Animal Physiology
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Lecture - 16

Welcome back to the lecture series in animal physiology in NPTEL. Today we will be talking about some of the diseases of the spinal cord especially the lower motor neurons.

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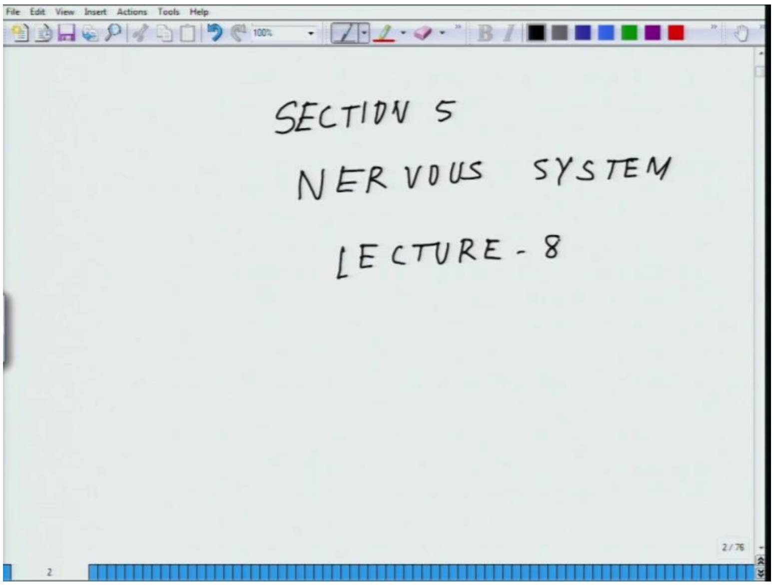

Let us start of it. We are into the section 5, nervous system. This one is your lecture 8. We have talked about the problems of the higher brain functioning, and how it is being compromised in alzhaimer disease in epilepsy, especially in alzhiemers when the pyramidal neurons of the hippocampus starts to die because of trafficking. Along the axons starts dying. Then we have talked about the Parkinson's disease and how the neurons in the sustention Niagara, lose their contact with the lower motor neurons, which are present in the spinal cord and we talked about the eloper therapy.

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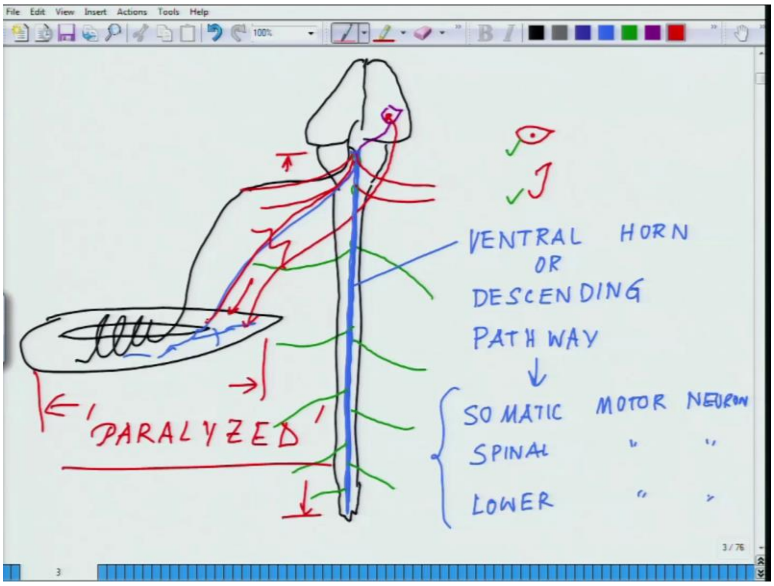

Today we will be talking about the lower motor neurons. In other words, we will be dealing with if this is the brain, and this is the brain stem, and this is the spinal cord, and around the spinal cord you have the ventral horn, which is this central blue line, what I am drawing in the center, and which is basically the zone where all the motor neurons are sitting. These are the motor neurons, which are getting signals from the upper motor neurons or the cortical motor neurons. Based on that they execute their functions.

