

DISCUSSION

Audience and Panel Participants: Ming Tsuang, Michael Lyons, Roy Pickens, George Uhl, Howard Chilcoat, Meyer Glantz, Seth Eisen, Roy King, Al Mirsky, and Howard Moss

Dr. Uhl: Can you speak any more to the drug class specificity issues?

Dr. Tsuang: We actually are starting to analyze the more recent data, and we hope to be able to talk about that issue later. But, I'd like to stress what you have just said in your commentary, that we never claimed that this is a representative sample. I hope that we can do a stratified random sample among the general population. If NIDA would like to really make some dent in this area of research, as a psychiatric epidemiologist I'd like to recommend that a stratified random sample in a well-defined population is very, very important to do. What we have in terms of twins is that we have this unique twin sample that God sent to us, and we are trying to capitalize on that. So we are very aware that this is not a general population representative sample, but yet it's a unique population of twins.

I was very impressed that in such a short period of time, you can really go into the gist of what we are trying to do and come up with the area of interest in this diagram. Today, I intentionally tried not to talk about the significance because the data are coming in and it may change and I don't like to give the P value, so to give the false assurance that something is there. With the experience of teaching medical students or school of public health students, I don't like to put the P there. Once a P of 0.05 is there, they always say, "That's it," and never think about the implication of the false error and so on. And I think Dr. Lyons has more to say in terms of the current new data. We are getting more pairs. What I presented is actually based on the June 1993 data, and we have already updated some of them.

Dr. Lyons: Well, we are only beginning analysis on the data set with over 8,000 pairs. Some of the other things that we're looking at with the twins that were not included in the presentation is the subjective effects of drug, as was mentioned earlier. For example, we found that feeling paranoid after smoking marijuana has a strong genetic component to it, whereas reporting feeling creative after smoking marijuana seems to have more of a common, shared environmental component to it. So, in terms of what was said about the heterogeneity of the phenotypes of drug abuse, we're hoping that the

data we've collected already will help us to home in on some endophenotypes. The proposed high-risk paradigm really is a way to try and get at these endophenotypes that may be more clearly related to genetic and/or environmental factors than we've previously been able to determine.

Dr. Glantz: Just a quick question for clarification. Dr. Tsuang, did you say that your sample included twins who were comorbid for alcohol?

Dr. Tsuang: Actually, in terms of affected, we exclude alcoholism from the new study, but in what we currently have we didn't exclude it. For the new proposal, we'd like to have a very well-defined affected/nonaffected sample. But, for the current study we have all kinds of studies.

Dr. Glantz: So, the data you showed just a minute ago included twins who were comorbid for alcohol?

Dr. Tsuang: Yes.

Dr. Glantz: This is a problem, as I'm sure you're aware. Because alcohol use is associated with drug use, or because drug use is often associated with alcohol use, what you might be seeing here is drug use that's riding on the back of alcoholism that's going on in your sample. So, what would appear to be higher MZ than DZ concordance for drug abuse may reflect nothing more than higher MZ than DZ concordance for alcoholism. It's good to hear that your new sample will be such that you could exclude the alcoholics from it and see what is happening. I heard you say you had a sample that would potentially look at the shared genes between alcoholism and substance abuse and a sample that would not look at those.

Dr. Lyons: Right. In the data we've already collected, one can model those various things. But, even with a sample of 8,100 people, when you start subdividing into heroin users who are not alcohol abusers, who are not serious abusers of marijuana, the cell size gets very small. So, for some models I think we're going to be able to distinguish shared contributions of alcohol to given drugs, but for others the models won't resolve even with this large a sample.

Dr. Glantz: How about the same question related to comorbid psychiatric disorders?

Dr. Lyons: I think it's basically the same answer. Again, the modeling procedures allow you to factor those in. For example, one can look at using cross-sectional twin data and make some inferences. For example, where there is a co-occurrence between substance dependence and major depression, one can look at whether the causal arrows go from the substance dependence to depression, from depression to substance dependence, and whether it's reciprocal. We can consider to what extent they share common genetic influences on both, and so we'll be looking at it that way. Again, the power to address specific questions will depend on the frequency of the given outcomes in the sample, but that certainly is to be included.

Dr. Glantz: You have to wonder, once you've factored out all of the different possible comorbid conditions, how representative the resultant group will be in drug abusers.

Dr. Lyons: Well, it's not stratified, per se. With the biometrical modeling procedure, everything is in the equation at the same time. So, they're statistically handled rather than having one group who has X and Y, one group with X, one group with Y, and crossing your fingers that you have enough N in each cell.

Dr. Glantz: Then you do have to make a decision where the variance is to be attributed. I understand what you're saying, but at the same time the decisions you make may still lead to some conclusions that are...

