PROFESSOR: Good afternoon. When we parted last time, I was -- you just did that demo with Sam, who was either collecting stamps or lady's undergarments, depending. And the point there was to describe the fact that any behavior is going to be distributed across the population in some fashion. It may well be that the extreme of the population is abnormal in some meaningful sense, maybe even pathological in some sense, but that the border between what is normal and what is abnormal is going to be necessarily ambiguous. There's not going to be some nice, neat line that can be drawn in all cases. I was arguing that something like schizophrenia is a bit more like that, where the abnormal state really does look quite different from the normal state and less like that it's on a continuum.

You will notice on your handout that it says Lecture 20. And those of you who are particularly observant will say, last one was called Lecture 20. And that's true. I just liked 20. No, this is really 21. And with a bit of luck, I'll label the next one 22. Otherwise it'll just turn out that there's 20A and 20B or something like that. Anyway, it really is the right handout. You'll discover that it is closely related to the later pages of the last handout that we didn't get to last time. Yeah, it's kind of the same is what people are noting. But I didn't have any faith that people would remember to bring the real Lecture 20 handout.

Anyway, what I want to talk about, at least initially here, is to talk a bit about how you would end up in this abnormal bin of schizophrenia. And one reasonable question to ask is, well, it's on the handout. It says, is there evidence for a genetic component? And the answer is yes. And the way you get one of the important sources of that information is similar to the data that we were talking about in intelligence testing.

Take a look at people who vary in the amount that they are genetically related to each other. Notably here, MZ stands for monozygotic or identical single-egg twins. And DZ stands for dizygotic two-egg twins who are no more similar than siblings. Concordance means what the chance is of Twin Two having the disease if Twin One has it. And so what you can see is that for monozygotic twins, if one of a pair of identical twins becomes schizophrenic, there's a 50% chance that the other one will, too. That tells you two things.

Well, it only tells you two things if you look at the dizygotic. The dizygotic twins have a much lower concordance rate of about 15%. So that tells you first of all that there's a probable genetic component there, and second of all, that it's not absolute. If you have the genetic mutation that makes you color-blind or color anomalous, you'll be color anomalous. There's no big mystery at this point about that. If you have whatever the genetic predisposition is for schizophrenia, something else has to happen before you would end up showing the disorder.

Now, these twin studies run into the same problem that the intelligence testing twin studies did, which is that monozygotic twins are simply more similar on all sorts of things. You know, they're treated more similarly and so on. One way to look at whether or not there is a, you know, to try parceling this out, is this third line here. This was a population of dizygotic twins who thought they were identical. You know, they looked alike. Presumably they're the same sex and stuff like that. Thought they were identical. You'll see that their concordance rate was less than the 50% that the true monozygotic twins had. So there does seem to be something to being really genetically identical.

You can also do twins reared apart things. But look, if you have a set of -- twins reared apart -- not common. But all those twins have IQs. You can always measure their IQs. If you take twins reared apart and then take the cases where one of them has schizophrenia and ask what the concordance rate is, the answer is it's quite elevated. But, you know, it's a really small population of people. You know, twin reared apart and schizophrenic, it's not a big crowd.

Now, when you go look for the genetic marker, since the late '80s, there have been a slew of papers on genetic markers for schizophrenia. The way you look for this -- one of the typical ways to look for this is that schizophrenia runs in families. And if you go and analyze the genetics of families, you can find specific loci that seem to be abnormal in the schizophrenic members of the family. The difficulty or the interesting aspect of this genetic story is that the story that works for this family doesn't necessarily work for this family.

In the early days of this, there'd be some big article in *Science* or *Nature* or something saying gene locus on chromosome eight for schizophrenia or whatever. I'm making it up. And then, you know, either in the same issue or in the, you know, next week, there'd be another thing saying, but not in this family. Clearly schizophrenic but not clearly having the same defect. It suggests that there are multiple roots, genetic predispositions, to schizophrenia. It's also possible that you need more than one genetic insult. That's jargon -- you don't say, you got an ugly gene. You need to have perhaps more than one defect in order to have the susceptibility

to schizophrenia.

One of the curious little wrinkles that I dug up in my reading on this -- and I've only read this in a secondary source. I have been unsuccessful in tracking down the primary source. But I'll tell you anyway -- is a study -- it turns out that there are two types of identical twins. There are, sort of, plain vanilla identical twins. You know, Twin One is right-handed. Twin Two is right-handed and so on. And then there are so-called mirror twins. They're genetically identical, but the phenotype, the actual organism, is mirrored rather than identical or something like that. So if one's right-handed, the other is left-handed. You know, swirl on the top of your head, if it swirls clockwise for one twin, it swirls the other way for the other twin and so on.

And the curious finding reported in this one relatively small study, I think, is that the concordance rates for identical identical twins, the right hand, right hand identical twins, very high in this study, like over 90%. If one twin was schizophrenic, the other was schizophrenic. The mirrored twins, the left, right ones, were concordance rate down at about 25%. Both of these are genetically identical pairs of twins. It's abundantly unclear what it is that makes these two groups different, if indeed that turns out to be a reliable result. I went hunting in the databases, and I think I found the guy who did it. So I sent him an email, but he didn't get back to me in time.

Oh, that reminds me. It's a little late in the day to tell you this, but if you discover that something that you're looking for in primary source land, you know, you're looking for the Journal of Hoozy Phoozy Results or whatever, and oh my god, MIT doesn't carry it so you don't have access to it, it's often very useful to go and see if you can find the website for the lab where the work was done. Because many, many of us post all of our publications, or as many as we have PDFs for, on the website to be downloaded. And so you can dig things up. You can dig things up that way.

