

Irving Gottesman  
American Society of Law Medicine & Ethics  
DNA Fingerprinting and Civil Liberties Project  
RO1-HGH002836-02  
Workshop 3 Presentation  
May 3, 2005

I didn't feel comfortable talking about the entire field of behavioral genetics and it was suggested by the organizing committee that I narrow it to topics of more interest to this particular audience. So I've narrowed it to aggression and anti-social personality.

Before anyone else accuses me, I have to make clear right off that we are not in the business of genetic determinism. That's not what behavioral genetics is all about. We are in the business of probability just like anybody else who is interested in beating the odds when they are making predictions. The kind of disorders or traits of behaviors that I'm going to be talking about today were mentioned in passing by Leslie when he set me up to talk about the genetics of complex traits and the genetics of complex disorders.

We're dealing here - where there are significant genetic influences on a trait- with the effect of many, many genes, combined with many, many effects of different kinds of environmental inputs - maybe prenatal, perinatal or postnatal. And they certainly are not limited to the kinds of things that occur within your own family, such as your relationships with your parents or your siblings. It could involve such things as the quality of the water supply.

I liked this quote because it will help cover my ass later in the talk. This is something that Curt Stern said. He was paraphrasing Goethe. It was interesting because Curt Stern was a Jewish geneticist who escaped from Nazi Germany just in time to conduct the rest of his career here in the United States. "Truth and the search for it can be suppressed not only by ill will, but also by good will." That will make more sense to you as I go through some of my presentation.

We in no way sweep this under the rug. The fact of the matter is that the founder of psychiatric genetics is considered to be Ernst Rudin, one of the biggest - I'll say "S.O.B.s" in the field of biology, psychiatry, and genetics. He was also one of the biggest boosters of Adolf Hitler. He not only prepared for some of the things Hitler was going to do after he was elected to power in April, 1933, Rudin and his group of individuals around him at his research institute were all set to go. This is from a speech he gave, I think it was on the occasion when he ended up getting a medal from Hitler or Hitler's birthday. "It was only through him that our more than 30 year old dream has become a reality and racial hygiene principles have been translated into action."

The kind of actions that he was talking about were immediately apparent within just a few weeks after the German democratic election of 1933. These laws were passed in rapid order, just the beginning of many, many draconian type laws that were passed in a

democratic fashion in a country that was considered to be following democratic principles. You'll be interested in the sterilization law of July of 1933 and, a little later in November, the law against dangerous criminals. The short abbreviation is called the 'castration law.' It allowed the castration of sex offenders, not all that different from what the United States had done in the first decade of the 1900's in the state of Indiana.

This research program - which actually wasn't based on research, but on fiat and the assumption that these characteristics that you see in this table were indeed heavily genetically influenced - had some consequences. I'll point out that there was no way to tell whether somebody's deafness was on a hereditary basis. There was no way to tell whether their blindness was on the basis of their genotype. The same is true of various kinds of mental retardation and these other characteristics.

The sum total was some 400,000 individuals being sterilized because of their presumptive ability to transmit these non-economic, meaning they use up the resources of society, to the next generation.

This warning from Diane Paul summarizes it in a moderate fashion. I'm sure that if she were here, she would put it much more strongly. The sense of this is a fact today: "These people worry. It keeps them nervous what we in the field of behavioral psychiatric genetics may be up to. Do we have a hidden agenda?" I don't have a hidden agenda. To the best of my knowledge, 99.9% of my colleagues don't have a hidden agenda.

I take these kinds of criticism pretty seriously based on my personal pedigree. I have one aunt who survived Auschwitz and after just a few hours of doing research in the Holocaust Museum, I had already come across 200 names of my mother's relatives and my father's relatives.

This is something that you're all very familiar with, I'm sure. The reason I'm showing it is because I'm trying to make the point that crime - criminality - is much too important to be left in the hands of just the people in this room and your colleagues outside of this room. There's plenty of room for you to get all the help you can get, and some of that help will come from the fields of behavioral and psychiatric genetics.

