As always I am happy to do this presentation, which is my favorite topic in addiction medicine. I am an internist, and I have done healthcare for the homeless in Springfield as well as been the medical director at our city detox for the past 25 years. After teaching myself addiction medicine for 20 years, I decided to become certified in addiction medicine. And it was during the addiction medicine certification seminars that I went to that I was introduced to the concept of the neurobiology of addiction. And the reason that it is my favorite topic is it really sheds light on some of the most mysterious problems with addiction, primarily why are some drugs so addicting and why are so many other medications and drugs not addicting? And why is it so hard for patients to stay sober once they go through detox?

During the course of this seminar we are going to cover the neuroanatomy of the reward system because as we will discuss, this is where addicting drugs have their effect and where we can have some interaction as far as relapse prevention. We are going to go over some interesting animal models of both addiction and relapse and then discuss each drug of abuse independently as far as how it works on our central nervous system and how these actions cause typical withdrawal syndromes and also cause craving and compulsion. And then finally we will discuss the biological basis of relapse.

Now to begin with, the definition of addiction: Addiction is a behavioral and mental disorder characterized by an impaired control over drug self administration, compulsive drug self administration, continued self administration despite obvious harm to yourself and significant others and a - very importantly, drug craving.

And if you look carefully you will see what we call the 5 C's of addiction. Addiction is a chronic disease. We liken it to something like asthma or hypertension or diabetes. It's not a short-term problem that can be cured. Patients have to think of this as a chronic illness that they are going to work on throughout their lifetime to control but not cure. Also, when we are asked if this person is an addicted person or someone that's just having difficulty with drug dependence, we look for a loss of control over drug use. There is also obvious compulsive use -- very importantly, the continued use despite obvious harm -- and craving, which speaks to the problem with addiction.

Now addiction, as I said previously, is not physical dependence. This is a very commonly confused issue. Any medication that causes an adaptive response in the body can lead to physical dependence -- for instance, beta blockers and certain medications like clonidine. This is a normal adaptive process due to the continued presence of drug in your system, and it causes a down- or upregulation of the receptor where this medication works or the enzyme system that it regulates. And so the body reacts by changing access to the site of action or the secondary effect. And so if you have an abrupt dose reduction or cessation of this drug use, or if you administer an antagonist which counteracts this medication's effect, it causes a fairly typical withdrawal syndrome. And the withdrawal syndrome is typically opposite the drug's effect.

If you give any person a prescription of something like Valium and have them take it on

a regular basis for 4 or 5 weeks and then suddenly stop it, that person will have a withdrawal syndrome, and that is not synonymous with being addicted. Same thing with if you give someone an opiate and have them take it on a regular basis for 4 to 5 weeks, if you stop that medication abruptly they will go through withdrawal syndrome. That does not mean that they are addicted.

Similarly, there is a topic called pseudoaddiction in that patients who are inadequately treated appear to have drug-seeking or drug-using behavior due to inadequate treatment of the disease for which the drug is given. We primarily see this in pain disorders and anxiety disorders. Patients are given inadequate amounts or inadequately strong medications to control pain. They tend to overuse it, and people think, "Oh, this person is addicted to their pain medication." But if their pain management program is changed and then their pain is better controlled, this apparently compulsive-type behavior goes away. Same thing with anxiety disorders. If patients are given inadequate anxiety treatment, especially with benzos, they frequently appear to be overusing their medication or abusing their medication. But if their treatment is adjusted, this type of problem behavior is resolved.

There is also an idea called pseudo-dependence in that some patients have stable management of pain or anxiety and suddenly seem to be going through their medication more often than they should. If you step back and look at it, this is commonly related to some disease progression, some superimposed new disease or some change in physical activity or lack of compliance in their medication, and if the dosing regimen is adjusted, this apparent misuse of their medications go away.

Now why are some chemicals addicting while others are not? Or more importantly, with all the thousands of chemicals that we can use as medications, why are so few addicting? Well before we get started on that, many people haven't talked about neurology in many years. And so just to briefly go through a summary of the neurology we are going to be talking about, the neuron is a specialized cell in your central or peripheral nervous system which is capable of generating an electrical action potential. On the neuron are dendrites, which are the input side of the cell. And this is where the membrane-bound protein receptors, which are specific for certain neurotransmitters, are found. These receptors can either make the cell more or less likely to fire. When these receptors are stimulated, the message goes through to the cell body, which is where the nucleus of the cell and most of the energy production parts of the cell are located. And this is where the secondary messengers affect cell functions by up- or down-regulating these receptors and also up- or down-regulating energy production in this cell. The axon is the long extension off of the cell which carries this electrical action potential down to the synapse, which is where the action happens in nerve cells. The synapse is where the cell releases specific neurotransmitters which are stored in intracellular vesicles at the end of the nerve cell. And these react on receptors downstream from the neuron. Each nerve cell has multiple inputs, and each nerve cell has multiple outputs. Now the neurotransmitter only has a very brief existence in the synapse, and it is either metabolized, taken back up into the cell, or it just diffuses away and is excreted.