So anyway, there's pretty strong evidence for a genetic component. And then there's pretty strong evidence that that by itself is not enough. Unlike a variety of other neurological disorders, there are plenty of neurological disorders where if you've got this problem with your genome, it's going to munch up your brain in the following fashion, you're going to have this problem. And fortunately most of these are very rare. But they're straightforward genetic stories. In schizophrenia, something about the environment seems to be important to trip it off. The leading notion is stress.

So, actually, does anybody remember? The book used to go on at vast lengths about the stress diathesis model of schizophrenia. Does this sound familiar to anybody? Has anybody looked at the relevant parts of the book yet? Nobody knows. All right, well anyway, one of the leading notions about what it is that actually produces the florid disease, is that you need to have some genetic predisposition and then you need something like stress to drop-kick you into pathology.

Now, this is an interesting -- this raises interesting problems for public policy. I think we talked last time about, you know, when is it OK to force somebody to be medicated, right? This is a similar sort of problem. Suppose you are applying to MIT this year. Should I be able to -- should I go and suggest to the head of admissions that we really should get little tubes of blood from everybody? Because if we got little tubes blood from everybody, we could genetically screen them.

And we know where -- we don't know exactly which loci are critical, but we know a bunch of loci that seem to be related to family histories of schizophrenia. And anyway, there's all sorts of other interesting genetic markers out there at this point. We could screen the incoming population or the population of applicants and systematically decide not to admit people who had the genetic marker for schizophrenia or for some other -- well, schizophrenia is a good example.

Why in the world would we do this? Well, is there anybody currently present who believes that MIT is a at least modestly stressful environment? All right. Short of Guantanamo Bay or something, you know, it's right up there. All right. The state of the art is that we know that stress is a contributing factor to a variety of mental illnesses, notably in this example schizophrenia. If we admit people to an environment that we know is highly stressful, we are asking for a certain number of psychiatric problems. Isn't it our responsibility to prevent that from happening?

Well, now, typically the -- I won't take a poll, but the typical answer is, no, that doesn't sound right. You know, that somehow that sounds a little too paternalistic, too invasive for me to be screening your genes. And, you know, who knows? Down the line, we take a look at this hunk of the genome and we say, you know, sorry, you're just never passing 18.03. You know, what would we ever do with information like that? But the disease case, it doesn't feel right typically to people.

But on the other hand, we spend a lot of time worrying, believe it or not, about your mental health. The dean's office has substantial branches devoted to mental health issues as does the medical department. We know that university environments kick up a certain amount of psychiatric problems. And we know that that can be catastrophically bad for the person and for people around them. Wouldn't it be our responsibility to do something about that? Well, look, I'm not going to give you an answer to that, and I promise not to ask on the exam, you know, should we get blood samples from everybody and, you know, the choices are yes, no, all of the above or something like that. I raise that as an issue to think about.

When you take a look at the brains of schizophrenics, by the way, they don't look like the brains of healthy, normal individuals. So you get things like shrinkage of grey matter. You get enlargement of the ventricles. The ventricles are those nice, empty fluid-filled spaces in your brain. Great answer for a -- if you're looking at the multiple-choice question on the final, and you're thinking, I'm going to go for, you know, the third ventricle as the answer, you're probably getting suckered here, right? Because the ventricles are empty fluid-filled spaces. It's not where any of the more important mental functions are thought to be localized, at least not since the Middle Ages, where people did think that memories were stored in the ventricles, because after all they looked like store rooms.

Anyway, the ventricles get bigger. That's presumably not a good thing because it's reflecting loss of brain tissue. What's not absolutely clear is whether or not abnormalities in brain structure precede disease. You know, are they there somehow from birth? Is part of what the gene is doing somehow changing the structure of the brain in such a way that it makes it vulnerable, or is it that having the disease itself is bad for the brain? In any case, the point to take away here is there are lots of different routes into the kingdom of schizophrenia. It's not a nice, clean simple diagnosis where you say, you get this bacterium, you get this disease, we give you this antibiotic, and you're OK. Multiple routes in and treatment options are, you know, getting better but remain difficult.

Let's see here. Oh yes. What I think I will do is switch gears and talk a bit about depression. But in order to talk about depression, what I want you to do is to decide how you want to treat my three invented patients on the handout. The third one is on the back of the page. So play with that for a second.

Kristen, can you do me a favor? Go find me a bottle of water. I'm going to expire today otherwise.

AUDIENCE: I have some. Do you want some?

PROFESSOR: I don't know. Do you got any interesting diseases?

AUDIENCE: No.

PROFESSOR: I don't want to steal yours. Find me something somewhere. Thank you. I'm recovering from a cold still, and I can feel that I'm going to run out of moisture. And my tongue is going to get all big and like a parrot or something. I won't be able to talk.

All right, have you managed to do this? Still working on it. All right. Don't cheat off your neighbors. But I promise you this time, none of these guys are dealing in lady's undergarments. Here. Let's collect some. All right. Let's collect us some data. OK. Everybody pretty much done here? Make assenting noises or something. OK, that's good. That sounded very assenting.

OK, so Sarah had a bad day. How many people would, let's see, so that -- slow numbers are the "no way, we're not going to medicate this depression." How many people -- oh, that was quick. That was good. Thank you. How many people are going to give her no meds? Oh, OK. So the answer is everybody, more or less. Don't worry if you said, I'll give her a little bit of med. That's OK, too. But I won't bother asking about it. These really are all the same, by the way. There's no fifty-fifty split. This is just straight up, normal. I'm not tricking you this time. OK.

