Neuroscience of Human Movement
Department of Multidisciplinary
Indian Institute of Technology, Madras

Lecture – 73
Parkinson's Disease – Intro

Welcome to this class on Neuroscience of Human Movement. In today's class we will be talking about a particular dysfunction of the basal ganglia called as Parkinson's Disease. So, this is the intro class on Parkinson's Disease, the other videos on Parkinson's disease will focus on specific models of Parkinson's disease and possible therapeutic approaches.

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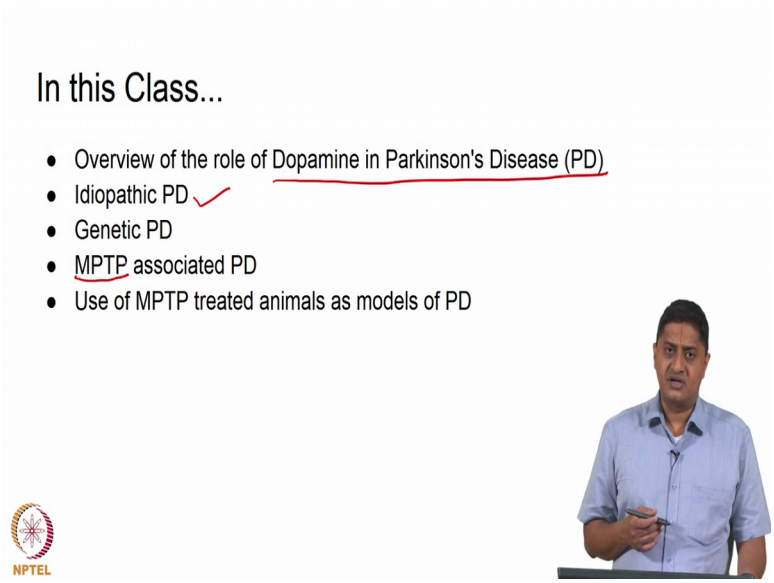

So, in this class we will review the role of dopamine in Parkinson's disease. We have discussed the importance of dopamine in earlier classes many times. And we will describe a particular case or a particular form of Parkinson's disease called as idiopathic Parkinson's disease. So, it constitutes the great majority of Parkinson's disease is so, the great majority of Parkinson's disease is idiopathic. So, the other form that is known to be genetic or specific genes that cause PD have been identified in a smaller proportion of the cases. So, about 10 percent of diagnose Parkinson's disease is actually genetic. The remaining the large majority continues to be idiopathic right. And then a particular form of Parkinson's disease that is acquired due to consumption of specific drug or a specific chemical called as MPTP. And how the discovery that MPTP consumption leads to irreversible damage to neurons in a substantia nigra pars compacta actually resulted in a

particular experimental approach in basically in using animals for development of convincing anatomical and phenotypically convincing models.

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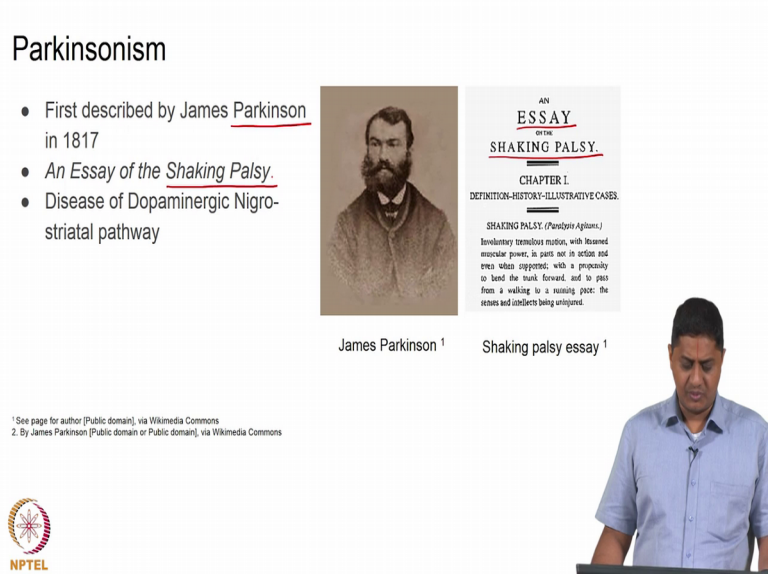

So, Parkinson's disease was first described by James Parkinson of course, that is the name that is the reason the disease has his name because it was first very elaborately described by James Parkinson in his essay on the Shaking Palsy. So, he called it as the shaking palsy. Later it was found that this is a disease of the dopaminergic nigrostriatal pathway. So, this is a disease that is caused due to degeneration or selective degeneration of neurons in the nigrostriatal pathway or those neurons that are responsible for producing dopamine right.

