first-degree relative in St. Louis, as well as relatives marriage and socioeconomic status were made according to Jeafford the diagnosticians. Introducing a blind family study differences disappear. Appre found in probands' relatives can probably be attributed to et al. (submitted for publication) identified by family study with Pitts and Winokur findings of this study strongly supports alcoholism.

With one exception, the of familial transmission of a consistent with a purely environmental influences theory. Two lines: of nature and nurture: twin.

Twin Studies

Results of four twin studies twin and alcohol abuse regis twin studies there. Kajii (1960) reported on to temperance boards in 100 searched and 214 probands surviving to age 15. Of the 3 established using appearance cases. All twins were admin behavior was classified in two board records.

If environments of more equally correlated, then any genetic factors. However, cc First, a pair is pairwise concor not ill. The second and prec...
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Pits and Winokur (1966) conducted the only investigation to be reviewed using a blind family study methodology. They interviewed all available first-degree relatives of 62 alcoholics at the Renard Hospital in St. Louis, as well as relatives of controls matched on age, sex, and marital and socioeconomic status. Diagnoses for probands and relatives were made according to Jellinek criteria from a list of symptoms afforded the diagnosticians. The results are shown in Table 1. Clearly, introducing a blind family study method has not made alcoholic-control differences disappear. Approximately 10 times as much alcoholism was found in probands' relatives as in control relatives. These high rates can probably be attributed to the family study method, since Andreasen a.e. (submitted for publication) found that only 56 percent of alcoholics identified by family study were identified by family history. Since the Pits and Winokur findings cannot be attributed to biased assessments, this study strongly supports the concept of familial transmission of alcoholism.

With one exception, these studies strongly support the postulation of familial transmission of alcoholism. Of course, such transmission is consistent with a purely environmental, a purely genetic, or a joint influences theory. Two lines of evidence afford a stronger separation of nature and nurture: twin studies and adoption studies.

**Twin Studies**

Results of four twin studies are given in Table 2. The existence of twin and alcohol abuse registers in Scandinavia has favored conduct of twin studies there.

Kaj (1960) reported on twins born since 1840 who were reported to temperance boards in southern Sweden. In 1953 these records were searched and 214 probands in 174 pairs were found with both partners surviving to age 15. Of the 348 twins, 292 were examined. Zygosity was established using appearance ratings, with blood grouping for doubtful cases. All twins were administered a structured interview. Drinking behavior was classified in two ways: by interview data, and by temperance board records.

If environments of monozygotic (MZ) and dizygotic (DZ) twins are equally correlated, then any excess concordance in MZ twins is due to genetic factors. However, concordance may be computed in two ways. First, a pair is pairwise concordant only if both members are ill or both not ill. The second and preferable method of computing concordance