Dr. Lyons: Well, for example, in the high-risk paradigm that we're proposing here, we're suggesting that high-risk twins—that is the nonabuser cotwin of an abuser—will be at elevated risk for antisocial personality disorder, which would suggest that that's a vulnerability indicator. We're suggesting they won't be at elevated risk for depression because we're suggesting that that's a consequence. That is, we're suggesting the abusers will have elevated rates of depression versus the nonabusers. So, there's a sort of more intuitively straightforward way to address some of those issues too.

Dr. Glantz: And the power is going to come from addressing specific hypotheses rather than general exploration?

Dr. Lyons: I think we'll do both. But, I think it is more powerful to be able to state one's hypotheses a priori, and then go about testing them.

Dr. Chilcoat: I just had a question about the role of time in genetic studies, in twin studies, in terms of the natural history of drug abuse. That's one of the things I was looking at—not just lifetime prevalence of either disorders or use, but changes over time. One thing in relation to Vietnam vets that comes into mind is Robins' studies of people who used heroin or opiates in Vietnam but stopped once they came here, and I don't know if your sample size may limit any analysis of that time. You may be breaking it down into too small numbers. But, it would be interesting to look at those people who were exposed and continued versus those who stopped when the environmental context changed over time. And also another role of time, I think, to keep in mind is the importance of cohort effects, that over time we have cohorts of twins, or individuals, who are exposed to different... As you say, you've got to have the drug. It has to be present for the dependence to occur. Pre-Vietnam there was little exposure to a wide variety of drugs, and even now we see some changes, at least in terms of younger individuals' initiating drug use. Even though the drugs are probably out there, attitudes have changed somewhat in terms of initiating use. One question to consider is what's the impact of these different sorts of variable exposures on genetic estimates to the contribution of genetic factors and drug dependence?

Dr. Eisen: It's certainly true that we would have loved to begin collecting data on our twins at the time they were in military service. One of the advantages of this dataset of twins is that we did originally abstract a considerable amount of data from military service records, so we do have a fair amount of data.

Dr. Chilcoat: Do you have a retrospective report?

Dr. Eisen: Yes. And we have collected that data in our current dataset. We're always very concerned about the retrospective collection of data. There have been three data collections: one by us in 1987, a second by NHLBI in 1990-1991, and now ours. So, we are beginning to collect a large set of data over time. Unfortunately, of course, we would have liked to have collected data between, let's say, 1970 and 1987.

Dr. Lyons: I think also, to address your question about changes in the environment, that the estimates of how heritable, how much the environment contributes, are very relativistic. I once heard it suggested that asking whether it's nature or nurture that determines the outcome is like asking whether it's the length or width of a rectangle

that determines its area. You can't have a rectangle without length and width; you can't have an organism without genes and the environment.

As an example, under the kinds of methods that we're using here, if you did a twin study of PKU you would determine that it was 100-percent heritable. But, if phenylalanine was not ubiquitous in the environment, if only 10 percent of people were exposed to phenylalanine, it would be maybe 50 percent heritable and 50 percent from the environment. If everyone had the PKU gene and 10 percent of people were exposed to phenylalanine, it would be 100 percent environmental, zero percent heritable, even though the mechanism would not have changed at all. So, the kind of estimates that we get here of heritability in a common environment really are very relativistic and, as the environment changes, those estimates change.

In some ways the study we're proposing is to extend this a step further and try and use what we're already learning to leverage information about the mechanisms that are going into the phenomena that we're observing here.

Dr. Tsuang: Of course, from an epidemiological point of view, the prospective controlled study will be the best. But, it's time consuming and you have to wait for the result. And it's expensive. Particularly now Congress would like you to have immediate results. So, what we are actually doing is capitalizing on what we have. The beauty about our sample, now that I've reviewed the dataset, is that we are not just asking the past history; we are still asking the longitudinal picture, although it's retrospective. We ask when did you start it, and are you still using it, and how many times you use what sort of drugs. So, essentially there is an abundance of information there. The issue is that because of the polydrug abuse, if we start to tease apart each drug, you may not have the abuser with just one drug and the N is going to become smaller. So, we are very cognizant of the limitation of this. What you mention is very important, the longitudinal aspects of it, and we are trying to do it.

For the new proposal, we are trying to essentially answer that in part—that the non-drug abusers and actually the cotwins of the drug abusers are carrying the genetics for predisposition. We should be able to tease apart what areas are actually a comorbidity prior to the drug abuse that is actually the consequence of that.