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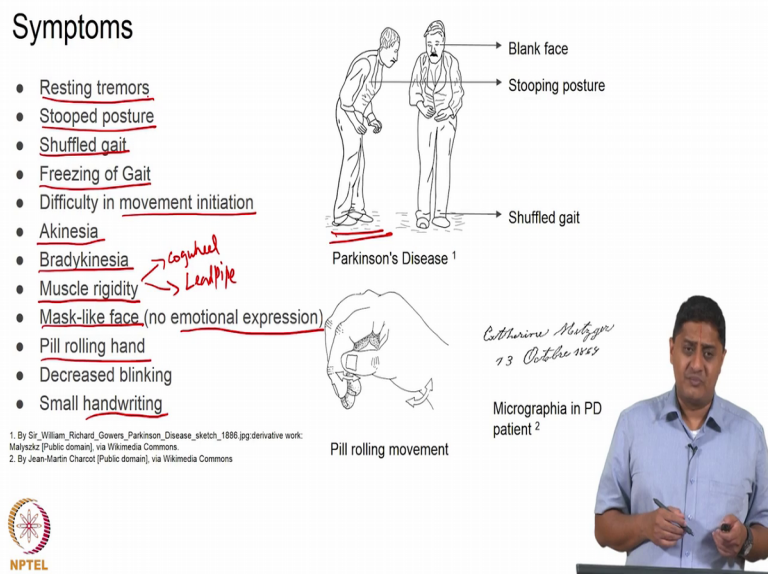

And let us remember what the role of dopamine is right. Role of dopamine is to cast a net excitation at the thalamocortical level right. So, what are the symptoms of this disease right? Classic symptoms classical symptoms of Parkinson's disease right; stooped posture right so like that like you see this person here right like that stooped posture. Inability to take the first step this is called as a freezing of gait and if the person is walking you see what is called as shuffled gait right like that.

So, actually the videos that you could see on YouTube are much better I am not able to actually reproduce that its shuffled gait. And in general a difficulty in initiating movements, akinesia that is in the absence of a voluntary movements, bradykinesia; slowness, rigidity; this is of two types; cogwheel rigidity, lead pipe rigidity, the part of physiology in these two cases are different.

Importantly these people have an inability to express emotions by facial expressions. So, their faces are like a mask all the time no reaction, for any particular neurons anything you tell them there will be no reaction in their face. So, no emotional expression by changing the facial muscles so why because in general movements are compromised, facial emotional expression is essentially movements right expressing an emotion through the face essentially involves moments of the small muscles that are involved right. So, in general when movements are compromised then these movements are also

compromise leading to a situation when the person looks like a mask right mask like face.

Then pill rolling movement of the hand like that you know, I am not able to exactly reproduce. There is a movement that is caused by the index finger and the thumb like that right. And that movement is happening like that and that is accompanied by a tremor of the rest like that both of these simultaneously happen right. So, this is called as pill rolling right and in general reduction in blinking, micrographia or handwriting size becomes smaller then resting tremors.

So, basic essentially pill rolling then develops into different from called tremors resting tremors right. So, these are the classic symptoms among these anybody can recognize this some of the most more classic symptoms. Tremors shuffling gait stooped posture classic symptoms of Parkinson's disease right.

