Workshop On The Genetics Of Drug Addiction
November 13-14, 2003
The National Academies Steering Committee
On The Genetics Of Drug Addiction

Presentations and discussions of a panel of experts created by the National Academies, at the request of NIDA, to look into the ethical, behavioral and social consequences of genetics research on drug abuse. Experts were selected under the auspices of the Board on behavioral, Cognitive and Sensory Sciences (NAS), chaired by Mr. Rick Harwood. Proceedings will be the primary output; there is no intention to produce a consensus statement.

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Summary of Presentations

1. Science of Genetic Research

Presenter: Remi Cadoret, Professor Emeritus of Psychiatry, University of Iowa

Dr Cadoret began by pointing out that, for him, science is the endeavor of identifying repeatable and generalizable patterns. The attempt to extrapolate the resulting hypothesis onto other people could be the source of ethical conflict if the applicability of principles that have been derived in that fashion is not recognized by some who view themselves as fundamentally different from the original experimental cohort.

Next, he emphasized the importance of considering the impact of the interactions between genes and environment when thinking about ethics. The known strong connection between the two adds a developmental dimension to the discussion: There is no "gene for stealing cars", rather, there may be genes that lead up to a behavior that, given the right rearing milieau, given there is a car there and you like its appearance and you need a ride, all combined may result in a theft and a felony conviction.

Then he contrasted the rather transparent modes of genetic transmission with inheritance patterns that can be easily traced onto family trees, whether caused by dominant (Huntington's) or recessive (Cistic fibrosis) traits, with the significantly more cryptic and multifactorial patterns of inheritance suspected to operate in many behaviors such as drug abuse. Pedigrees for the latter do not show regular patterns: if it runs in a family it could be due to genetics or it could be due to the environment or both.

He introduced the work of Galton in 1875, who used the history of identical and non-identical twins to establish criteria for the determination of the relative powers of nature and nurture to conclude that "nature prevails enormously over nurture." Twin studies have been widely used to determine that there are genetic effects, in just about any human condition. More recent epidemiologically sound samples of twins show that there are genetic effects in adult substance abuse, smoking and alcoholism. But results are confounded by the fact that in most cases these twins are raised in the same family, so that environmental effects get subtracted. This is why it is so important to do studies on separated twins, which are very difficult to find.

Galton started the Eugenics movement as a result of his interest in things like the inheritance of intelligence. After his death it was proposed (Richardson, 1912) that studying adoptees would be a clever way of getting at the difference between genetic and environmental factors. This line of research is Dr Cadoret's expertise.

Key findings:

- Having an antisocial biologic parent(s) was a strong predictor of an adoptee with antisocial personality.
- Adoptees from alcoholic biologic parents were 4 times more likely to be alcoholic themselves than if their parent was a control parent.
- There is a high correlation in adoptees between alcohol consumption and antisocial behavior.

Key issues to consider that were mentioned:
Generalizability of the scientific product
Nature-Nurture interactions
Developmental and epigenetic influences
Complex genetic traits: multigenic inheritance
Twin studies; adoptee studies
Importance of longitudinal studies—we need mechanisms to do them (and review committees that understand them)
Importance of reproducibility—and understanding issues behind non-replication

Excerpts from the discussion (led by Marc Schuckit)

In complex, genetically influenced disorders roughly half is explained by environment, maybe a little less; genes explain about half. The genes are heterogeneous, relating to a variety of phenotypes. Any one gene we find, if we are really lucky, will relate to a specific phenotype, which impacts on risk, and that one gene explains maybe three to four percent of the variance. We must never forget the importance of the ethical issues related to what we are doing. We can learn more about someone's overall risk by looking at family history, a heterogeneous influence that will probably never emerge from finding a specific gene [but we should be able to consider that genes are a part of the family history]

The gene allows us to identify people at risk -- no one of who can be pointed to and say they will develop a disorder -- there is a heterogeneity regarding phenotypes and specific genes.

2. Conducting Genetic Research

Presenter: Marc A. Schuckit, San Diego Veteran Affairs Medical Center

This presentation applied mostly to alcoholism, with extrapolations to drug abuse.