They could be either called as, this the ventral horn or descending path way. Because they are bringing the signals from the brain to the target tissue, their sending pathway, and these harbors all the, they are sometimes also called somatic motor neurons or, there are several terminologies; somatic motor neurons or spinal motor neurons or sometimes, they are also called a lower motor neurons. They are all synonymous to each other. Depending on their positions, say for example, they have been numbered as L1, L2, likewise. There are different numbering scheme. Based on the position they are having, say for example, if I just put a, likewise, like which one is coming out from where, likewise, the processes of motor neurons are coming out. Depending on, some of them go and innervate the eyes, nose, and then the ears, like some of them are taking care of other body parts, likewise.

Depending on the damage or depending on the problem, at what zone it is, for example, if there is a problem out here, automatically the eyes will get affected. If the problem is here, may be, the hearing may get affected. Or, if the problem is somewhere here, maybe, then movement of the hands may get affected. Depending on the zone, where the injury takes place or the problem takes place, which leads to the necessary, subsequent problem.

What exactly happens? We have already talked about, from the motored cortex, you have the higher motor neurons, which are synopsizing here. We have already talked about the different circuits, like, these are the muscles, and within the muscles, Here the innervations, and these innervations are being, some of the innervations going all the way to the brain and their reflex circuits, which are coming back, bringing the signal and based on that, the neuromuscular junction functions

Whenever there is problems out here, these signals, which are suppose to come from these somatic motor neurons, spinal motor neurons or lower motor neurons, will not reach the target. If they do not reach the target, basically, what happens, this muscle of yours is paralyzed. It will not be able to function, the way it should function. Now, in this situation, what will happen? You have two options; either someway or other, you by-pass this route, and whatsoever signals, which are coming all the way from the brain, is directly transmitted to the muscle, or they have something else, which could repair this circuit.

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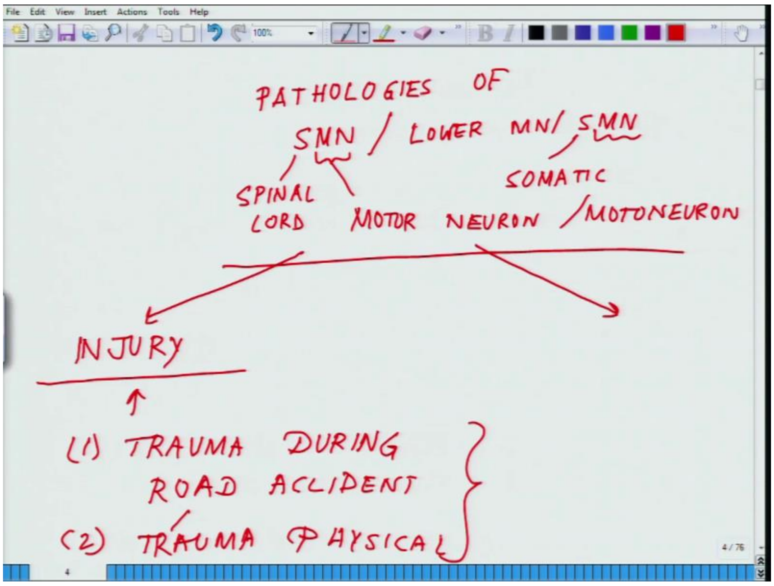

First of all, let us talk about the diseases of the spinal cord or the pathologies of spinal cord motor neurons. I am putting a short form, that spinal cord motor neuron or lower motor neuron or sometime, SMN, somatic motor neuron. It could be either somatic or spinal cord, standing for motor neuron. With the motor neurons, peoples sometime write as two separate words; motor and neuron or sometime, they write like this. So, these are all just depending on which country and where it is being used. Now, coming to back to the pathologies, there are two ways. One is when there is an injury in the ventral horn; these injury could take place, either due to trauma, during road accidents or any other form of accidents. Mostly, these spinal cord injuries are from road accidents or some other physical trauma, due to some other act.