A couple of other terms we are going to use: A compound is called an agonist if it binds to a specific receptor and activates it and causes its downstream effect. Something is referred to as an antagonist if it just binds to a receptor and blocks it, and therefore it inactivates it and eliminates its downstream effect. There are compounds -- most importantly Chantix and buprenorphine, which we will speak about later -- which are partial agonists, which means they bind to the receptor but only partially activate it. This causes an attenuated downstream effect but blocks the binding of the natural compound.

This is a very busy slide, but the reward path that we were talking about starts in the anterior bed nucleus here, runs through the hypothalamus to the ventral tegmental area. The ventral tegmental area connects to the nucleus accumbens, which has very important connections to both the ventral pallidum, the frontal cortex -- which is the gateway to higher lobes in humans -- and also the hippocampus and amygdala, which are very important in memory and especially emotional memories.

Another important part of the reward circuit is here in the brainstem, where the periaqueductal gray area, the lateral tegmentum and the locus coeruleus are involved in some of the autonomic function that takes place with these medications. So as I said, the anterior bed nucleus communicates via myelinated neurons, which are quick-acting neurons to the ventral tegmental area. From this ventral tegmental area along this median forebrain bundle the nucleus accumbens is stimulated, and it also synapses both in the amygdala, the prefrontal cortex and the olfactory tubercle. The nucleus accumbens, as we have said, projects to this ventral pallidum. And the locus coeruleus is important in the brainstem, where dependence and analgesia are produced.

Now how do we know this is a reward center? Well it turns out that if you electrically stimulate any area on this circuit, animals from rodents all the way up to primates find it both rewarding and conditioning. This means that animals will do work to have this area stimulated and will also do work to avoid getting an antagonist. If you allow the animal to electrically self stimulate, it is even more rewarding and more conditioning. And interestingly, if you electrically stimulate any other area in the brain, you are unable to demonstrate this rewarding or conditioning behavior.

Now the key neurotransmitter in this circuit is dopamine. And all addictive drugs cause the release of dopamine in this circuit. And this correlates with the "high" or "hit" from drug use. Dopamine antagonists microinjected into the circuit are both aversive and also block the rewarding effect of electrical stimulation. Now why is direct stimulation of this reward center so rewarding? Well, our body has a built-up set of filters which tends to minimize the effect that naturally occurring sensations have in this reward area. But electrical stimulation directly stimulates this -- bypassing the natural filters -- and powerfully releases dopamine into this reward center. Direct electrical stimulation is 3 to 5 times more rewarding than natural sensations. And very importantly, when you directly stimulate this area, neutral environmental cues are stamped in with the reward experience and become associated with the reward. Also very importantly, if you

directly electrically stimulate this area there is no delay in reinforcement, and animals find this very rewarding.

So having discovered this area, scientists developed several interesting experiments which, again, have been repeated both from rodents all the way up through primates. The simplest was allowing an animal to roam around a cage with an electrical stimulus planted into this reward circuit. When an animal pulls down an electrical bar, the - an electrical stimulus is sent to his brain. And initially, a random behavior which pulls the bar down very quickly becomes established as a compulsive habit. And this is the famous experiments where animals will stand and literally stimulate their addiction center hundreds of times per minute -- ignoring food, water, animals in heat in the cage -- and will do so until they are completely exhausted and die. You can set this up so that one bar stimulation will allow one stimulation to the brain. And, again, animals will perform this compulsively and ignore other stimuli and also will tolerate fairly significant aversive stimuli.

There is another experiment where there is a progressive ratio, where if an animal presses the bar once it gets a reward. The second time, it has to press the bar twice, then 4 times, then 8 times. For electrical stimulation animals will press the bar hundreds of times to get one stimulation.

In experiments using different medications or drugs, scientists look for what's called the breakpoint, where the reward is no longer worth the effort. And they use this as a measure of how addicting certain medications are when medications are in development.