Goals of health care professionals: recognize vulnerabilities and then develop procedures to minimize the risks associated with those vulnerabilities. Alcohol dependence is an easy model to work with because of the high prevalence. Lifetime risk in men is at least 10 times higher for alcohol dependence than for other drugs of abuse.

Categories of questions:

Is it familial? Look at inheritance power in first, second and third degree relatives. An affirmative answer points to either shared genes and/or environmental factors. Next, is the similarity for dependence on alcohol higher among identical twins than among dizygotic or fraternal twins? Also very valuable are the adoptee studies. Then come the animals studies that identified a large number of characteristics (traits) related to alcohol consumption that are genetically influenced.

The difficulty, however, is that a large number of underlying genetic configurations can result in a seemingly unique behavior such as alcoholism or drug dependence. Heterogeneity of genetic substrates for common disorders is an extremely important

concept. It applies to all multifactorial syndromes, from heart attacks to substance abuse. Thus, the study of the "genetics of heart attacks" is doomed to failure. A workable strategy would involve:

- Assessing whether a specific disorder is genetically influenced. Differentiate *dependence* from *use*.
- Breaking it down into phenotypes (some will be generic, some will be drug-specific).
- Searching for candidate genes for each of the phenotypes.
- Looking for how genes interact with the environment (this is where prevention and issues related to treatment can be found).
- Producing a list of likely "classes" of environmental factors, e.g., peer's behavior, stress, family, etc., each of which can be broken down into specific types, such as the stress associated with sexual abuse.
- [Early identification in youth could allow for greater vigilance and better "pre-emption." Genetic counselors do this all the time, but with single gene disorders. It wouldn't be typical genetic counseling in this regard, but something along those lines could be important for addiction clinics. If used properly, gene findings could lead to better treatments and better treatment approaches]

Excerpts from the discussion (led by Shirley Hill)

While some may think the prospects of genetic research of complex behaviors are hopeless others think the progress made points to a very promising future. Genes are obvious contributors, yet with this realization come the dangers associated with genetic studies of addiction, which carry a substantial risk to the families, if the information falls into the wrong hands.

The issue of IRB diversity was also brought up. Some are being very open to doing a variety of things while others are very conservative. Ethical and social considerations have to be addressed in such a way that research can continue.

In this context, the question was raised as to *whether or not a new science needs to be developed on how to communicate genetic and phenotypic information to parents, teachers, etc., and on the best ways to use this information and how to prevent its misuse.*

3. IRBs and conducting genetic research

Presenter: Lauren M. Broyles, University Of Pittsburgh

Ethical considerations for the IRBs of protocols in genetic research in substance abuse. Research at the intersection of genetics and substance abuse has the potential to magnify ethical concerns associated with each domain. Different ethical concerns attach to different addictions, thus stigmatization index for drugs>> alcohol>>tobacco. Likewise, different levels of concern are raised by the following genetic research related topics:

- Privacy concerns
- Vulnerability status
- Physical and psychological welfare

- Stigmatization and psychosocial sequelae
- Autonomy infringements

Develop a preventive approach to ethics, taking steps to identify, address and prevent patterns of conflict and concern. IRBs are charged with this anticipatory preventive approach, which covers all areas of potential concern.

Areas:

Privacy: in relation to recruitment and data management issues; aim to avoid *stigmatization* of probands and their families and *discrimination,* particularly in employment and insurance. Both are rooted in largely mistaken beliefs of *genetic determinism.*

De-identification methods: safeguard against breaches, PI's are responsible for brainstorming about preemptive practices.

Consent: it is important to use the recruitment and informed consent processes to create an accurate understanding of the *promises* and a balanced assessment of the *risk* implicit in the research. Need to be mindful of the fact that, while substance abusers are not considered a vulnerable population per se, they are often simultaneously members of one or more federally designated vulnerable populations, particularly cognitive (deliberational capacity), allocational (lack of social goods) or juridic (accountable to authority). All of these could impede the potential participants' understanding of the consent process and study requirements. Meaningful discussions of the elements to be disclosed are an integral part of the *informed consent process*. IRBs need to fully evaluate risks to participants' autonomy. IRBs and PIs should avoid blanket assumptions about decisional capacity or the volition of any group. IRBs should also be aware of how to implement vague criteria regarding the applicability of "waiver of consent" for certain situations. Since, in general terms, the waver approach is on very shaky ground, it would be advisable to strive for a clearer and narrower definition of what constitutes or defines a subject.