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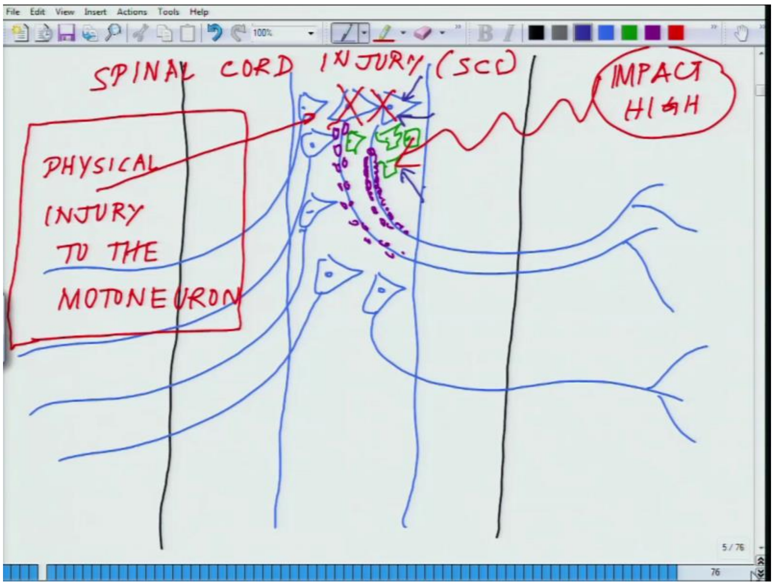

What exactly happens is this. If you look at this circuit, this is how it happens. Now, I am going to blow up the ventral horn. This is the spinal cord and a blow up zone, I am talking about, and this is ventral horn. This is something very interesting to note. For each one of these muscles, there are different routes. When paralyzes happens, say for example, still the complete paralyzes takes a lot of time. Still, some part of the muscles will move. There are always redundant pathways, which help us still to regain some of the functions.

Let us look at the path ways, how these motor neurons are arranged here. These are the bodies of the motor neurons, which are coming out going to their target tissues, all over like this, likewise. They are sitting at different level. It is just like a different staircase, kind of situation. In between, you have the different astrocyte glial cells, which are present here; all these astrosides. Then, you have the oligo dendrosides, which are covering, myelinating the axonal terminal. These are the oligos, which are around the axonal terminal.

Now, think of a situation when, there is a huge impact falling, because of some kind of road accident or something. Whenever such impact happens, what happen immediately is, these cells or some of these cells, because of the impact, starts to dying. There is a physical injury which it leads to. As soon as there is a physical injury, we are now talking about the spinal cord injuries; just for spinal cord injury. Sometime in the literature, you see, it is being represented by SCI; spinal cord injury; the short form is spinal cord injury. This is the high impact; very high impact, this leads to physical injury to the motor neurons. As I have already mentioned, these motor neurons are the ones, which are formed very early in the development. So, these are extremely susceptible to injuries. When in the where, there is a physical injury; the next thing what happens is very interesting. At the sight of injury, there is a rushing of microglial cells, soon posting Duracell. Let us see.

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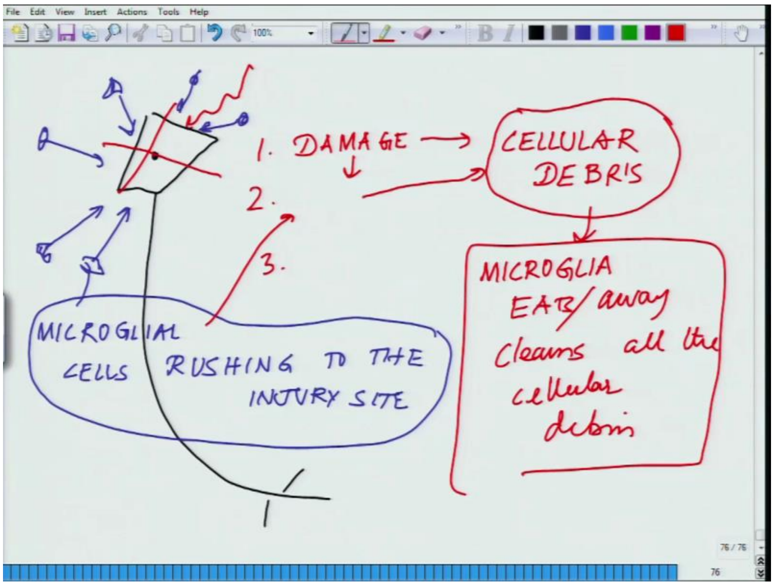