And by contrast if we look at Sam, Sam's depressed, no particular reason, just happens. And he oscillates between manic and depressed states. How many people think no treatment or unlikely to medicate? How many moderately like, you know, somewhere in the four to seven department? Well, a few people in there. And you have all embodied the ethos of the yeah, yeah, OK, good. I mean, I don't know if it's good or not, but it's clearly where medical science, I suppose, is these days, which is that he would be a candidate for an antidepressant in a way that she wouldn't. Why not? Why wouldn't you give her an antidepressant? She's depressed.

AUDIENCE: It's normal for her to be depressed. Like, anyone could be depressed in that situation, but if you're depressed for no reason, then that [UNINTELLIGIBLE] problem in the brain that could be solved by medication, whereas with her thing, all that needs to happen is the problem's [? cured. ?]

PROFESSOR: There's a couple of things that are worth picking up on here. One is, I mentioned last time that

the exact mapping between cause and treatment shouldn't be seen as one to one. So even if we take as correct for present purposes that Sam's got something biochemical wrong with him, it wouldn't necessarily be the case that the only way to deal with this would be by a biochemical kind of treatment. There isn't that necessary one-to-one mapping. But it's not an unreasonable thought.

And the other part of that thought was, you know, she's depressed for a reason. And we don't want to shield her necessarily from that depression. Though this gets raised as an issue too now. I talked last time about treatments for post-traumatic stress disorder. One of the notions is that you could give people medications that would in a sense prevent them from feeling as bad about something horrible as they normally would. I mean, this is a real something horrible now, you understand. But we're going to get you -- something horrible has happened -- we're going to give you a pill that is going to decrease, we hope, the chance of you having a post-traumatic stress disorder, but it's going to do that by blunting your emotional response and your memory for that event. Is that something that we want to get into?

Now, Sam I described as having this -- if this is now, oh, I suppose, mood -- Sam I described as having one of these oscillatory or bipolar conditions where he bounces back and forth between -- well, let's see, which end is this? This can be the manic end and the depressed end. You sometimes think that it might kind of be worth it, right, because you have to put up with the depression, but the manic energy thing would be good. Well, the manic energy thing is kind of good here, maybe. You know, you get all your problem sets done in ten minutes or something. But by the time you get out here, you are just as abnormal, if you like, or just as crazy if we want to be colloquial about this, out here as you are down here. And you can be pretty hard on your friends and neighbors and yourself, in fact. I don't need -- I mean, this is very MIT, right -- I don't need to sleep anymore. I can talk all night. You don't want to listen to me? Well, I'll talk anyway.

I remember reading a memoir by the child of a manic depressive mother, who as I recall comes home -- the child comes home from school one day, discovers mom has decided we're going to have a great old-fashioned Christmas this year. So she went out and bought like thirty-five Christmas trees. And you walk into the living room and it's just, you know, forest in there. She's stuffed the Christmas trees all over the -- and, you know, this is, I'm sorry, I'm glad you're feeling really up, but this is nuts too. It's not working.

It's an interesting observation. There are interesting data suggesting that this sort of bipolar

disorder, this oscillation between deep depression and this wild mania, that that's overrepresented in at least some creative populations. The notable one is poets. It's notable because a woman named -- what is her full name? -- well, anyway, Jamison is her last name. I think it's spelled like this. Anyway, she wrote a book called *Touched by Fire* where what she did was she went and looked at the biographies of, in particular, sort of the run of famous English poets. And over and over in their biographies you get these descriptions that -- you know, they didn't have the diagnosis in 18th century England, but it sure sounds like a manic depressive disorder. You know, Shelley or Keats or somebody writes eight million poems and then lies in bed for a month. It's that sort of thing. Now, great, you know. I can be a famous poet. All I have to do is put up with this.

The problem -- well, there are a number of problems with this. First of all, you become a little intolerable to your immediate surroundings. The other thing is that a very serious consequence of deep depression is the threat of suicide. Interestingly, you would think that this was a continuum thing, right, that you go way, way down here and if you get this far down into depression, that's when people commit suicide. Turns out not to be the case. When people describe their really deep -- there's a huge genre here. It's a very popular genre at the moment. If you're into depression, your, you know, Christmas reading list can be all set out because there's all sorts of people who are happy to describe -- happy to describe their depression? -- anyway, more than willing to describe their depression in volumes thin or thick.

Jamison actually has a volume of her -- she got interested in this because she was a manic depressive and trained in psychiatry. So she's coming at it from every which way. Anyway, she has a memoir -- I don't remember the title of it -- about her own depression that's actually nice and slim. It's not a bad read. But what the descriptions sound like is that when you're really, really deeply depressed, you just don't do anything. You might in some sense want to be dead, but that's just too much effort to do anything about that.

The danger for suicide in bipolar disorders turns out to be -- well, let's get rid of this -- turns out to be when you're on your way back out. Still depressed, but now you're activated enough that you can do stuff, but you're not convinced you're ever really going to get better. I mean, look, most of us have not been really clinically depressed, but many of us can tap into this, into this aspect in the sense of have you had the flu or some, you know, relatively disgusting disorder of some variety where you're sitting there thinking, "I know rationally that I'm going to get better, but am I really going to get better, or am I just going to be barfing forever?" So

you're coming on your way out, and that's where the suicide risk is high.

Now, that phenomenon may be related to something that hit the news a lot this year, which was concerns about giving antidepressants to children and adolescents. Because there are data out there that say that the suicide risk in depressed adolescents taking antidepressants is elevated. Exactly what you don't want to have happen, right? What you really want to not have happen is people committing suicide when they're depressed. What is the cause of this? Well, we don't actually know, I don't think. At least I haven't seen anything definitive. But there are a number -- one theory is that antidepressants work differently in young brains than in older brains. That's one possibility. But the other possibility is that what the antidepressant did was it moved the patient along to a point where they weren't so paralyzed by the depression that suicide became an option. It sounds weird and disturbing, but that is one possibility for where this elevated rate of suicide in antidepressant treated young patients came from.