Remuneration: While compensation should avoid undue inducement the IRB should not assume that it is automatically coercive. [Participants may just want monetary compensation….they may not fully appreciate the depth/length of research to which they are consenting].

In order to create a safety net to protect participants:
- Actions should be taken to prevent any life-threatening harm and
- Participants must have a clear understanding of what actions researchers will and will not take in order to promote and preserve their individual welfare.

Finally, it is time for researchers and IRB to recognize what has become a central tenet of genetic counseling: providing information is, in itself, a form of intervention.

Excerpts from the discussion (led by Paul Applebaum and Joe Cubells)

Genetic diagnosis can both trigger feelings of genetic inadequacy or diminish attributions of responsibility.

At the population level, the issue of "*group harm"* has to be confronted (e.g. the frequent headlines that link a particular ethnic/racial group to a disorder). This is one of those things that are bad outcomes of valuable things that we do. The only countermeasure to the slippery slope that ends in the eugenics process is *education.* [includes educating the researchers, IRBs, government regulators, physicians, public, policy makers, and media].

Question (Maaloof): Does genetic research, by moving the focus of drug addiction away from a behavioral problem, have an impact on treatment? Is it giving patients a defeatist kind of attitude?

Answer (Cubells): By biologizing substance use disorders there is a de-stigmatizing effect that can be very positive. In my clinical experience, substance abusing people have gone far beyond ever enjoying the drug. Most of them really want to quit and they just can't. The relief that ensues can be harnessed psychoeducationally. It could also be a great mechanism for denial.

Comment (Applebaum): I think that saying to people your disorder (mental or drug addiction) is a brain disorder [anchored in genetics] could turn out to be more stigmatizing than whatever they thought previously. Now they *know* they have something *permanently* wrong with their brains. They are different.

4. Implications for criminal responsibility

Paper by Stephen Morse, University of Pennsylvania
Presenter: Henrick J. Harwood, The Lewin Group

One has to first recognize that *genetics is just one of many causes of addiction.*
Two underlying theses:

- *The discovery of genetic or of any other physical or psychosocial cause of action raises no new issues concerning responsibility.*
- *Discovery of such causes does not per se create an excusing or mitigating condition for criminal or any other type of behavior.*

The paper acknowledges that when we talk about drug addiction or dependence on any substance, there is always this debate between brain disease and moral failure.
It concludes that most addicts should be responsible for most criminal behavior motivated by addiction, but that addiction can in some cases affect the person's ability to grasp and be guided by reason.

Yet, *criminal law is about actions and not about genetics.* On top of this, genetics accounts for about 50% of the overall variability of addiction, thus genetics is not *the only mechanism*. [heritability can also mean environmental influences, it is not just what is inherited.]

Since the law deals with intentional actions as the determinant factor in effecting justice, the heart of the matter is twofold. On one hand, there is a relationship between craving and compulsion (as understood in the context of the internal coercion theory), and then the extent of responsibility on the other. In short: are craving and compulsion mitigating circumstances? The gist of the paper is that because of the vagueness and subjectivity of these terms, this would be a very slippery slope. ***The lack of scientifically validated***

measures for intensity of craving and compulsion are problematic; and the fact that we have (now) discovered more information about biological and other causes for these states of compulsion and craving does not help us a whole lot.

The author does not think that the theory of irrationality in a drug addict provides for a mitigating circumstance either.

Excerpts from the discussion (led by Mark Rothstein)

So two main conclusions of the paper would be: First, addiction is not a defense; and second, for purposes of legal responsibility, it really does not matter if the basis of the addiction is genetic, environmental or both. So, *can we go home now? No, because the supposed or proven correlation of genetics with addiction (and with aggression, impulsivity, risk taking, etc.) might work at various phases of the criminal justice system. Examples are bail posting, sentencing, and parole. In all of these cases the justice system might want to consider that these are not hired killers but people who have problems and that they have done terrible things, but they should not be treated as maximally harshly as the law might allow.*

The genetic argument, however, can be used by both sides, depending on timing.
Convict: I am genetically predisposed, you've got to give me a lighter sentence.
Prosecutor: He is compelled to do these things; if he's out, he'll do it again.