It's just incredible to people in this country, especially to people outside of our country, to find that there are 7 million people in this country who are under some kind of control of the so-called criminal justice system, including all people on probation and parole. Now 3.2% is an average across all ethnicities. If you break it down, you'll actually discover that 9% of the black population of the United States is under some kind of supervision because of a crime that they have committed.

This is not an empty topic. It's been taken seriously in the past. This book is small and obtuse so feel free to come up and browse through it in the next day or so. This book and the meeting on which it was based was organized by Sir Michael Rudder, a world famous child psychiatrist in the UK. He is recently retired but about as retired as I am at the

University of Minnesota. We seem to be as busy as ever. In that book, you'll find an extension of my remarks and of the papers that I put in the briefing book, not all of which were written by myself.

I find that unless you identify the phenotype very carefully, you're going to end up analyzing garbage: garbage in/garbage out. The DSM criteria for Antisocial Personality Disorder is not as good as the international classification of diseases for characterizing these individuals with what is called there "Dissocial Personality Disorder". Not everybody with Dissocial Personality Disorder will be a criminal or will have been convicted yet. Many of them will never be convicted because we're dealing here also with white collar crime. I won't mention the long list of people who have occupied the White House and other places of power who will meet many of these criteria. Some will be over the threshold. When they are over the threshold, the law – eventually - catches up with them. I think that Canada is way ahead of the United States, for example, because of the research program of Bob Hare in Vancouver. He uses these kinds of criteria to identify the individuals that he wants to bring in to the laboratory in order to find out what makes them tick. He has not yet moved to a genetic research program but he has a heavy program in the psychophysiology.

Lifetime prevalences of Antisocial Personality Disorder are worth noting, especially because of inside information that I will now reveal to you. These studies were done in the 1990s. The ECA is the more well-known project. The National Comorbidity Study published in 1994 here in Boston was a follow up to this kind of work.

The prevalence of Antisocial Personality Disorder in males is 7.3%. You won't find that in the written material about the ECA and the reason is because I'm using the information derived at the site at which I was working, which was Washington University in St. Louis alongside Lee Robbins and John Helser. The government – the OMB - would not allow certain questions to be asked in this door-to-door survey of an excellent nationwide sample conducted in five centers. These questions were considered to be too sensitive, so the Washington University site obtained private funding to ask people about their drug dealing, about their child and spouse abuse, about their activities on the street – all with the guarantee of confidentiality as no names were collected. That raised the rates by about 25% more than the rates in the other centers. You can see that just changing the amount of data you collect can have a huge impact on the prevalence rate. That will then determine the magnitude of the public health problem or the magnitude of the potential problem for the criminal justice system. For females, it was 1%.

In terms of raw numbers, it means that 8.9 million males out there have the potential – have an enhanced potential - for getting into trouble with the criminal justice system.

Hare has shown in Vancouver that not all individuals with a diagnosis of Antisocial Personality Disorder will end up in prison, and not all people in prison will end up with a diagnosis of Antisocial Personality Disorder. There is another category in DSM called "adult criminal behavior".

The break down by race is very important. It has been ignored generally, but there is no difference between these two ethnic groups, whites and blacks, in the United States. They both were right at about the same level. I won't bother you with the rest of those numbers.

When we go to meta-analyses of all those published studies that deal with antisocial behavior at various levels, and here we're dealing with individuals aged 18 and over - these data were reviewed by Terry Moffit and by Riand Waldman - when you do this for over these 100 plus studies, you find that the contributions to the variants to reliability for behaving in an antisocial manner, as defined by DSM, that 50% of that variance is attributable to genetic factors. That doesn't tell you about the factors. It just tells you that if you want to partition the variances as fashioned, to give you clues as to how to allocate research funds, you might be guided by this information.

30% of the variance and liability was attributable to idiosyncratic, or person-specific, experiences and to error of measurement. Shared environment, that is, those things that you share in common with your siblings within your own family of rearing, only accounted for some 20% of the variant.