Now, I'd like to ask a question for our research proposal. We tried to get into this endophenotype business and, as you say, in terms of drug

abuse we reviewed all the literature under the sun to try to see if any neurochemical aspects had actually been confirmed; the literature is actually very soft. Could you, or anyone here in the neurobiology area, advise us if with this sample, this strategy, what sort of an exploratory measurement can we do? As you said very clearly, we actually trans-formed our schizophrenia research paradigm into drug abuse, and you rightly pointed out even that, in drug abuse, is still very preliminary. But, we'd like to look for any innovative area of measurement that can serve the purpose of capitalizing on this very unique sample size.

Dr. Uhl: This is clearly a limitation of the drug abuse field in general. I think that the data that you saw this morning on dopamine receptor geno-types are as replicated and as robust as any other physiologic concomitant of substance abuse of which I'm aware. That's a fairly radical statement. My impression is that certainly looking at a number of different candidate genes in such a sample would be of interest and would fit with the genetics.

Having said that, I think that later on in the meeting other individuals will. Dr. Herning will talk more about the evoked responses. We'll hear some about the fancy and maybe not generally applicable, but maybe doable in a small part of the sample, the functional cortical changes in response to drugs and so on.

Dr. King: I just wanted to add that you might consider looking at measures of arousal, particularly the hypothalamic-pituitary-adrenal axis. Dr. Moss' group and my group have found correlates with impulsivity and conduct disorder in these types of samples, so that might be worthwhile I think.

Dr. Comings: I have two comments. First of all, when we looked at our drug patients and compared the different drugs used by relatives with drugs versus those without, we got the identical sequence that you did, a most severe genetic loading for psychotropics, then heroin, then sedatives, then cocaine, and marijuana the least. One might argue that this is not necessarily an indication that there is anything unique genetically about, say, heroin, but about a combination of factors such as availability of the drug and other factors.

The other thing is in this modern molecular biological era—and I understand that most of your interviews were done by telephone, is that correct—you can now send out a little set and you can get blood smears in the mail. We've gone out to some of our patients, and we

were able to get 100 different DNA tests out of one of those little samples. So, this would be something where you could take the higher end of your twins with the most loading, or drug use, and the lower end. Just pick 50 of each and do a very nice study, depending on what you want to look at.

Dr. Tsuang: The twin registry usage of this sample has a specific instruction. Each time you are going to add one thing you have to go to the committee to ask for special permission. Currently, we are doing a very intensive telephone interview. One subject may last for 2 hours, 3 hours, and sometimes they just finish the first phase and then on the following day to do another telephone interview. For this new proposal, I am trying to really warn NIDA to carry out this research, to really go into the field, to do all kinds of measurements—you can immediately think about the astronomical budget. So, I'm thinking from this conference we can actually zero in, phase-by-phase to determine which phase should be primarily for which measurement and to really divide into Phase I, Phase II, Phase III to carry out. Otherwise, as we know, there is a restricted amount of money to really carry all this out. So, this is just a theoretical issue that we are talking about. By reviewing the literature is this mono-amine oxidase really real, or is it really something we don't jump into? Could I get some sense of it? I'm not a specialist in this area.

Dr. Moss: One of the confounds with using MAO-B from platelet is that Tabikoff and colleagues have shown that the consumption of ethanol, in itself, lowers platelet MAO activities. It's an enzyme that's exquisitely sensitive to having alcohol in its milieu. So, some of the early studies on alcoholics linking low MAO activities with alcoholism may have been really due to that particular confound where they did not allow for an adequate sober interval to have taken place before a sample was drawn.

We recently looked—Dr. Tarter actually—at MAO-B concentrations in adolescent substance abusers, and we do not find them to be lower than control levels.

Dr. Mirsky: The largest N I was ever associated with was something like 435, so I'm stupified at these Ns, and my hat goes off to you folks for this sample. But, just a couple of questions about what we might call the premorbid functioning of these people.

In some studies on World War II, and I think Korean vets, an important variable was, in some neuropsychological investigations, the

premorbid intellectual level as assessed by the Armed Forces Qualification Test, or something like that. It turned out when the data were examined, it helped explain certain things that otherwise might not have been interpretable.

I also wonder about the effect of SES, socioeconomic status. I would guess that you have a fairly restricted sample as people served in Vietnam if they couldn't get out of it some way. But, I wonder if you folks—you probably are—are looking at that variable as well?

And one last thing. It is clear that you are going to try to compare the—I think I'm using the right word—the prevalence of drug abuse in this sample in comparison to some other sample to see whether or not you have more drug abuse here or less, or is that just an unsolvable conundrum?

Dr. Eisen: Well, in terms of that, one of the kinds of data we've abstracted from military service records is the Armed Forces Intelligence Test data. One of our concerns is that there is some variation in the tests that were administered by military service. Secondly, we have some concerns about the quality of those data. So, as of yet, we've not utilized the data in any of our analyses, but we're always aware of it and may return to it at some later time, certainly as we get into our analyses of substance abuse.