Let's see, what else do I want to say about Sam and Emma here? Oh, Emma's the one on the back. All right, so how about Emma? We need to collect some data on Emma. Did I describe Emma as dysphoric? Yes. Emma is a dysphoric. That's the opposite of euphoric. So it's not depressed. It would be sort of lying around here somewhere. Just kind of flat. All right. So how many people voted that we'll leave her be? OK. How many people voted maybe? And how many people voted sure? Well, OK, we got a normal curve out of that. Well, I could have gone -- it looked sort of like this to me. So people are sort of unsure about -- oops. Well, I guess it's going over there now. People are sort of unsure about it. So what are the issues here? Why wouldn't you give it to her? Yeah?

AUDIENCE: If she doesn't want it.

PROFESSOR: Oh, yes, yes. Well, that's a separate issue. Did I say anything about it? No, no, no, this is just -- well, actually, we'll come back to that. That's an interesting problem. But yes, I was not suggesting that we jam it down her throat, which is by the way not the problem with Prozac. Let's imagine that the antidepressant is Prozac here, or one of its newer friends. Prozac gets a lot of play in the public sphere. Whoops. Well, I'll put a P there now. Uh oh. C or K?

AUDIENCE: C.

PROFESSOR: C. Yes. Thank you. OK. Prozac is a serotonin -- that's a neurotransmitter -- selective -- thank you, where was that coming --

AUDIENCE: It's first.

PROFESSOR: Oh, it's a selective serotonin, not serotonin selective. It's SS. All right. All right. It's a serotonin selective -- reverse -- uptake, reuptake -- can I do reuptake?

AUDIENCE: [INAUDIBLE]

PROFESSOR: Yeah. Yeah. OK. Reuptake inhibitor. Or an SSRI, which makes it understandable how I would have thought it might have been an SSRI rather than an SSRI. But let me explain what this is doing actually. So remember that in schizophrenia, the first big psychopharmacological breakthrough was the discovery there's too much dopamine in bits of the brain. If we block some dopamine receptors, we reduce the symptoms. In the case of at least some forms of depression, the problem seems to be too little serotonin -- or a problem. Seems to be too little serotonin in some parts of the brain.

And so you've got a synapse. And serotonin is being released here and binding to the other side. But now, in order to have this synapse be reusable, once you've released some serotonin, you've got to get rid of it. You've got to get it out of the synapse so you can do it again and again and again. One of the techniques is to take the molecules and suck them back into the originating neuron. That's called reuptake. Now, if you don't have enough serotonin here to do the job, one thing to do is to slow down this reuptake so that the serotonin hangs around here longer. And that way you get more bang for your molecular buck.

And so that's what Prozac is doing. The reason I put Emma on here is that Prozac seemed to do good things for dysphoric patients, patients who did not meet a clinical criterion for depression but who found -- I think in part because the drug manufacturer gave the docs piles of free Prozac. You know, patient comes through and says, "I feel kind of down." So, "Oh yeah. Try this. This is new." You know, "All right. Hey! I feel better. I feel a bunch better. I'm not clinically depressed, but I really like this stuff. And not only that, if I go off it, I go back to my dysphoric state. I go back to -- "

The example says something to the effect of, that's just the way she is. If she goes off Prozac, there are lots of reports even in the popular literature of this, of people who said, you know, if I'm off Prozac, I'm just, ughh. But if I'm on Prozac, I'm just a better me. Well, do you give them the drug? Do you give them the drug? Do you allow them to continue taking the drug for the rest of their natural born days, particularly since we have no idea since it's a new drug -- well, now it's over a decade old.

But, you know, we don't know what happens if you take this for twenty, thirty, forty years. Who should pay for it? You know, if you think that this drug makes you feel better, that's lovely. Should your insurance company pay for it on a continuing basis? So those are the Emma issues here. The issues about whether or not it's OK to make somebody better than they, in some sense, better than they were. Are you the same person? Is this, you know, is this the real Emma, or is this some medicated Emma?

And, well, all right, now let's look back to the comment about forcing them. Well, you know what? It works on kids, too. And you know that there's a fairly substantial industry in feeding psychiatric drugs to kids for various and sundry problems. Suppose, well, we know that shy -- how did I describe old Emma here? Is she shy and withdrawn? No, that was what's his name collecting the underwear, wasn't it? Oh well.

I could have described Emma as shy and quiet. We know that the kid who's shy and quiet in first grade doesn't get the same amount of attention that the bouncy, active kid gets. And in fact, there's some evidence that if you feed something like Prozac to this kid, the kid will move from here in the -- well, we've got to change the axis again. You know, I don't know, what's the axis here? Bounciness? Technical term. You know. So the kid's going to move from being unbouncy to, you know, Tigger is up here somewhere. As are several -- couple of people out there halfway up the -- so there's Tigger, I guess. But, you know, move them up here, let's say. Get them above average and the teacher's going to pay more attention to them. Is it OK to medicate your kid?

AUDIENCE: No.

PROFESSOR: If it's -- all right, it's not OK to medicate your kid. I'm not going to medicate my kid. Uh oh. The neighbors. They're medicating their kids. So what they've done -- my kid was right here. He was average, right. All right, now what the neighbors and the population as a whole has done is they moved the whole distribution over. Because they're all handing out Prozac in the lunch box. Now is it fair to my kid -- this is a hypothetical my kid. This is not a real issue on my street in case you're wondering. But is it fair to my kid to not medicate him? He's going to fall behind.