What does this do? It sets the stage for taking further action. It doesn't give you any answers because this number, 50%, is actually the value of the heritability of reliability. I find that telling my students and others that will listen to me that the concept of heritability is like being licensed to kill by James Bond 007. You have to have a license in order to use the statistical concept of heritability wisely. If you don't use it wisely, it could get you shot down, rather than you using it for some other purpose. It is often misused in a kind of king-of-the-mountain fashion. Some of the researchers, they're in the minority, thank heavens, want to increase the magnitude of the heritability estimate for what they're looking at, because then they can jump to the improper conclusion that we don't have to spend so much money on righting the wrongs in society. We don't have to spend so much money on Head Start types of operations because the heritability of I.Q. test scores is .7 or .8. Here - for ASP is about 50%. It has nothing to do with how to right the wrongs in society.

I depend a lot on my research, and there are a whole bunch of us who do this, using twins as a kind of initial search and find out strategy. It's a low cost way when dealing with traits of unknown origin or whose composition could range from 0% heritability to 99% heritability or 0% environmentability to 99% environmentability. How do you get a handle on this big question?

The answer is you use a twin strategy. You can use twins in elementary school, in high school. You can use twins in the armed forces. I happen to be the chairman for the IOM - the National Twin Committee. We have 16,000 pairs of twins on our files. All of them were drafted, both of them during World War II. We now have only 4,000 of these pairs - both of which are still alive - but we have data on them going back to the time when they passed their draft board examinations. We have access to that information and we have been using it. We have a web page at the National Academy of Science under IOM.

You can find the medical follow-up agency and see all the various kinds of studies that have been conducted that range across a very wide range – from heart and lung disease to alcoholism, schizophrenia, and other things.

If I do a kind of meta-analysis in order to differentiate among the kinds of antisocial behaviors, then I use one definition of such behaviors, such as juvenile delinquency. Not to say that juvenile delinquency is an absolutely terrible phenotype for genetic analysis, and that's because it's handed to us by the criminal justice system. There are so many ways and so many impacts on whether or not you- you people in this room – have been called juvenile delinquents between the ages of say 6 and 18. If you came to the right neighborhood, you would not be called a juvenile delinquent, even though you did the very same thing as somebody a few miles away. They'd erase your name from the blotter. They'd call your parents. In fact, they often knew your parents by name and they would say, "Johnny's been a bad boy and he threw a rock at a squirrel or he threw a rock at a squirrel and it missed and went through a window. That's okay."

Your father says, "I'll pay for it", and then it disappears.

That's not true of people living in different parts of your cities. When we do twin analyses and compile them, there are only four systematic studies in the literature. You find that the rates in identical twins are exceedingly high – 90%. Now if you want to jump to a conclusion based on that, you'd be making a terrible mistake because you would probably say something about how important genetics is. But then, when you look at the rate in same sex fraternal twins, it's almost as high, and way, way too high to be thought of in terms of the kinds of ways you see genetic factors behave.

We don't expect rates to be over 50% when genetic factors are importantly involved in fraternal twins who are just like you and your sibling. When you do the same kind of analysis with adult criminality, then these individuals, and this time we're talking about 7 studies in the literature – one of which I have conducted with colleagues in Denmark. I'll give you the details in a few seconds.

Here you find a nice split – nice if you're looking for the evidence that there is something genetic going on that's worth our attention as psychiatric or behavioral geneticists. You get a very different split in your perception of whether genetic factors should be pursued. I'd say yes here and here I'd say no.

The rationale for twin studies is straightforward. This is the simplest version I could think of and it ends up with a reasonable conclusion. You only end up with a guesstimate of the genetic importance or the genetic unimportance – the unimportance of genetic factors easily revealed by twin studies. When you do a twin study of measles or mumps or some other highly infectious disease, you get the kind of results I showed for juvenile delinquency. You don't really have much of a leg to stand on for pursuing a genetic research program.

Now in the case of some infectious diseases, you will still get a heritability coefficient, even if it's as low as 5%, 6%, 7%. That tells you that there are genetic factors involved

in the resistance to developing a highly infectious disease. That information is worth knowing. If we had that information for HIV positive individuals, we could be on the trail of finding some genes that may be useful in telling us about the pathophysiology of resistance to certain kinds of infectious diseases.

