DISCUSSION

Audience and Panel Participants: Meyer Glantz, David-Comings, David Lykken, Remi Cadoret, George Uhl, Howard Moss, and Ralph Tarter

Dr. Comings: I was somewhat surprised, as I see you were also, about the negative heritability, zero heritability, for conduct disorder. Then I was pleased to hear you say—if I heard you right—that this tends to come from a lower socioeconomic group of individuals.

There's a beautiful study by Satterfield, probably 20 years old now, where he looked at respective scores, ADHD children grown up and stratified by socioeconomic status. And those in the higher and middle status had a twentyfold increase in the respective controls, and the lower socio-economic status only had a fourfold increase. So, obviously the people where you get the group from can make an enormous difference in that.

Dr. Lykken: Yes. I think that's right. My primary interest is in psychopathy and general socialization problems. And I've always thought that the best way to get a pure psychopathic group is to begin with a group with intact parents, middle-class parents, where you can attribute the problems to environmental effects. Psychopaths occur also in the underclass, but there it's more complicated and it's harder to tell them apart.

I may make a couple of slight responses to the comments. I'm not really that apologetic about the question of the gene effects on substance abuse. My colleague Matt McGue, who wrote this paper, is much more conservative than I, and there is an interaction between us such that my presence tends to make him all the more conservative. So, knowing that I was going to talk about this he was very careful, trying to curb my behavior.

And, I should explain that you're quite right; we don't want to study substance abusers or twins—only twins whose parents are alcoholic because that gives us the problem of coaggregation and special classifi-cations. So, we merely enriched our sample with parents who are alco-holic, and we intend—fully intend—to study the two groups separately.

Dr. Cadoret: [Editor's note: The following is a minipresentation from the floor]:

I think that the twin studies and the adoption studies are good ways to come up with models as to how people get to be substance abusers. I'd like to

demonstrate this with some of our adoption data, starting with a model that I developed back in 1985 and then giving you results of a study I just finished for National Institute on Drug Abuse of about 200adoptees separated at birth.

If we look at the first figure, we see adoptees who are adopted away at birth by nonrelatives. We use a kind of case-control method. I match an adoptee who has a know biologic background of psychopathology with a control adoptee. We match the adoptees with another adoptee from the same agency, same sex, same age, as a control. This figure shows a model that was developed for males back in 1985 for alcohol dependence. We found that there were several pathways to alcohol dependence. One was a direct pathway from a biologic parent who was alcoholic to adoptee alcohol abuse/dependence (figure 1, relationship 2). These are adult adoptees, and we determine their psychiatric condition by giving them a

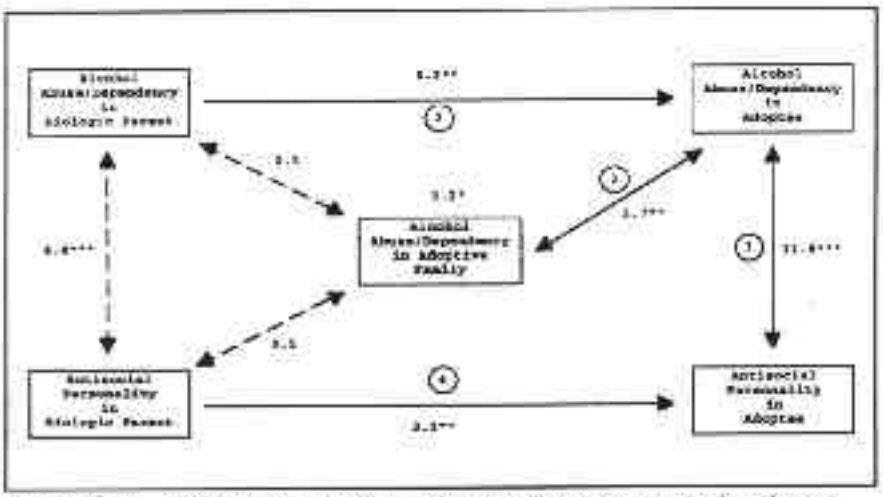

FIGURE 1. *Interaction diagram of etiologic factors for male adoptee alcohol abuse/dependence and antisocial personality.*

KEY: * = odds ratio significant at 5% level; ** = odds ratio significant at 1% level; *** = odds ratio significant at 0.1% level;
→ = relationship found in data; - -➤ = relationship forced into model to control for selective placement. Circled numbers refer to relationships.