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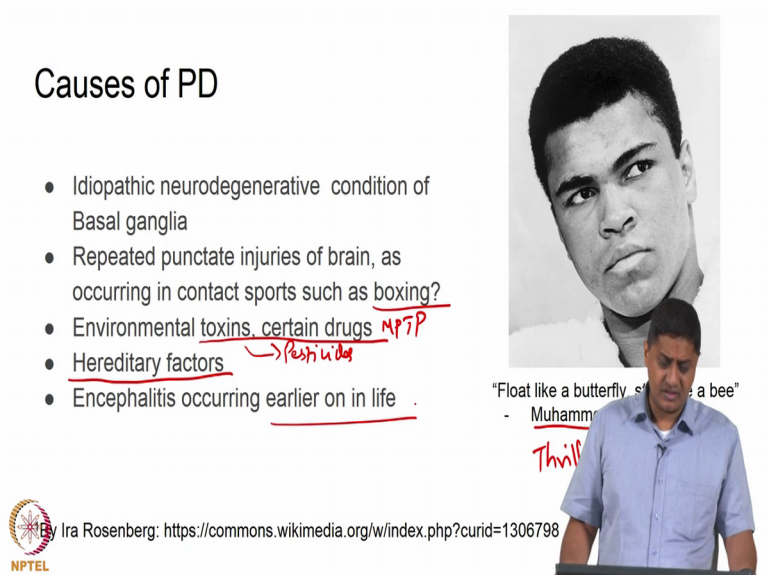

What causes? Well, what is known is that it is a neurodegenerative condition of the substantia nigra pars compacta of the basal ganglia. Then there is a hypothesis there is an idea that repeated punctate injuries of the brain such as those that occur in contact sports such as boxing. So, here we have the picture of the greatest of Muhammad Ali right. He suffered from Parkinson's disease for nearly 4 decades before he passed away recently. Let us take a moment and appreciate his philosophy to movement's right float like a butterfly sting like a bee.

What is means is that well it could have any number of meaning is not clear for me exactly with what meaning he mentioned that. This was of course, before a fight when he taunted one of his opponents. Of course, he was known to be very talkative especially expressive before the fights and he used to taunt his enemies; there are many ways in which he played his game this was one of his psychological games. Of course, you should definitely try to watch his fights, the famous fights such as the Thrilla in Manila was a fight that took the boxers close to death right.

There were there are others that you should this right or the so called the Rumble in the Jungle right and so on and so forth, there are several. Float like a butterfly, sting like a bee; it is not clear with what meaning Mohammad Ali said that. In my view this means, the importance he is emphasizing to me is emphasizing the importance of grace in the boxer's movement. Essentially, when somebody is hitting you is very important for you to float like a butterfly for you to gracefully escape from the opponents punch. At the same time when you hit the other person right we are talking about boxing when you hit the other person it has to be power pact like that of a bee sting like a bee right.

So, essentially why is this being discussed in this course because this is a course on movement's science, right. The importance of movements in everyday life in sports and other activities artistic activities, right. Here you have to float like a butterfly means what? You have to gracefully move your foot in such a way that you escape the opponent such was the statement at least in my view that is my interpretation of what Mohammed Ali might have meant.

But at least one thing is clear he was a true master of his art right. Is it possible that it was a art that ultimately consumed him? His fight was mostly with Parkinson's disease, he the longest battle his longest battle was with Parkinson's disease not with you know Foreman, not with Sonny Liston right. Those were not his opponents, the major opponent for him the major disabling refer for him of course, was Parkinson's disease, he which he suffered for a very long time right. Is it possible that Parkinson's disease in Mohammed Ali was caused due to the number of hits that he took due to the trauma that he took?

That is an interesting hypothesis, yet it is not clear what could have cause. It is entirely possible that could this could have been genetic this could have been due to other

environmental factors. There is no evidence to suggest that this is purely due to traumatic brain injury type of this. But at least it is important to keep in mind that this could be one of the contributing factors right. Of course, other environmental toxins and drugs are known to cause Parkinson's. It is in the case of drugs.

For example, MPTP adulterated drugs frequently cause Parkinson's disease, toxin such as pesticides. These are usually mitochondrial toxins that selectively knockout the neurons in the substantia nigra pars compacta leading to a situation typical of Parkinson's disease.

And then hereditary factors of course, genetic factors and encephalitis occurring earlier on in life for reasons. Essentially multiple reasons we actually do not know why Parkinson's disease is caused may be due to some dysfunction of mitochondria due to the exposure to toxins. This is the dominant hypothesis of course there might be some genetic factors which have not been completely understood. So, some genes have been identified. But those only constitute a very small proportion of the total number of disease cases.