Is this systematically different, you know, is this sort of morally or ethically different than the Kaplan or Princeton Review approach to SAT tests? What Princeton Review and stuff does is it takes the population and it shoves it on -- everybody gets to gain those hundred points or whatever. So is it OK for you to say, "My kid doesn't need to do that. I didn't do that when I

was a kid, and no kid of mine's going to go off and get tutored. He'll do it on his own brains. It's an aptitude test after all." Right. You know, is there a difference between everybody being signed up for Princeton Review versus everybody being signed up, you know, going down to the nurse's office for the daily Prozac dose? Or is there a difference between just sitting there saying, "I'm not going to go and make myself into a better me by popping Prozac all the time. I'll stick with --" What is that, Mountain Dew? You know, twice the caffeine of whatever, right?

AUDIENCE: Late night last night.

PROFESSOR: Yeah. OK, well, that's good. You're vertical. That's encouraging. Give some to the guy next to you there. He's gone.

[LAUGHTER FROM AUDIENCE]

I shouldn't have said that. Anyway, we do this all the time, right? We self-medicate. We self-medicate, particularly with caffeine. But perhaps with a variety of other things. The use of alcohol as an antidepressant is probably a mistake, but is not uncommon. So when is this a sort of an unwarranted medicalization of your life, and when is it, you know, a lifestyle choice?

And again, there's not going to be a question on the final that says, "It's OK to drink Mountain Dew: yes, no, only if it was a late night." But you can see that there are issues to wrestle with. And the doctors ended up with or have ended up with a serious problem, which is what do you do with these patients who you cannot in good conscience give a clinical diagnosis of clinical depression to, but who say, you know, if you don't give me my Prozac, I'm just going to be so depressed, who really need that or who think that they really need that.

Oh, by the way, OK, what's this? Want to make sure that I do what it says. Oh. Well, OK. Let's say something about how antidepressants work. Here's a mystery for you. Take Prozac. It blocks the reuptake pathway within hours. It doesn't take much time at all. OK. So you are down here, clinically depressed. You come into the doctor's office. He says, here's your Prozac. You take the Prozac. A few hours later, more serotonin at all those synapses. How do you feel? Well, you feel depressed, actually. It takes typically at least days, more like several weeks, before an antidepressant of this sort has an effect, beyond perhaps placebo effects. There are placebo effects where you can take any old damn thing and you feel a little better if you're convinced that it's going to work.

But the main effect of antidepressants seems to take a long time. That's a mystery. At least as

far as I know, there's no neat, clean answer to why it should be the case that the pharmacological effect is there instantly almost and the psychological effect takes a vastly longer time. The reference that I put on the handout is a theory. It's not proven. But it's an interesting theory about what might be going on. As I think I mentioned earlier in the course, one of the interesting new findings in neuroscience is that we grow new neurons. We didn't used to think we grew new neurons. But now it's pretty clear that you grow new neurons.

And there's a pretty strong suggestion that this neurogenesis, as it's called, is depressed in depression. You're not making those new neurons. And one theory is that what an antidepressant is doing is jump-starting the neurogenesis, that this is the beginning of a cascade of events that leads eventually to the birth of new cells, new neurons. And only when you manage to sort of grow yourself a new bit of brain, in a sense, does it help you to break out of the depression.

The data on how well these things work is a little depressing in its own right. Antidepressants, like a lot of these -- antidepressants don't work as well once they go off patent. It's a mysterious thing. You want to worry about this. Over and over again you get some cool new drug like Prozac. It's got no after effects. It cures the disease like that. And everybody is better, and it's a miracle drug. Amazingly, by the time, you know, Eli Lilly or whoever's patent has worn off, it now has side effects, doesn't work all that well, but you want to try my new amazing wonder drug. So the last few reviews I've read of the effectiveness of antidepressants have been, well, they've been sort of depressing, actually, that they're not magic bullets.

Now, there are several ways to treat depression. And how you treat it depends -- there are also several flavors of depression. Not all depressions -- well, certainly not all are bipolar. And there's evidence that they differ both in their symptoms and in their neurochemistry. So for instance, say, I think it says on the handout -- yeah, typical versus atypical depression. I'm sure if I rummaged around I'd remember which was which. But in some forms of depression, people sleep too much and eat too much. In other forms of depression, they sleep too little and eat too little. They're both depressions in terms of the mood, but they are clinically distinct and psychopharmacologically distinct.

Actually, bipolar disorders, the treatment of choice for long before Prozac came on the scene was of all things lithium chloride. It's just the salt of lithium. You know, just move right up from sodium chloride. Jamison credits lithium with keeping her alive, that if she had not been put on lithium as a treatment for her bipolar disorder, that she thinks she probably would have ended

up committing suicide. Anybody an expert on how lithium works? No. I think I don't know the answer to this. I'm not sure it's known. The last time I checked on it, we didn't know how it worked. It was -- how was it discovered? It was discovered in some bizarro fashion. You know, where do you find lithium? Like a salt -- I'm remembering some odd story about, you know --

AUDIENCE: Batteries?

PROFESSOR: Fine. Batteries? That people -- that's --

AUDIENCE: 7 Up.

PROFESSOR: 7 Up. OK, if you dissolve your battery in 7 Up, I don't know what happens but I don't imagine it's good because the mercury and the rest of it probably isn't really good for you. The other treatment for -- now, sadly not all depressions are amenable to pharmacology. Oh, first of all, the big mistake, which I think the insurance people are growing out of, was the notion, OK, now that we've got these cool pills, we'll pay for the pills, but that's it.

So if it's going to take you several weeks for the medicine to work, it turns out to be very helpful if you're actually talking to somebody during this time, if there's some psychotherapy of some sort going on. Because if you are down here in the depths of the depression and some genius hands you a pill and says, "Go away. Don't bother me no more." You know, if it's true that as you're slowly coming out of the depression, that's when the suicides take place, you know, this is a recipe for disaster. And if it takes a long time to work -- you know, if you take a medicine and nothing happens for weeks, what do you do? You stop taking the medicine. And so what you really need typically as part of a sensible treatment for a depression is not only somebody who will give you the medicine, but somebody who will talk to you about it too.