Now another experiment along the same lines are you rig an animal up as in the first experiment but put them in an environment where there is a particular stimulus, whether it's a sound or a light or a smell. And if it has an option to go to different rooms where it doesn't get the reward, but there is one room or one situation where it does, the animal very quickly will start to prefer that room and will watch for that stimulus. In other words, if a sound - bell goes off, the animal will go right to the room and start to push the lever and get the reward. This is fairly simple Pavlovian conditioning, and this is what's called conditioned place preference. You allow this to be present in one environment but not in another.

Another experiment very similar to this is that you allow the animal to develop this self-stimulatory behavior in a certain situation, but after awhile you stop giving the animal the cue signal and stop giving them a reward. And very quickly the animal doesn't prefer that one setting more than any other. But if they are given a free stimulation, the animal very quickly will go back and start to press the bar again, even though it never receives another reward again. This is mediated by dopamine release and the reward system, as it is attenuated by an antagonist.

You can also show drug-craving type behaviors in the animal. And this is where the animal is given a stimulus in a particular setting with a particular cue and very quickly

learns that that is the place where the cue allows it to be stimulated. If you take the animal away from the environment for an extended period of time, it tends to forget the stimulus. But if you reintroduce either the stimuli -- like the sound or the smell or the light -- or if you allow it access back to the preferred place, the animal will very quickly reinstate this behavior despite the lack of reward. In other words, even though you don't give the animal a stimulation, the animal will go back to that same area and continue to hit the bar. The origin of this behavior is in the temporal lobe nucleus of the hippocampus and amygdala, where the emotional memories take place. And very importantly, the neurotransmitter involved in this is glutamate. And as we'll see later, some medications tend to reduce this glutamate effect. So this is the hippocampus and amygdala. This is also somewhat involved in the frontal cortex. These all tend to -- through a glutamate pathway -- interact in both the ventral tegmental area and also the nucleus accumbens.

Now you can also show a different type of drug-craving behavior with stress. In other words, if you get an animal to develop a conditioned self-stimulatory behavior but stop the reward, the animal will gradually stop doing the behavior because the reward is stopped. With relatively minor stress, such as lowering the temperature in their cage by several degrees or cutting their food rations back by 25 to 30%, despite no reward the animal will go back and begin to press the bar again, looking for the reward. This is mediated by corticotropin releasing factor in the amygdala and also norepinephrine in the brainstem, corticotropin releasing factor affecting the reward system and also these very important brainstem areas which are involved in norepinephrine.

Now what causes these behaviors? In the initial drug-seeking behavior, if you stimulate the animal's reward system you prime the pump. In other words, you let dopamine be released in the reward system, and downstream all the compulsive behaviors and motor memories are triggered in anticipation of future dopamine release. So even though the animal doesn't get any further stimulation, the dopamine release triggers the memory of the previous events, and the animal will go back and start to push the bar repeatedly.

In the drug-craving situation, where an animal develops a cue-related phenomenon with the reward circuit, glutamate is released when the cue is reinstated. And even though no further dopamine is released, you get the pumping primed by this glutamate, causing the release of dopamine. When the animal is stressed, norepinephrine likewise stimulates the reward center. And even though no further reward is given, the dopamine release tends to trigger the anticipation and the previous behaviors.

Now none of us have wires coming out of our head. And so what does it have to do with drug addiction? Well it turns out that all addictive drugs mimic the self-stimulatory behaviors. You can put a tiny pipette and allow an animal to push a button and give itself cocaine or alcohol or nicotine or heroin in the reward circuit. And the animals will only administer these addictive drugs in the reward circuit. In other words, if you put little pipettes in any other part of the brain, the animal will not chronically stimulate itself and no addictive behavior will occur. Animals will self administer drugs in both fixed

ratios or progressive ratios. And as I said, some medications animals will push hundreds of times to get one reward. Some medications animals will give up and reach the breakpoint at much lower ratios. Now you can repeat the same experiments with drugs, causing conditioned reinforcement and place preference. And you can also cause drug-seeking behavior in the animals. And interestingly, any drug of abuse triggers this behavior. In other words, you can have an animal become addicted to self administering itself cocaine. But give it a free dose of alcohol in the reward system, the animal will go back to the bar where it learned to give cocaine even though it had never seen alcohol before.

This is what's led to the concept of the universal pathway of addiction and why people who are trying to stay sober from alcohol who are given opiates tend to have a higher rate of relapse. This is also, interestingly, why people who continue to smoke early in recovery have a higher rate of relapse both to alcohol and opiates than people who are able to quit smoking.

You can also demonstrate drug-craving behaviors, both related to cues and also stress in animals.