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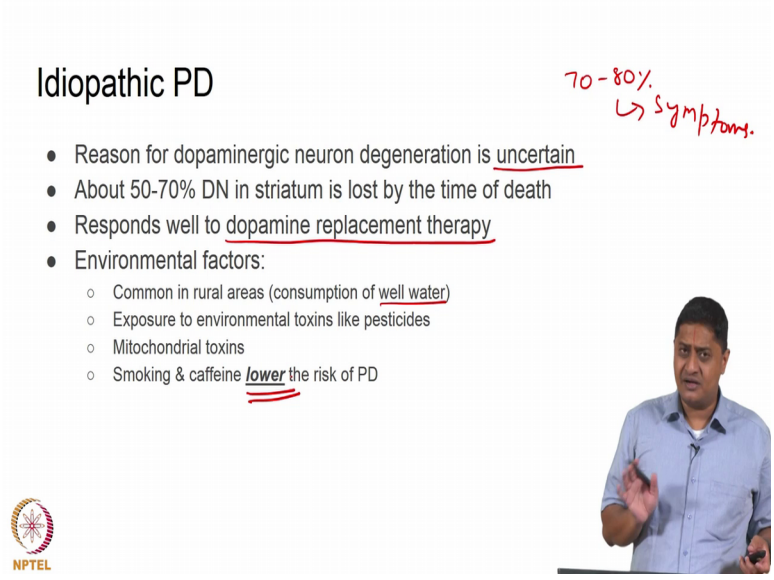

So, in idiopathic PD the reason for the degeneration of the dopaminergic neurons of the substantia nigra pars compacta is not known, it is uncertain, we do not know, we are still studying this. It turns out that about 50 to 70 percent of the dopaminergic neurons in the striatum is last by the time of death. Actually, what happens is in many cases about 70 to

80 percent of the dopaminergic projections of the connections are lost by the time the patient presents with the symptoms, not the cell death this is the projections.

So, essentially symptoms appear very late right. So, by the time the symptoms appear this too late usually it is too late right. How do you know that this is Parkinson's disease? Well usually dopamine replacement therapy such as drugs such as L Dopa or dopamine organized receptors sorry or dopamine receptor agonist right are known to improve the condition so, because of this reason.

So, how do you know the dopamine is depleted in the system, you cannot actually open up and see right there is not an easy way of doing this. One simple way of doing this is to give L Dopa to the person and see if he improves right. If the person improves then that is Parkinson's disease because in the absence of L Dopa the person is not able to improve. By giving the medicine he is improving. By the way let us remember here we are treating the symptom not the disease right. In other words this is not going to save the neuronal cell death. So in other words this is not going to save the neurons that are dying right those neurons that are dying will continue to die this is only treating the symptoms.

Actually this also does not work on the long term basis it works for sometime right. For a environmental factors, well rural living well water believe to be some of the causes exposure to environmental tax and such as pesticides, so farming pesticide exposure to other potent mitochondrial toxins. Let us remember that essentially PD is due to death of neurons in the substantia nigra pars compacta. Why do this neurons die because of mitochondrial dysfunction right. Or in other words if there is a toxin that affects mitochondrial function in the substantia nigra pars compacta then this neurons will die essentially. So, surprisingly smoking and caffeine reduce a lower the risk of PD, not increase right.

Smoking and caffeine essentially reduce the risk of PD. Of course, there are other reasons why you we should not be smoking there are so many other risk that come with smoking. But PD is not one among them. A question is how is this true? So, if you take a group of how is this even done, I am taking group of people in the general proportion I am taking a group of people in the among smokers right. And I compare the two; the incidence of finding Parkinson's disease patients among the general population is higher than among smokers.

So, nicotine apparently has some sort of neuro protective effect that is the hypothesis at least right. How, what is the neuro protective component of nicotine? We do not know. So, lot of these things are not understood and genetic factors that that cause Parkinson's disease.

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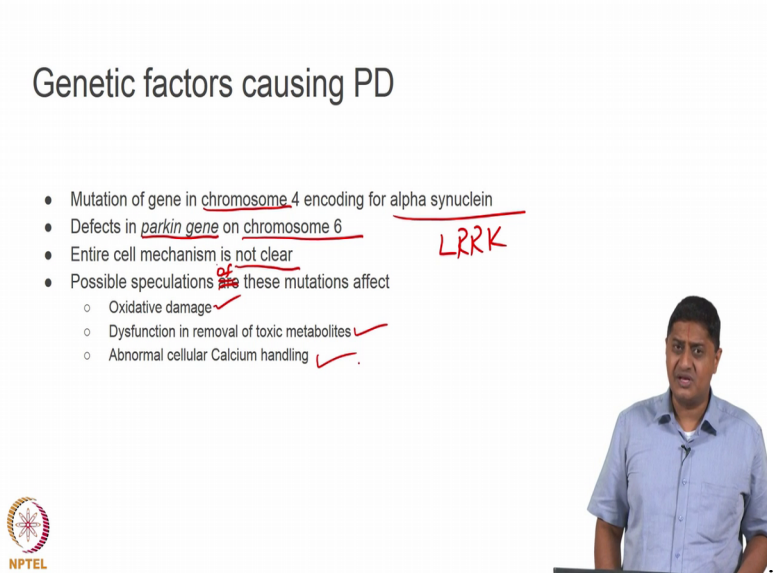