Go to the next slide. Here is an, say for example, this is the motor neuron, which got damaged, because of the impact. As soon as there is damage, this is damage; physical damage, followed by physical damage, next thing happens; all the microglial cells which are small cells, they start rushing to the site. These are the microglial cells rushing to the injury site. What the microglia cells does after reaching to the injuries site is that, this cell, soon after the damage, this leads to, second step is this. So, followed by the damage, there is a lot of cellular debris; is just like there is a car crash and there is lot of debris of the car crash. The microglial, what it does, it goes there and eats away all this cellular debris. That is the function of the microglial here, eats away or cleans away; you can call it eats away or cleans away all the cellular debris. This is the first step what happens.

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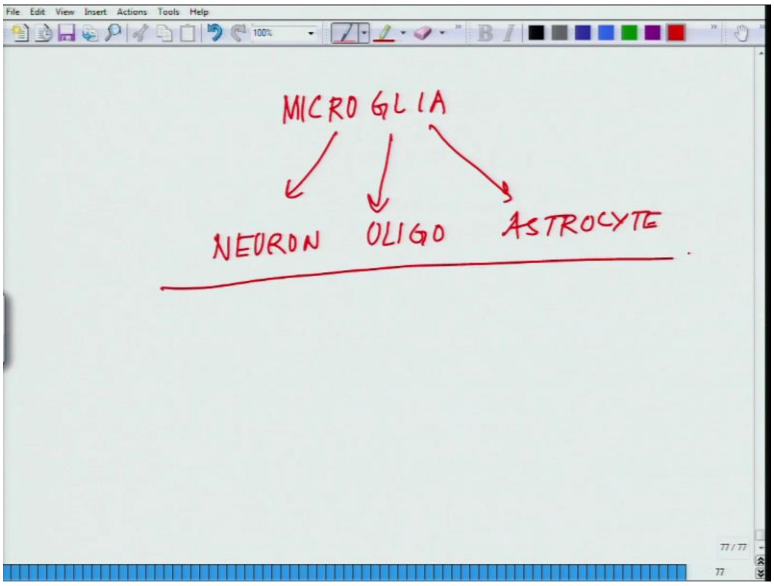

And microglial acts on all kind of cellular debris at the of site of injury; it could be neuron; it could be oligo; it could be the astrocyte; whatsoever.

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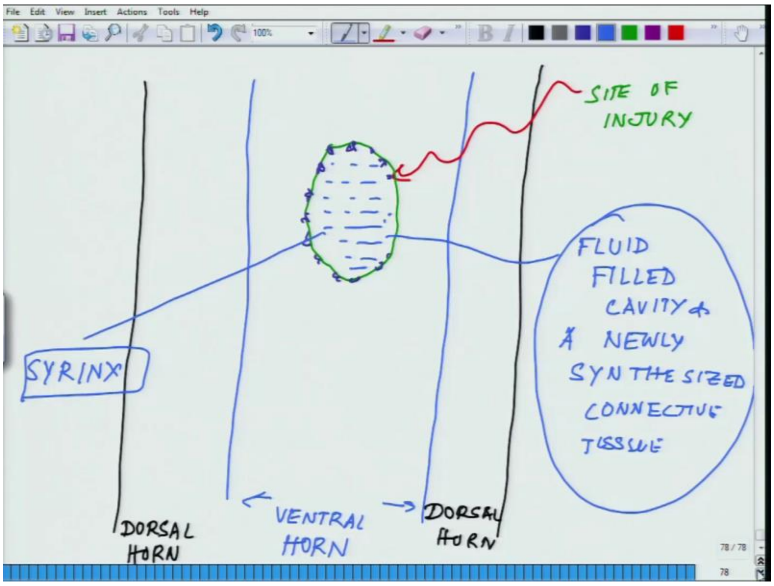

Then it forms, for example, the way the shape looks like is, say for example, this is the ventral horn and these are the flanking dorsal horns. Here, you have the ventral horn and here, is the site of injury. This is the site of injury because of heavy impact. The site of injury, soon after the microglial cells, does their cleaning up act. This site is now filled with a specific kind of a fluid, likewise, and some connective tissue.