But even so there are depressions that are not amenable -- or don't seem to respond well to any of the medicines that we have at the moment. And under the heading of even more unlikely treatments that really turn out to work, more unlikely than feeding them lithium salts, is what's known as ECT for electroconvulsive therapy. I talked about this a bit when we were talking about memory. Remember this is little rats. They step down. You run electrical current through their heads. You shock their little feet. You run electrical current through their brains. They don't remember that you shocked their feet, so they step down again, you know.

Sound familiar? OK, good. Well, this is a treatment for depression. Not abundantly clear why it works, but in my circle of friends, I have a friend who actually went back to -- graduated

college, went off, did a whole bunch of stuff, then went back to med school, then became desperately clinically depressed and had to be hospitalized. And what got her through it was electroconvulsive therapy. Not an entirely benign procedure. It does have memory side effects.

But it used to be that nobody in an intro psych class thought this was a good idea at all because everybody had seen *One Flew Over the Cuckoo's Nest*. How many people have seen that movie? Oh, so still a fair number people have seen it. That's a movie that does nothing good for the reputation of electroconvulsive therapy. Electroconvulsive therapy these days is, you know, you give somebody a sedative. They don't thrash around. They don't hurt themselves. It still has memory consequences, consolidation of memory consequences, but it really does seem to mysteriously break up depressions.

Now the latest wrinkle on this, you know, what boils down to smack-them-up-the-side-of-the-head treatments of depression is the use of, very new, is the use of transcranial magnetic stimulation, which I think I also talked about earlier. But basically what you do is you put a giant electromagnet or strong electromagnet next to the skull. You fire a big pulse of -- a big magnetic field that induces an electrical field locally and knocks out neural activity locally. And there's some evidence that properly applied, that this is a sort of a kinder, gentler version of ECT, that it acts to break up depressions. I don't -- anybody know if there's a brilliant theory for how that works? Uh, who knows? But it's very new. But I expect that in a few years, I'll be lecturing more about that. Because it, at least initially, sounds rather promising.

All right. I think this would be a good time to take a break. Let's take -- unless you're too depressed to get up, take a break.

AUDIENCE: I read Jamison's book.

PROFESSOR: Uh huh. Which one?

AUDIENCE: *Prozac Nation.*

PROFESSOR: No. *Prozac Nation* is somebody else's book.

AUDIENCE: Not Jamison?

PROFESSOR: No, that's somebody else. I can't remember who wrote it, but yes, that's a cool book, too.

AUDIENCE: Yes. That's what I thought you were talking about.

PROFESSOR: Nope. Nope. But you'll come back and tell me who wrote it. Because we're both forgetting who wrote it.

AUDIENCE: Have they ever done, what is it, using sugar pill and Prozac and hand them out to patients and just seeing if the sugar pill --

PROFESSOR: It's a big problem in mental illness in general and certainly in depression, which is, particularly if you've got a cycling depression, who's going to get better? Right? And, yeah, the difference between placebos and Prozac is, at least in some of the studies that I've read, a lot less dramatic than you would think. And the problem with a population like us is that we're too well informed. Placebos are great. The side effects are really limited.

In the good old days, your doctor would come around, have no clue, you know, how to treat you, but give you, you know, Dr. Hoozy's magic elixir, and you'd feel better. And it's a great pity that now if I fed you Dr. Hoozy's elixir, the first thing you'd do is Google it and discover that it's snake oil, and feel worse and sue me. So, yeah, if you turn out to be particularly interested, send me an email and I can send you a couple of the references of things that depressed me when I read them. Because they weren't that much good. On the other hand, my mother absolutely swears by this stuff. She's had her own issues with depression and thinks that Prozac is wonderful.

[PRIVATE CONVERSATION]

PROFESSOR: I want to talk about a couple of other disease, you know, mental illness states, in part as a way of illustrating -- I guess what I really want to illustrate in the last bit of this lecture is the, sort of, mind and brain links. We tend to like to make up theories that are one or the other. And the current popular trend is towards brain explanations. Oh, you're depressed because you don't have enough serotonin happening for you. We'll boost up your serotonin. You'll be fine. It's a very brain kind of thing. Freudian theories were very mind kinds of things.

But there's a number of cases that really illustrate, I think, well, what you sort of know intuitively, right? The brain isn't here and the mind is here. It's, you know, waves and particles. They're two manifestations of the same thing. And brain stuff and mind stuff bounce back and forth here all the time. So let's think, for example, of panic attacks. Which I didn't put on the handout at all, I see, but I suddenly developed a need to talk about because I was feeling

really anxious and -- no.

So panic attack is this feeling of anxiety out of the blue. People report that they just suddenly feel very, very, very fearful and anxious. And it's scary and it's unpleasant and so on. You may recall that Freud and his followers had a perfectly nice notion about this, which was that anxiety was warning you that you were about to tread on the super ego. And it was the warning sign of the ego that was saying, don't go and do that. But that hasn't worked that well. More modern notions tend to focus on the idea that it's essentially neurochemical. You get too much of some juice, some neurotransmitter. It fires off the bits of your brain that are responsible for the experience of anxiety. And you feel this anxiety.

And this is a lovely case of looping back to a prior mode of understanding. The notion that you feel too anxious because you have too much of this fluid, it's an awful lot like the notion that you feel melancholic because you have too much black bile. The difference of course is that we think we've got a better scientific grounding than we had. But the form of the argument is rather similar. So is it the case that panic attacks, the clinical condition of a panic attack, is just too much of some juice. It's possible to think about it as being somewhat more complicated than that.