SOURCE: Modified from Cadoret et al., *Arch Gen Psychiatry* 42:161-167, 1985. Copyright 1985, American Medical Association. Used with permission.

DIS. It's given to them blindly by our research assistant who doesn't know anything about the biologic background. So that is one pathway.

The other pathway seems to come from biologic parents who are antisocial, increasing the chance that the adoptee will be an antisocial as an adult (figure 1, relationship 4). I think that the direction of effect goes from antisocial personality to alcohol abuse/dependence as the second pathway (figure 1, relationship 1). There's a third pathway: An adoptive family that had someone in the family who was an alcohol abuser or dependent increases the probability of an adoptee's becoming an alcohol abuser as an adult (figure 1, relationship 3). So, these are three independent pathways to alcohol abuse/dependence.

This is a log-linear model, and all pathways are independent of the others. We control for selective placements by forcing relationships into the model as shown by the dotted arrow in figure 1.

Figure 2 shows what we found with a model with 95 male subjects [Cadoret et al., "Adoption Studies Demonstrating Two Genetic Pathways to Drug Abuse." Arch Gen Psychiatry 52:42-52, 1995]. In this study, we start out with a biologic parent who has alcohol abuse or dependence and you can see there is a direct effect to adoptee drug abuse and dependence (figure 2, relationship 2). There is also an effect to antisocial personality, which is mediated by adoptee aggression (figure 2, relationships 3 and 4). Biologic parent antisocial personality increases the chance of aggression (figure 2, relationship 3), which in turn leads to adoptee antisocial personality and thence to drug abuse/dependence. Of course, there is a high correlation between abuse and dependence and alcohol abuse and dependence (figure 2, relationship 6). Here again is a model that shows that there might be a direct pathway and an indirect pathway, both leading to adoptee drug abuse/dependence. This implies that these may be different genes, and I think it would be very interesting to see if some of the allelic studies that we heard about earlier this morning would be more characteristic of the induced pathway than of the direct pathway.

Figure 3 shows what happens when we add to that model environmental factors. As an environmental factor we selected variables that indicated disturbed adoptive parents such as psychiatric or behavior problems, marital separations, and divorce. These factors were added together to form a disturbed adoptive parent variable that, when added to the model just shown inn figure 2, increases the chance of an antisocial personality diagnosis in the adult adoptee (figure 3, relationship 3). This augmented

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model is shown in figure 3. Here again are three independent pathways to substance abuse. These findings are relevant to the question that we have been struggling with today of how do you determine genetic and clinical heterogeneity in your sample. Adoption studies like this could indicate how much effect these different environmental factors have in producing what you see clinically, and help distinguish genetic from environmental effects.

Dr.Uhl: I was just going to comment that in a group of incarcerated individuals, virtually all of whom were substance abusers and roughly half of whom had psychopathy diagnoses, Dr. Steven Smith found no difference in our hands between the dopamine receptor gene frequency in

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the psychopathic drug abusers compared to the nonpsychopathic drug abusers (Biological Psychiatry 1993).

Dr. Cadoret: That may be a very extreme sample. Once your dopamine is so off that you end up in prison, it may not matter much whether you're on drugs or not.

Now, I think one of the advantages of twin and adoption studies is that you're dealing less with a clinical sample than with population samples, and, for instance, our correlations that we get between adult antisocial personality and adult drug abuse or alcohol abuse are very similar to what the ECA reports in population samples. The sample is picked out because they're adoptees, not because they're coming for help. As a matter of fact, most of the abusers in these samples have

never sought help. The usual tip of the iceberg sort of thing. But, I've always thought that information from this type of study could be used to improve the prediction of what phenotype really represents a genotype, if you see what I mean. If you know an environment has caused a phenocopy, then I think you're in much better shape, and I don't see how you can do it from other types of studies.

Dr. Moss: A question for Dr. Cadoret about the study you reviewed with us. Can you tell me whether or not there was spousal resemblance among the biological parents for substance use disorder, or was only one parent affected?

Dr. Cadoret: It's usually one parent. We made the diagnoses on the parents from actual hospital or prison records, so we're pretty sure of their diagnoses. Unfortunately, you don't have the same amount of information available on their mate.

Dr. Moss: So, the effects that you see could not be ascribed to social homogamy—well in this case not—among the parents, or assortmentive mating?

Dr. Cadoret: Well, I think there probably is some kind of assortitive mating. I think the old song about "birds of a feather flocking together" is very true here.