So I'm not pooh-pooing it when you have infectious diseases. When there's a genetic component to resistance, it's well worth knowing because that may solve the problem in a hurry.

These are the details. I usually don't show them, but I figured this audience could handle lots of numbers on one slide. Furthermore, these data don't have to be written down because they are in the briefing book in one of the papers. Now these are the results from the Danish National Criminal Twin Sample. This project was started by the late Carl Otto Chrisjansen. He was trained as a lawyer and a sociologist and he was one of the ranking criminologists in Scandinavia. I was very lucky to have been partnered up with him during my sabbatical in Denmark.

You can see where we had large numbers of twin pairs. This is the base population. I should point out that Denmark, like many other countries that have national health insurance or that have a strong social conscience about social welfare, thought that it was important to have a national twin register. Their National Twin Register goes back to 1870. You heard me right – 1870. We have more than 130 years worth of twin births in Denmark that I can access as long as I give them my first born son as a hostage. When I worked there I worked with and for their federal government and nobody has ever been embarrassed by any unauthorized release of information.

The thing I'll point out for you is that as geneticists, we're interested in this last column of correlations within twin pairs. But, it's easiest for me to talk about the concordance rate in identical and fraternal twins, including opposite sex fraternal twins. Nobody else studies those but we have access to that in the Danish national population.

What I'm pointing out to you here is that the rate in identical twins, male/male for felony offending that gets you put into prison, even if it's for a short period of time – they don't have long sentences in Denmark, they figured out a way around that – is 51%. This number is to be compared with the rate in fraternal same sex twins, dizygotic, of 30%. That generates these correlations here, which are, as I say, more important, easier to work with. These numbers by themselves will generate a heritability for the liability of committing a felony offense in Denmark, under those environmental circumstances, which are particular to Denmark and you may be able to generalize to Norway and Sweden. I'm pretty sure that you can generalize that much.

It will tell you that there is an appreciable genetic component in the liability to felony offending under those conditions and they would be worthwhile to have some kind of a genetically oriented research program in addition to the other kinds of research programs into poverty and health care delivery generally seen.

For the females - most people are not able to study female felony offenders - we had 15 pairs altogether. They have a concordance rate of 33%. The female/ female fraternal pairs had a concordance rate of 13%.

When you go through the manipulations of these statistics that are standard, you find that the heritability of a felony offending is the same in males as it is in females. It's very interesting to us. I won't go further than that but; again, you can go into the details of this in the paper in the briefing book.

Now a lot of people have said, when we published those earlier findings, that, well, what do I care about what Danish twins were doing in 1890 or in the year 1900 when they would have been teenagers? I say, well, there might be something there. Meantime, using the National Vietnam Era Twin Register -I was one of the people that set up the National Vietnam Era Twin Register from all men and women who served during the Vietnam War period. These men and women served not only in Vietnam but our control group served in Western Europe - Mike Wyance, who's here at Boston University, was the leader of this research team, and they showed that when you dimensionalize the features of anti social personality as they're laid out in the DSM, you can then have a graduated scale of severity of juvenile antisocial traits which leads to a diagnosis in the DSM of "conduct disorder". You can't get that diagnosis as an adult. You have to be under age 18. Then we have adult antisocial traits which leads to a diagnosis of Antisocial Personality Disorder. You can only get that diagnosis after age 18. By dimensionalizing and then conducting interviews over the telephone to this sample - you can see this sample size is huge - it will also tell you how many men and women served during the Vietnam War, compared to what we're now facing in the Gulf War and Iraq and Afghanistan.

We're interested in those twins, but we have so many twins - we have a backlog of twins and we're starting a contemporary twin register to cover more of the armed forces. Almost none of our twins came from the Air Force. The vast majority came from the Army. We are interested in those men who served in the Navy and Air Force and we hope to catch them the next time around.