And, well, I didn't put that reference on the handout, because I didn't. But I'm stealing a story from -- who am I stealing it from? Oh, Dave Barlow, who's over at BU. This is a three-step route into panic attack. And the first part of it is that you feel the visible symptoms of anxiety. Your heart starts -- remember the shaky bridge experiment all about misattribution of arousal? You're feeling "ooh-ooh-ooh" and you see *her*, and you just think you're feeling "aah." Right? So that can work in all sorts of ways. Suppose that your heart is going through -- there are a variety of things that cause your heart to go pitter-pat. Suppose that you get these sort of symptoms and you don't interpret it as love, you interpret it as "I feel nervous about something. I can't quite tell exactly what it is. But I don't --"

People don't have panic attacks, by the way, typically, when they're exercising vigorously. Because they've got a good account of where that symptom is coming from. Your heart's pounding, you're sweating, and stuff like that. Yeah, all right, fine. If you're walking down the street and your heart is pounding and you're sweating, you need a different interpretation. Now, this is unpleasant. So you develop, flipping back to an earlier piece of the course, you develop a conditioned fear of these symptoms. So you start avoiding situations that would produce the symptoms, or that you think might produce these symptoms. And this can be

quite unconscious, right? This is good classical association learning or something of that sort.

And that in turn -- that's sort of step two, is sort of a learning story that is going to cause you to start -- you're going to act to avoid situations that make you feel nervous. But, all right, remember Pavlov? Bell, tone. Bell, tone. Bell, tone. Now I ring the bell by itself. No. Bell, tone. That's stupid. I'm not supposed to be the one who notices that first, guys. You're supposed to -- "What's he talking about?" Anyway, bell, food. Bell, food. Bell, food. Eventually the bell by itself produces salivation.

So you make this association in your own mind. So when did this happen to me? I was outside. OK. So now I'm outside, it doesn't happen to me. But I feel -- I get the conditioned response in effect. So now something else acts as a trigger for the panic. The initial feeling of panic might have been, I don't know, too many bottles of Mountain Dew, right. You drink enough caffeine, and you'll get *b-b-b-b*. Forget that you drank -- your brain doesn't remember the caffeine part of the story. And you're going *b-b-b-b*. And you say, "Oh! I'm having a panic attack." Then you don't want that -- this is an aversive event. It's just like the business of the rat stepping down, right? The rat steps down -- oh, all right. Rat's up here, rat steps down, gets his little feet shocked. That's unpleasant. Rat's put back up here. Does the rat step down again? No. Why? Because he's got this anticipatory fear. You can actually measure the fear physiologically.

All right, so you caffeine overdose or whatever. You have this unpleasant experience. Now you're in that environment again sometime later and you have the experience again because it's a conditioned response now, no caffeine involved. You come to the reasonable, if perhaps unconscious, conclusion that what makes me nervous is being outside in public or being on shaky bridges or whatever. Then you get step three, which is again learning theory kind of stuff like Thorndike's Law of Effect. You start doing things to avoid this punishment, right. You're going to avoid the aversive stimulus. So you can get secondary symptoms to the panic, like a fear of open spaces, let's say, because you've now, perhaps completely unconsciously, concluded, "If I go out in public, the sky is so big. I feel so small. I get panicky. And so now I'm not going to go outside."

And so what you end up with is the possibility that the clinical thing that you see, what you get in your office if you're the clinician, is somebody who says, "I have, you know, I have uncontrollable panic when I'm outdoors. This is crippling my life because I don't go out anymore." And what this may be is a cascade of events coming from some sort of an initial

physiological issue that you then learned about, if you like, using the laws of animal learning, in ways that that don't work well. Well, what are you going to do about it? Well, one thing you might do about it if you believed that there was a significant learning component here is to use learning theory kinds of things to treat it.

Now if it turns out that there really is a chemical imbalance and every time the chemicals go out of whack, you feel panicked, you might want to do something about the chemicals. But if you've got one of these situations where the person has basically scared themselves into maladaptive behavior, you've now got to un-scare them. So what are you going to do? One of the standard techniques for these sort of disorders would be desensitization methods. Is it Barlow who was doing this? So one of the versions -- you can imagine -- I did a version where you became scared of the outside. Another version is you have a panic attack in an enclosed space and you become very nervous about enclosed spaces. You won't go into elevators and stuff like that. I can't remember if it was Barlow -- I got a feeling it was -- whose technique for -- there are a variety of ways of using learning theory to get around this. One is the kinder, gentler one.

So you come to me. You say, "I'm really afraid of being in enclosed spaces."

You say, "OK" -- the first cure out in this field that you've come to, that I'm using for my doctor's office at the moment -- "Imagine that you're in a space. Can you deal with that?"

"Oh, it's making me nervous, but, yeah, OK, I can deal with that."

"OK, now we'll go to 10-250. It's a big enclosed space. And then we'll go to a smaller room and a smaller room. And eventually we'll put you in a closet for a while. And you'll discover -- what you'll do is un-learn the response, in effect. You'll learn nothing bad happened to me."

And this behaviorist sort of therapy does work to break up these sorts of behaviors in many cases. I think it's Barlow who has been advocating a much less kinder, gentler version, which is to shut people in car trunks. So none of this business of doing it gradually. This is known in the trade as flooding. You just take the -- the guy says, "You know, I think if I'm in an enclosed space, I'm going to die."

"All right. Boom. You dead yet? No. OK. You're cured. Good. Out."