It forms a fluid filled cavity and newly synthesized connective tissue. This filled cavity is called, there is a specific term for this, and this is called syrinx. The formation of syrinx is an immune reaction, in order to ensure that the debris, which are present at the site of injury, does not affect the metabolism of the cells, in and around it. But, because of the formation of the syrinx, and the presence of the newly form connective tissue, which I have indicated out here; the nodes, this acts as a, syrinx does not allow.

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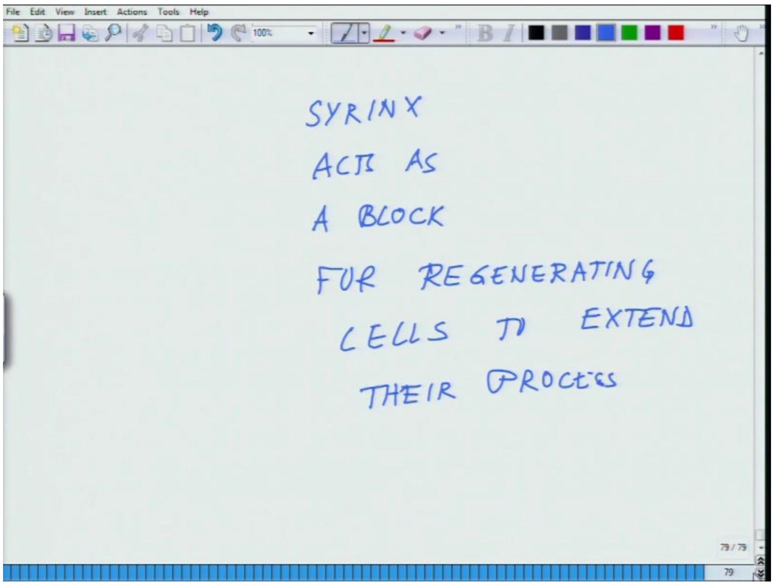

Syrinx acts as a block for regenerating cells to grow. What does that mean? Regenerating cells to extend their process. I will just diagrammatical show you.

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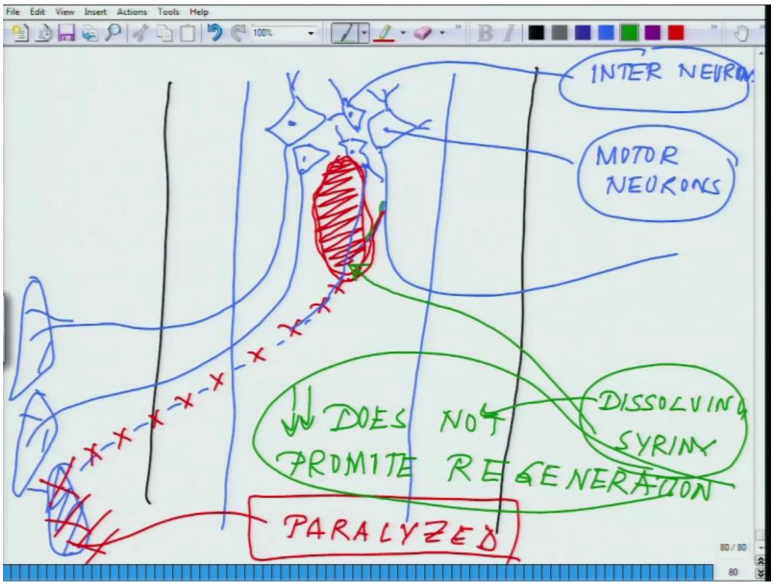