You can see here confirmation of what I'd shown you earlier, that when you look at antisocial behaviors committed by juveniles the genetic component is virtually nil. The most important contribution to that variant is non-shared environment, unique aspects of your environment - you - as you were growing up - things that happened to you that did not happen to your brother or your sister. This would include your choice of friends, the kinds of substances that you chose to smoke, drink, inject - things that you did that your brother or sister did not. Those kinds of things are the important things. Within-family environment is also important but at a much lower level.

When it comes to adult antisocial traits, remember, these are veterans of the Vietnam era. They are not criminals. They are being asked in the telephone survey yes or no kinds of questions to the criteria in the DSM that leads to such diagnoses. We find here that the largest component to adult antisocial behaviors is, again, the non-shared environment.

The genetic component is certainly high, but not quite as high as what I calculated for the Danish twins who were felony offenders. I can tell you that there is much unanalyzed data that we have in the Danish Twin Register because we also have access to arrest records. If you were arrested but not found guilty, we could still analyze that data but we found ourselves being drowned in such data and we didn't think it would pay off. We're saving that for some graduate student.

This is another way of illustrating the role of severity of offending in regard to whether you were able to or not able to detect signals that would lead to a genetically oriented, in part, research program. When we start out with adolescent delinquency, we're interested in which delinquents go on to commit antisocial personality kinds of behaviors. There aren't too many. Fewer than half of adolescent "bad boys" go on to commit adult acts that are even worse. In some cities, such as Minneapolis, which is a very civilized place, we found that between 5% and 10% of juvenile delinquents went on to commit adult crimes. There's not a forecast of a dire outcome as an adult criminal.

When you divide up the samples of twins into those that went on to commit an adult ASP behaviors, maybe got a diagnosis, meeting the criteria - when one or both twins developed adult Antisocial Personality Disorder - we find the genetic factors are important but the shared environment, again, is rather small, 10%, and that the unique environment is the most important, looking like some of the other data I have shown you. We were using the standard twin methods, slightly enhanced with techniques that are called - the computer program is called MX, the reason I tell you that is because it's online. It's maintained by Mike Neal of the Medical College of Virginia in Richmond and you can have access to the entire computer program from that website- and this criteria, which is a severe one.

Let's look at the other part of the sample where neither twin went on to develop Antisocial Personality Disorder. Using the genetic component as determined by these sophisticated models - another name for them is ACE Models, the additive, the common and the environmental variances - you find that the person specific is by far the most important. The unique non-shared and the shared environment goes up to 35%. Again, these are just numbers, but they help orient the scientist and the research program.

If we only had twin family data, you could still say, 'well I bet it was a shared environment, somehow or the other and we just need to work harder at getting it out, teasing it out.' Fortunately, at the same time that I was working with Carl Otto Chrisjansen in Denmark on the adult criminal twins, Sarnoff Mednick and his colleagues, under the same NIH grant, were studying the adopted-away children of felony offenders. This is a classic study in the literature that I recommend you look at. It was done in conjunction with Barry Hutchings. Barry Hutchings, although he is of Welsh birth, is a Danish citizen and he's the one who did the hard work in the field. The important cells here - it speaks for itself, but when the biological parent - this would be the father - has been registered as a felon and the adoptive parents, those who actually raised the child, were not felons and had clean records (a very large sample size), 20% of those sons committed a felony offense.

How do you interpret that data? You have to look at this cell here – this is where the biological parents have not been registered as felons and the parents who raised them were also free of any kind of criminal behavior that was of a serious nature. For those sons, 13 ½% committed a felony offense. What's the base rate in the general population for non-adoptees? This data is constrained to looking at adoptees. In the general population at the time we were doing this work, it was 10%. That's because that would include such things as driving under the influence, above a certain speed. It would include such things as smuggling. It's very easy, they think, to smuggle. They have a high tax rate on cigarettes and alcohol. When you're coming back from Sweden, some people are tempted to become repeat smugglers and then they end up having committed a felony offense.