Note, this kind of Parkinson's disease is actually much lower in proportion right. Mutation of chromosome 4 that encodes for alpha synuclein right and defects in the parkin gene on chromosome 6 and the so called LRRK gene, right. The entire mechanism of how this works right. How the alpha sinucleina encoding is affected, what are the details right?

The moment you want to go into the details it is very unclear as to exactly how these happens. There are several speculations on there are several speculations of these right oxidative damage a dysfunction in removal of toxic metabolites and calcium handling is abnormal in this sense. These are all speculations of what happens it is not clear actually what happens. Many of these are just we think that this is happening many of these are actually untested hypothesis and then the interesting case of frozen addicts right.

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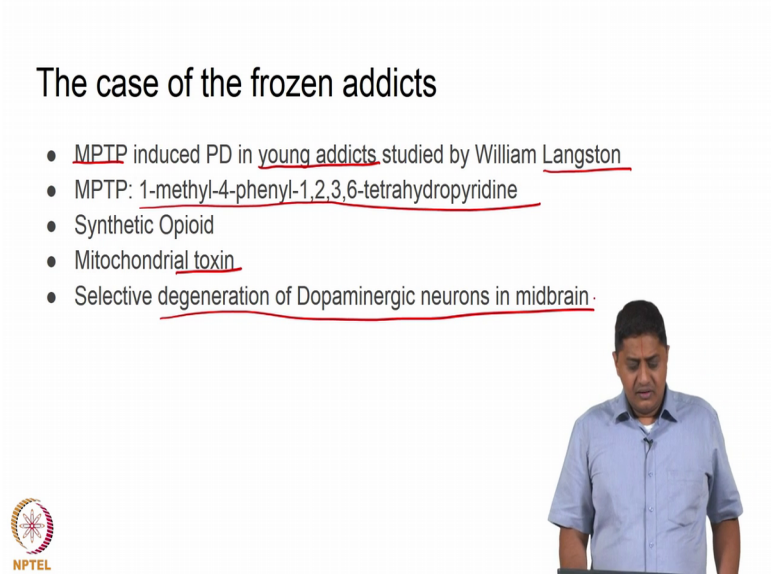

It turns out that group of individuals in San Francisco long time ago I think in the 80's consumed drugs or recreational drugs that were adulterated with a particular chemical called MPTP right. What is MPTP? MTTP is 1 methyl 4 phenyl 1, 2, 3, 6 tetrahydropyridine right. So, shortly MPTP that is actually 1 methyl 4 phenyl 1, 2, 3, 6 tetrahydropyridine. So, this chemical is mixed is usually used as an adulterant in more expensive recreation drugs. So, when that is mix and people consume that it turns out that people will develop symptoms typical of P arkinson's disease, the classic symptoms of Parkinson's disease right.

Let us remember the individuals who consume this were young. Usually Parkinson's disease sets or the unset of Parkinson's disease is at around age 50 give or take a few years right. So, these young individuals in their 20's if they got Parkinson's disease or they display symptoms similar to Parkinson's disease. That means, they must have consumed something that selectively damage the neurons in the substantia nigra pars compacta. What is more important is that doctor Langston actually gave the medication that was used in Parkinson's disease and they improved. So that means, these people have had irreversible damage of the substantia nigra pars compacta typical of Parkinson's disease right.

So, this is a very important mitochondrial toxin a very important mitochondrial toxin that has the ability to selectively knockout neurons in the substantia nigra pars compacta that produce dopamine right. So, essentially that selective degeneration of this.