Another important concept is that of prevalence. The insanity defense is tolerated in part because it excuses a vanishingly small percentage of defendants. We have to consider the implications of broadening the approach, to a situation in which 60 to 80 % of felons are intoxicated with something at the time that they commit their offense. This would undermine the entire criminal justice system.

The whole scenario would change down the road, only if we had an effective and conclusive treatment for substance abuse.

As a concrete suggestion, Mr. Hardwood proposed that if NIDA had some extra money judicial education would be a terrific opportunity. Mr. Applebaum added that educating prosecutors and the general public about genetics and its role in disease, and in addiction, would be very helpful.

5. Privacy and discrimination Issues

Presented by Mark A. Rothstein, University Of Louisville School Of Medicine

What are the ethical, legal and social implications of *identifying* a genetic component to drug addiction?

Over-arching concerns
Having such a component identified is a *double edge sword:*

- *The information can be used to lessen the impact of the defect*
- *It can also be used to show inevitability*

The identification of a genetic component also increases the risk of stigma and discrimination (in the context of employment and health/life insurance) against the individual, their relatives or an ethnic group.

Additional points

The erection of legal firewalls between third parties and the private information misses the point and is doomed to fail (e.g., a prospective employer can always get the information if the applicant is interested in getting the job). The real, and more fundamental, issue that legislators have managed to avoid is: what are the rights of life insurers vis-à-vis applicants, or employers vis-à-vis applicants, etc.

The issue of the *"time lag"* between diagnosis and possible outcome directly affects this discussion. For example, if I am tested now and found to be predisposed for Alzheimer's disease, 20-30 years down the road, can this be a consideration for selling me long-term care insurance? What about for hiring me? etc. Obviously, employers want to control health care costs, but they also don't want to make employees sick or sicker.

There are *2 classes of sources for genetic discrimination:*

- When the predictions are inaccurate (misreading of scientific information)
- When the prediction are accurate (should someone be unemployable at 25 because of a disease that will strike 15 or 20 years later?)

There are rational and irrational bases for hiring people. Both categories however contain acceptable (legal) and unacceptable (illegal) criteria to make hiring decisions.

As a society we are willing to accept the economic inefficiency that results from having to deal with the illegality of otherwise perfectly rational decisions. The cost of this practice is then assumed by the public for whom the social benefits are more important than permitting such kind of discrimination.

The question then is whether the irrational misuse of genetic information, is legal-irrational or illegal-irrational? Should genetic discrimination be prohibited like religious or sex discrimination?

The American with Disabilities Act (ADA) partially tackles some of the issues that arise from the conflict between privacy rights and legitimate business concerns.

- Pre-employment medical exams and inquiries are prohibited.
- Pre-placement (or post-offer) medical exams (no limits on scope) are authorized. An offer can be withdrawn on a medical basis only if it is job related.
- Exams on current employees can only be job related and consistent with business necessity or voluntary.

(Drug tests are not prohibited at any time because, by statute, a drug test is not a medical examination).

Pre-placement exams are not regulated, so ADA has nothing to say about genetic testing at this stage.

In any case, *the laws are extraordinarily problematic* for all sort of reasons starting with what is genetic, what is a genetic test, what is genetic information, does it include family health histories? If it doesn't, it is too narrow, if it does, it is too broad, etc.

For all these reasons *the speaker believes that to enact genetic-specific legislation would be futile. In practice, the law works to side with the notion that genetic predisposition is not a disability. Predisposition to drug addiction is not a disability.*

Regarding drug abuse ADA has its section 104 that says that: a qualified individual with a disability shall not include any individual who is currently engaging in the illegal use of drugs, when the covered entity acts on the basis of such use. Nothing in this section shall be construed as excluding an individual who has successfully completed rehab and is no longer using. Specific court cases show however, that this protection is tenuous at best.