We have a high base rate of 10%. We have a rate here that is higher, even when neither of your parents has been a criminal and we attribute this increment, which is a 35% increment over the base rate, to being an adoptee at that time. There are reasons for this. What are the characteristics in Denmark at that time of giving birth to an adoptive child? The vast majority of these adoptees that came up for adoption are the children of unwed mothers and fathers who are usually teenagers. They have certain characteristics of impulsivity, being unable to restrain themselves which may be reflected in the higher rate. I'm about to talk about that. This rate here, 20%, is significantly higher than this and is in line with the positive manifold we're having.

Fortunately, we have the mouse. Francis Collins and his colleagues wisely invested a lot of money in studying the mouse. They also study the zebra fish. They also study human beings as we've heard in the speaker before me. We learn a lot and it's very easy nowadays to match up the genotype of a mouse with the genotype of us in this room. There may be mice in this room. I don't know. You can find which parts of the mouse genotype are exactly like, or almost exactly like, the human genotype and then use the mouse information as a jumping off point to examine those genes in humans that are like those genes in the mouse that have been discovered. This is from a meta-analysis by Gene Maxum, University of Connecticut, and he's already identified these and other genes. I'm just giving you a sample that are involved in increasing or sometimes in decreasing the liability to behave aggressively or with violence in certain mouse experiments involving access to things that also lead to aggression in human beings - trying to get sex, trying to get food, things like that.

Then in an experimental situation you can breed the aggressive mice with aggressive mice and non-aggressive with non-aggressive and in that process you can quickly identify these genes as standing out. We cannot do that with human beings, thank goodness, but we can use ordinary association and the linkage studies with individuals who have been in experiments looking at violence or violence often combined with alcohol dependence.

I take this list from the research program at the NIAAA of David Goldman and many of these genes that you see here have been implicated and they deal with variations in the serotonin transporter system or in the serotonin receptor itself. We also have one

dopamine receptor up there that's been implicated across studies. We have MAOA, which has been implicated in a widely heralded study by Caspy et al. I should tell you that this study is much more important to people outside the field of behavioral genetics than the people who are in it. We would not have gotten as excited about it as did the editors of *Science* who featured it.

Then we also have one of the comp genes, which we know lowers frontal lobe performance. It would be interesting including these genes and I'd say maybe 1,000 others if I'm allowed to get some funding to come up with an aggression-specific chip to be used in studies with human beings.

I take this quote from a paper that David Goldman contributed to the *Journal*, which another paper from some issue of a journal that you see in the briefing book. He said, in addition to other things, that he hoped that I would not be tarred and feathered the way I almost was last time. This is worth taking very seriously. This is after he's digested everything I've told you, after he's taken into account the recent genotype by environment demonstration, by Caspy et al and some other individuals, usually featured in *Science*, usually featured in *Molecular Psychiatry* and sometimes featured in the *Journal of Behavior and Genetics*, all first class high citation count journals.

The main problem is that there's probably no allelic variant that has an isolated effect on aggression or anti-sociality. The effects are on things called endophenotypes that modulate such behaviors. Another way to interpret this, these statements from David, is "Go slow. Proceed with caution. Don't be too full of yourself."

Crime is not inherited. That's obvious to all of us, at least all of us in the business of doing this kind of research. What is? I've suggested, in respect to a lot of other traits, including this one, that it's the genes that underlie endophenotypes. These endophenotypes occupy a place in the gene to behavior pathway, which is a complicated pathway. We are working very hard on it. All of the efforts of the National Human Genome Project can be fitted into this without any trouble whatsoever.

These characteristics that you see here have been taken from research on infants, on children, on adults, because they are clues to intervening variables that lead to, in some unspecified way for the time being, traits or symptoms or features of the thing itself, the thing itself being criminal behavior or Antisocial Personality Disorder.

I'll show you one instance here, research on normal twins. These twins are from the state of Wisconsin, so they must be normal. They sometimes wear funny hats at Packer games, but that doesn't mean anything. I think it's just two of us in the room that care about that, but when you run correlations for these scales of infant behavior - at this time we are doing it with children, preschool children - you find that there is a large difference between the identical twin correlation and the fraternal twin correlation for such scales. These are normal elementary school or pre-elementary school children with such traits as anger, inhibitory control, high pleasure - getting a lot of pleasure from such things such as food or being held - impulsivity and low rates for the fraternals.