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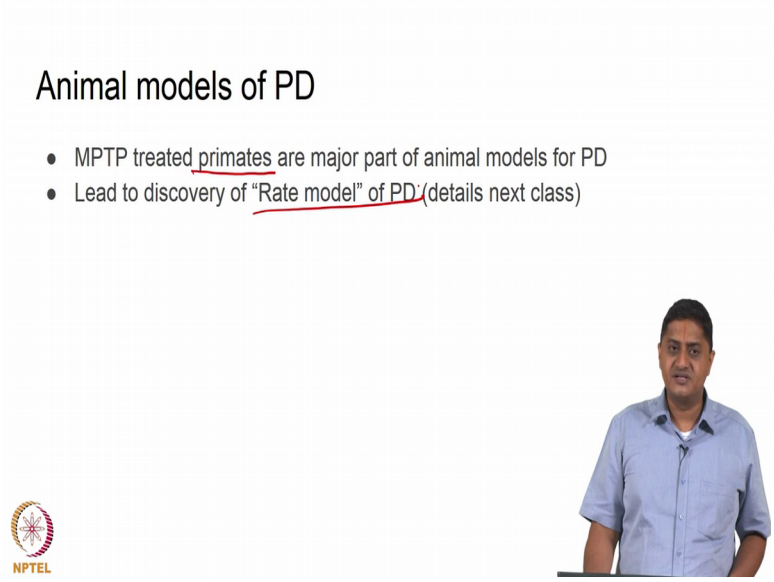

So this gave rise to the idea that we could treat animals with MPTP and then develop models of Parkinson's disease using animals. So, these primates right these animals from the major part of animal models for of Parkinson's disease. And let us remember that the following are the advantages of this right. This is a phenotypically and anatomically convincing animal model of the disease right. Nothing can be better than that right. Essentially what you are doing is you are inducing the disease like it happens in the real work. So, essentially you are you are knocking out the specific neurons, so, very convincing anatomical model right, anatomically convincing phenotypically convincing model right.

What are the problems? Let us remember that degeneration of neurons in real Parkinson's disease is a long term process right. It happens over several years, whereas in MPTP treated animals it happens in a shorter time. So, essentially these two are not the same; so this is a fundamental problem. In general this also forms the concerns related using animal models for studying humans, right. This lead to the discovery of the rate model of Parkinson's disease right this is something that we will discuss in future classes right.

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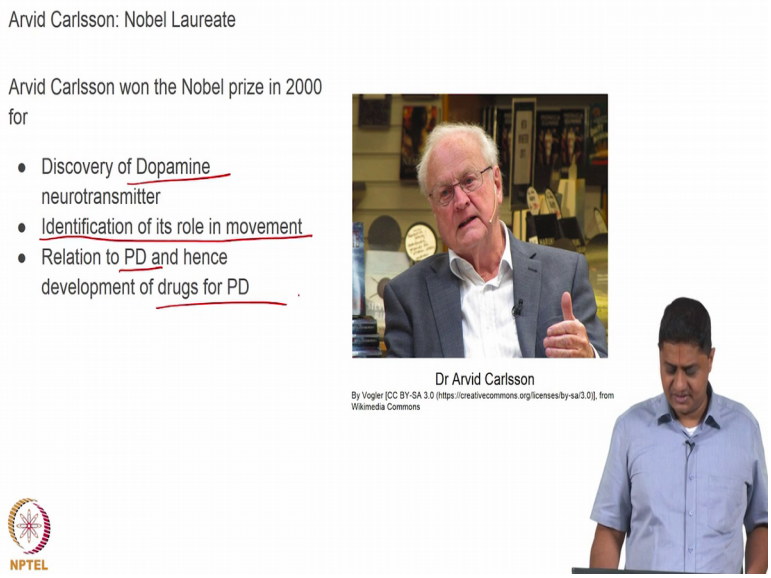

Doctor Carlsson who won the Nobel prize in 2000 for his discovery of dopamine and the identification of its role in movement. And relation to Parkinson's disease and hence development of drugs for Parkinson's disease.

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So, in summary we have introduced Parkinson's disease, we have discussed the various causes essentially much of Parkinson's disease is caused due to no particular cause. We do not know the cause idiopathic Parkinson's disease. Some of it is genetic some of it is due to recreational drug use and the role of dopamine in Parkinson's disease. And we

also discuss the specific case of MPTP treated animals as anatomically and phenotypically convincing model of pathophysiology in Parkinson's disease right. So, with this we come to the end of this lecture.

Thank you, very much for your attention.