Dr. Moss: Would that increase, though, the liability value in the offspring in the adopted offspring?

Dr. Cadoret: I think it would, and that's one factor that's not too easy to measure in adoption studies because we go back anywhere from 20 to 40years to get records. But, you know, when you look at the social circumstances under which a lot of these children are created, it's a drinking dad and he meets a mom who is also in the bar.

Dr. Moss: You didn't show a pattern of alcoholism in parents to alcoholism in offspring, but presumably that exists in both those cases?

Dr. Cadoret: In these log linear models, we just put in all of the variables and this is what comes out. This is the best fitting model. None of the pathways went directly, in this case, to alcohol abuse, just indirectly through drug abuse.

Dr. Glantz: It's kind of a shame that one of the variables that cannot be considered because of historical reasons is whether or not the parents would have used drugs if drugs had been more widely available. In other words, there were certain periods of time where, if you chose to use an abusable substance, pretty much you were limited to alcohol in most strata of society. Not that one would wish that more people had been affected by drug abuse, but it certainly, for control purposes, would have been interesting to see who would have gravitated toward which type of abusable substance in all of these lineage studies. In the future, parents will become available who had more choices. Then, we can perhaps determine what choice means.

Dr. Cadoret: We already see that. Starting about 20 to 25 years ago, there are a lot more notations in hospital records of polysubstance abuse by these biological parents. When we put a drug abuse factor in bio-logical parents in the model, it's close but it doesn't go into the model. If you look at the drug abusers, the biological factor tends to go to drug abuse, but it's not significant. We don't have a large enough sample, but, as you say, given another 5 or 10 years there will be a lot of those people.

Dr. Tarter: I have a speculative question both for Dr. Cadoret and Dr.Lykken. In light of those very elegant papers in the current [1993] issue of "American Psychologist and Sociobiology" with respect to the question of parental investment in these offspring, the parental investment in your own biological offspring, and the increased risk for that offspring to experience abuse and even death and the extent to which there can be increasing—well, equal—parental investment where you have two twins—I think that was even commented on in the paper—is there a heuristic basis for research with respect to substance abuse on this, on developmental pathways, from this perspective using these paradigms?

Dr. Lykken: Well, I'm not sure I have a bright idea, but it is clear to me that there is a big difference between the substance abuser, if he exists, who has good nurturing, intelligent, competent, providing parents with whom he has a good relationship and the substance abuser who has a more typical parental background. I think it would be fascinating to get a group of substance abusers, or a group of delinquents, or criminals who come from what we would think of as being ideal family backgrounds so that we can rule out that kind of influence and compare them to the general run of abusers. But, I'm in hopes that the study we're doing at Minnesota, because these Minnesota parents are pretty good by and large and dedicated, that we

will have an opportunity to look at that in a preliminary way, but I can't guarantee it.

Dr. Cadoret: Dr. Tarter, I'm sorry I didn't read that article, but I've always been intrigued by the sociobiology of the spread of antisocial genes, and wondering where things like altruism come in—behaviors that you don't usually associate with antisocials. But, I think that there is a possibility that for antisocials who drink, there's something about that situation that might lead to more sexual behavior and more spread of the genes under those conditions. An awful lot of women who give up children for adoption report that they were drinking when they got pregnant or they were drinking during pregnancy, so that the combination of antisocial genes plus sexual interaction promoted by drinking may even facilitate the spread and the maintenance of the antisocial genes in the population.

Dr. Glantz: I'd just like to say briefly that although it probably isn't all that likely, there is always the possibility that the effect is teratogenic and congenital, rather than traditionally genetic, at least in some cases.

Dr. Cadoret: Yes. I'm glad you brought that up, because 21 of our biologic moms were drinking during their pregnancy. Now, because the records are not the world's greatest, you don't know how much they drank, how much they smoked, how poor their diet was, and all those other environmental factors that are probably important. But, even when you put fetal alcohol syndrome into the equation you still get these direct genetic factors. What the fetal alcohol exposure does seem to increase is the number of adult personality disorder symptoms that people have in Group A and Group C and, of course, in Group B. And that's only in the offspring of the drinking moms, which is quite interesting. I just wish that our records were a little better, but fetal alcohol exposure is certainly a factor. However, you don't know whether it's a gene-environment interaction because we don't know how many of the moms who weren't alcoholic were also tippling during their pregnancy. You just don't get that kind of fine grain information.

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