Well, it's not quite that simple, but the basic idea is that if you have a patient who can actually

deal with this, that you can basically speed up the therapy rather dramatically by not moving gradually to -- this is used for all sorts of phobias. So, scared of snakes, you know, you're pathologically scared of snakes. OK, what we'll do is first we'll show you -- so the two versions are desensitization and flooding. The desensitization story would be:

"We'll show you pictures of snakes."

"Ooh, I hate it. I hate it."

"Are you dead?"

"No."

"Oh, OK." So now we'll go to the zoo. "And see that snake cage way over there? Are you dead yet?"

"No."

"OK, let's get closer. OK, that's a snake, right. OK, now you're going to get in with him. Yeah."

"Aah."

All right.

"But I'm not dead."

And the flooding technique is "You're afraid of snakes? Boom. See those boas? Are you dead?"

"Yes, actually."

[LAUGHTER FROM AUDIENCE]

So, anyway, the point from the panic attack example is that it's possible that what you're seeing as the clinical entity is a dance between physiology and learning, in effect, and that what you learn -- and that a mode of treatment would be to unlearn.

Now, let's take another example which I did put on the handout, which is obsessive compulsive disorders. Obsessive compulsive disorders are, well, there's the obsessive part and there's the compulsive part. The obsessive part refers to obsessive thoughts. What gets you into treatment is not some sort of obsessive thought that "I love him. I really love him. Oh, I love

him a lot. Oh yeah, yeah, yeah. I can't help but think about him." Yeah, it's a little obsessive, but tough. It's "Every time I look at him, I want to rip his guts out. I'm imagining the knife." You know, or something. It's disturbing thoughts that somehow won't get out of your brain. That's the sort of obsession that people seek treatment for.

And compulsive behaviors are behaviors where -- everybody has some degree of this. How many people here have left their room, gotten halfway down the hall, said "Did I really lock it?", and gone back to check? Everybody does that sometime. Or did I turn the stove off or something like that. That's normal on compulsion land. And almost always you have locked it, right? Because the time you didn't lock it is the time you don't go back to check, and somebody steals all your stuff. Very annoying. I donated a laptop to the criminal elements doing exactly that. Very annoying.

But anyway, if you have to go and, you know, get down the hall, "Did I lock it? Yep, it's locked. Did I lock it?" You've got to do that forty or fifty times and you can't get on with your life, literally. You can't get to the next event in your life. That's a compulsion that is likely to lead you to want to do something about it. It's interesting that these are compulsions -- rather like there are similarities in people's narrative dreams -- that compulsions seem to be drawn from a limited vocabulary of candidate compulsions. I mean, I'm sure there's one of everything out there, but there's lots of hand washers, right. Actually, I can see my hands are covered in chalk at the moment. I should go wash them.

But, you know, why do you wash your hands? Because your mother said so, right, and because there's germs on them. Can you see the germs? No. So you got to do the act and convince yourself that you've done it. OK, hands are clean. Are they really clean? I can't tell because there might be germs there. I'm going to get sick. I'll wash them again. If you have to do this so often that your hands are getting red and raw, that's a compulsion of some sort.

Now, you can treat OCD, as it's known in the trade, in a number of different ways. It turns out, for example, that Prozac is good against obsessive compulsive disorders. It breaks up the obsession, you know, the obsessive quality here of this sort of thought that doesn't quite work for you. You can imagine that you've got some little circuit in the brain somewhere that's a little checker. You know, did I do what I was supposed to do? And if that goes a little wacko on you, that that's got too much serotonin or too little serotonin, I suppose, or whatever, you know, you might end up in a sort of an infinite loop where, "Got to check. Got to check. Got to check. Got to check." And something chemical that gives it a kick will help.

OK. You can treat it that way. You can also treat it using the same sort of behavioral techniques that I was just talking about for phobias. So let's do it for hand washing. All right, Patient So and So, why do you have to wash? "Well, I'm just really concerned that my hands are dirty. When I get dirt on my hands, I get all excited and [NERVOUS SOUND]." Right. All right. So we can do the densitization business or we can do the flooding business. In the interests of time, we'll do flooding.

"All right. See this? This is dirt. Put your hands in it." Right. "Are you dead yet?"

"No."

"All right. How long can you leave them there?"

And you can basically desensitize this feeling of deep anxiety about not cleaning your hands. All right. So that's mildly interesting. What's interesting, the reason for raising this question or this example, comes from this nice article, now more than a decade old, by Baxter. You can see obsessive compulsive states in brain imaging. There are little bits of brain specifically in the caudate. It doesn't particularly matter for present purposes where that might be. But it's overactive. You look at the brain of an obsessive compulsive sort, and this little chunk of brain is busy, you know, just going nuts. If you give the patients Prozac, that chunk of brain now doesn't look weird anymore. It comes into the normal range. If you'd go and do behavioral therapy on a patient with the same story, the same piece of brain comes to look normal.

The point here is that you can reach this chunk of the brain, if you like, either through the brain sort of neurochemical route, or through the psych behavioral route. They're not necessarily either mutually exclusive or, you know, one works and the other doesn't or something like that. This is a case where you can get to the source of the problem, at least in a neurolocalization kind of a way. You can get to the source of the problem through either of these routes.

And I suppose the bottom line here is that in disorder after disorder, what you find is that there isn't just one way of treating -- one problem is that in most mental illness situations, there isn't one magic bullet treatment that automatically works for you. And then in many of these cases, there are both brain and mind routes to therapy. So when you're asking -- when you have like these patients we were cooking up, when you have a particular patient, there's a spectrum of choices that might potentially be of some use.

It says on the handout, "What happens when drugs make us better than we ever were?" That was the example I was talking about before of Emma, who feels better on Prozac even though she wasn't technically -- didn't have a reasonable diagnosis of something being wrong with her. So we've already talked about that. So I think I'll quit. See you next week.