We do have data, of course, on educational attainment. Perhaps a little surprising to some people is the high degree of educational status of veterans. Over 90 percent of registry members are high school graduates. These are data that were abstracted actually not only from their self-reported statements but also from military service records. So, those who participated who are subjects are unusual, I think, in having a higher educational level.

The question was the prevalence of substance abuse in relation to the general population. We certainly plan on examining the prevalence of substance abuse in our group in relation to probably the ECA data and other population-based data.

Dr. Lyons: The reason for that is just to ensure that there is not a twin effect for drug abuse. For example, twins may be at higher risk for autism, so using twins to study the etiology of autism may be misleading. As opposed to in schizophrenia, twins have a similar risk as singletons, so one probably can generalize in findings with twins and we would like to do the same thing with this sample. We're

hoping that it will demonstrate that twins don't differ in terms of drug outcomes from nontwin populations.

Dr. Eisen: The prevalence of drug abuse in our population is probably lower than the prevalence of drug abuse in the general population because there really is a screening process in entering military service. We have in our data looked at MZ twins and have demonstrated, for example, that military service has not had an effect on alcohol consumption, current alcohol consumption, by an analysis of MZ twin pairs. On the other hand, military service, and combat in particular, does seem to have an effect on cigarette consumption. Obviously, we'd be looking at using these same approaches to look at reported drug abuse.

Dr. Tsuang: One other thing with regards to the personality is that combat experience surprisingly is related to personality trait of novelty seeking. We happened to publish, or are in the process of publishing this.

Dr. Lyons: There is a genetic influence on whether or not someone went to Vietnam, given they were in the service, with how much combat they saw and self-report but also how many medals they won in combat, which is abstracted from military records. There is a significantly higher concordance among identical twins than among fraternal twins. I told that finding at the outset to a colleague of mine whose wife was a personality psychologist. He came back the next day and she said, "How the hell can that be? That doesn't make any sense." I then mentioned it to a good friend of mine who had won a number of medals in Vietnam, who is not a psychologist or psychiatrist, and he said it made perfect sense to him. He said, "Every day you made decisions that would influence the likelihood of being in a fire fight, of being wounded." He said, "Some guys like to volunteer to walk point, and almost every day they'd walk 200 yards ahead of the rest of the platoon through the jungle. Other guys stayed there a year without ever doing that." So, in fact individual differences, in part genetically influenced individual differences, may be related to those outcomes. As Dr. Lykken said, what's more surprising these days is to find outcomes that don't have at least some influence from genetic characteristics.

Dr. Moss: I was sort of curious about the analytic end of things and what sorts of models would ultimately be tested. For example, is the plan to test a liability threshold model and, if so, how? Will you

model severity and diversity of drugs used as well as individual kinds of drugs that people consume?

Dr. Lyons: Well, I think there will be a hierarchy of complexity. The main questions that we addressed today will really be addressed with t-tests and chi-squares. That is, here is the high-risk group; here is the low-risk group. Does P300 amplitude differ between the two groups? Following that, there will be increasing levels of complexity. We would like to tease out, for example, subjects who have concomitant alcohol problems versus those without concomitant alcohol problems and test the specificity versus generalizability. We probably will end up grouping substances. For example, amphetamine, cocaine, and marijuana might be one group and heroin, barbiturates, and marijuana in another group. It would be nice to get down to the single drug, but I think the reality, again, even starting with quite a large sample, to just get people who are dependent on heroin and never abused another substance I'm afraid we're not going to be able to address that.

Dr. Mirsky: You mentioned P300 again. Just logistically, how are you going to manage that? Are you going to bring 8,000 subjects to MacCauley's lab? Is that going to be a stratified sample?

Dr. Lyons: He's planning on expanding his lab. (Laughter.) No. Actually we haven't finalized the N. The rate-limiting step is likely to be the number of discordant pairs. Right now, it looks like, using a fairly strict definition of dysphorias, there are 228 pairs where one member was an abuser and the other member did not use any drug more than five times. Then, we will probably pick out a similar number, let's say 228, of people randomly selected from within a pair of concordant nonabusers for comparison and 228, one from each pair, of pairs where both were abusers. So, we'd be talking about an N in that case of around 700 people. We plan to have a center in Boston, St. Louis, and Chicago to minimize the distance that people have to travel to come in.

Dr. Tsuang: Again, probably it's because of our presentation in talking about the current study and then, based on this, to indicate the future study that gives some confusion. The current one is a huge N, as you say, but it's the questionnaire type of telephone interview. Then, the one that we are proposing is actually talking about the discordant cotwin versus the nonabuser or concordant twin. So, the pairs become smaller. So, I hope it is manageable.

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