This is again grist for our mill that suggests that we are on the path to discovering endophenotypes, especially important for traits that are complex and involve many genes and many environmental factors.

To our dismay, even now, at this late date in the field, which I say can be dated back to 1960 - that's when the first book was published that had the words "behavior genetics" in the title- we usually find for human traits that 50% of the variants are associated with the environment, unspecified, 50% of the variants are associated with the genetic factors, unspecified for the most part. What we had in mind was that these genetic factors, when they're discovered would individually account for appreciable parts of the variants, hence 5%, 6% - and then that would mean that you'd only need about 10 such factors in order to account for that 50% of the variants that are under genetic control.

What did we find? The world tells us, or the data tells us, that it is much more like this, where there are maybe 50 to 100 genes accounting for that 50% of the genetic variance that keeps coming up when we're talking about the liability to developing felony, recidivist felony behavior, Antisocial Personality Disorder, schizophrenia, bi-polar disorder, 50%. But, the genes or the gene regions, or the snips that are being implicated, account for a tiny proportion of the variants that do not allow you any clues at all to individual prediction, let alone new predictions; it doesn't work well here.

This is a figure that is in progress. I'm hoping to finish it by the end of next week. This is trying to use that template that I use for talking about variations in individual differences in cognitive ability. You can apply that to schizophrenia. I've done that as a paper in your briefing book. Now, we've extended this template notion of using the endophenotype strategy, these things in between, the genes down here and the behavior up here, which is bi-polar disorder, bi-polar spectrum disorder. We allow for the simultaneous contribution of age over time, feeding into your increment and liability, for going over some kind of threshold. We allow for variations in the environment, being a favorable environment, being a rotten environment. We allow for epigenetic influences to work throughout this stream of events.

Here I've snuck in words which you wouldn't notice. This says "promiomix", this says "transcriptomix", I want to be ahead of the game. In between here, we have implicated endophenotypes with regard to bi-polar disorder. These endophenotypes can be taken from any realm. Here we have something taken from functional MRI. Could we have something taken from MRI - reduced anterior singular volume? I should also tell you that this has also been implicated in antisocial behavior. Then we have other things here that are likely to overlap also with the topic of interest during my talk here.

I recommend this as a way to think about the problem and to prevent you from rushing to judgment. There's no way to rush to judgment when you start to contemplate all of the elements that go into this. This is the simplified version. This is not like those metabolic pathways you see on the backs of laboratory doors around Cambridge, Massachusetts. This is another way of looking at the concept of endophenotype. It's something not

visible to the naked eye. If she had had scuba goggles and dipped under the water here, she would have a different perception of this man's phenotype, because of the pot belly, because of his reduction - he's height challenged.

Now, I take a quote from Troy Dustier, a colleague who doesn't share a lot of my ideas, but he shares some. I've served on the AAAS committee with him for the last four years. We have numerous interchanges, but I like this quote because I'm going to flip it over. You can read this more rapidly than I can, so I won't read it out loud, but he said, "We must maintain vigilance to prevent snip profiling from providing the thin veneer of respectable science while inscribing the racial taxonomies of already collected data."

This leads me to a modest proposal. I don't have time to give it to you now, but maybe during questions you'll ask me or during a group discussion we can get to it. I do want to note that there is a new IOM project. The head of that committee is Larry Gostin. The title of this committee is *Ethical Considerations for Revisions to the DHHS Regulations for the Protection of Prisoners Involved in Research*. What I will suggest, and I will give you the details later on perhaps, is that there is no reason why a prisoner should be prevented from showing their good side. There is no reason to prevent them from being volunteers when the proper safeguards are taken to anonymize the data. I am hoping that I can get a conversation going on that topic.

Lastly, I take a quote from the British economist who helped the UK get through WWI and WWII without getting completely bankrupted and quickly, relatively quickly, recovering, "When the facts change, I change my mind. What do you do?" Thank you for your attention.