Regarding health insurance:
43 states have enacted laws prohibiting genetic discrimination in health insurance. The laws do not apply however to employer-sponsored plans (which insure most people). Result: only 5-10 % of the population are protected by the law. And, within this population, it only applies to asymptomatic individuals.

What comes through in all these examples is that *it is not really about genetics. It is however, an issue of relative economic power, the political power of individuals.* (By the way this is not an issue in Western Europe or Canada; only in the US). If genetic discrimination is the problem, the solution is certainly not a genetic discrimination bill. This would be "a half a loaf" approach and it has not worked. Obviously, the climate is not ripe for a whole loaf either (e.g., universal health care reform, for example). *The real thing holding us back is political.*

6. Field report on genetic research on tobacco

Presented by Caryn Lerman, University of Pennsylvania

Focus on the genetic studies of response to different pharmacotherapies for drug addiction, particularly nicotine addiction. Focusing on discrete phenotypes is a more refined approach than looking at whether someone is dependent on a drug or not. Looked at in this context, genetic information will be useful primarily to tailor pharmacotherapy treatments.

In the tobacco field, *some have looked at the reduced prevalence over the past 60 years and concluded that smoking addiction is completely environmental. The plateau over the last decade however, suggests the existence of strong biological factors at play.*

She proceeded to present

- A list of all the evidence supporting the notion that nicotine dependence is heritable (such as twin studies (30,000 subjects) showing an heritability factor of 56% for smoking initiation, higher for dependence).
- A list of good candidate genes that might be involved (highlighted the polymorphic (nicotine) metabolizing enzyme (CYP2A6), and
- A catalogue of treatments that might be effective for particular smokers based on their genotypes. (e.g., a specific metabolic profile would determine the length and concentration needed during replacement therapy).

Three key tests are suggested for the successful implementation of knowledge of genetics toward tobacco control or cessation:

- Confirmatory data on genetic associations.
- Establishing predictive value of genetic data (clinical effectiveness assessment).
- Careful evaluation (in a controlled research setting) of the risks and benefits of communicating genetic information to individuals.

During the discussion of this paper it was brought up by Katrina Karkazis, (Stanford University School of Medicine) that:

"Such [Diagnostic/Therapeutic] targeting is likely to have many unintended social consequences. Potential stigma is only one problem. *Of greater concern is the possibility that targeting of drug prevention efforts by race may reinforce existing social stereotypes, conveying the scientifically inaccurate notion that humans can easily be divided into biologically distinct categories that potentially matter."*

Perhaps the term race should be abandoned when discussing actual genetic variation and reserve it for more appropriate contexts.

She also points at the following risk: "By individualizing the problem, genetic explanations of smoking could be used to jeopardize mass oriented public health strategies that focus on preventing or reducing tobacco exposure."

[The proof, though, will come only after personalized treatments have been available and then we can see if incidence for smoking increases or decreases.]

Conceptual highlights from the workshop

I. Information Impact. Communication and education of genetic information will have to become more sophisticated than what genetic counseling currently offers. Providing information *is* a form of intervention.

II. Relevance. Genetic makeup, per se, is largely non-predictive for most instances of complex behaviors, particularly when it is part of a partial picture. It will be a long time before the outcome of gene-environment interactions is properly framed or understood.

III. In practice. Focusing on discrete phenotypes is a more refined approach than looking at whether someone is dependent on a drug or not. Genetic information will be useful primarily to tailor pharmacotherapy treatments.

IV. Diagnostic screenings. Genetic labeling is a double edge sword.

V. Ethical concerns. Ethical issues need to be dealt with from a preemptive and proactive stance, to avoid stigmatization, discrimination and invasion of privacy.

VI. Criminal responsibility. Discovering underlying genetic causes or pre-disposing factors raises no new issues concerning responsibility. Thus, they do not create excusing or mitigating factors for criminal behavior. Criminal law is about actions, not about genetics.

VII. Discrimination laws. As a society we are willing to accept the economic inefficiency that results from having to deal with the illegality of otherwise perfectly rational decisions.

VIII. Americans with disabilities act (ADA). In practice, the law works to side with the notion that genetic predisposition to a disease is not a disability. Predisposition to drug addiction is no different.