This means, again, I will just use a diagram to explain this. What does that mean? This means that, say for example, here, you have, I am using this diagram repeatedly. Here, you have the ventral horn and say for example, let me redraw this. The flanking zone and here, you have the, say for example, this is the site of injury. Let us put it like this as a red color; this is the syrinx and here, the ventral horn neurons, which are still going out, likewise, processes are going out. Some of the processes, which are suppose to move like this, have died out, because of the injury. Now, in this zone, there are another set of neurons, which are much smaller, which are called inter neurons. It is believed that some of these inter neurons, which are present here, have the ability to transform into motor neurons. Because, their functions are very similar to motor neurons, or their functions are very similar; their electrical activities or some of them, are very similar to the motor neurons.

But, at least, electrically, they have a very similar signature to the motor neurons. Pardon me, because I just keep to the functionalities, that is wrong. Electrical signatures are very similar, but these inter neurons are any of the neurons, say for example, this neuron decides to send out a process to make up for this, say for example, this starts sending out a new process. But, this process cannot pass through this cavity, because this cavity, which is formed here, will not allow anything to pass. So, you have to bypass it like this.

Some way or the other, for the therapy to take place, the biggest challenge is how to remove this syrinx. It is not an easy job because the very moment you have to approach the central nerves system, in other way, think of a real life situation. For example, for an individual, if I have to remove small syrinx kind of a structure from the spinal cord, basically, first of all, I have to do a surgery. The first surgery is a neuro surgery, should be a tricky surgery. You have to open this spinal cord. You have to really poke all the way to remove the syrinx and then all these, some form of neuronal regeneration may take place. Some of these neurons are something can move through and regain the path.

Say for example, this one is taking care of one set of muscle; this is second set and third set of muscle. This muscle is no more functional because the connectivity is lost. So, this muscle becomes paralyzed. This is exactly what happens. What are our options? Are we really helpless here? One therapy, we people are trying repeatedly, is some way, dissolving the syrinx by using molecules. Dissolving syrinx because remember this; syrinx does not promote regeneration. Syrinx has negative impact towards regeneration. One way that you have some molecules, some x y z molecules, which will dissolve the syrinx and this may promote.

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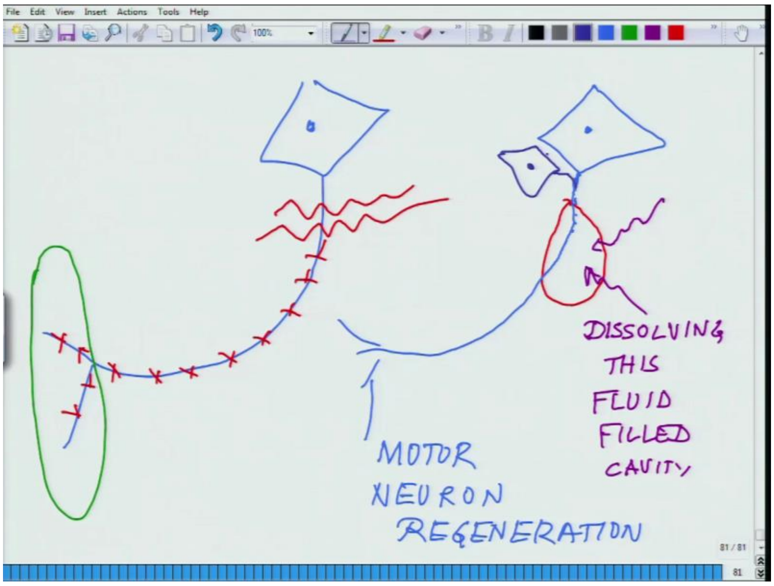

There is another situation which may happen. Think of it. Another situation may be, say for example, here is a motor neuron and here, is the original process it has. This may be the original, the first the muscle which it was innovating. Now, because of the impact, it loses this contact. Now, the motor neuron is sitting like this. It has a small process coming out and rest of this process dies out because it is no more getting any subtype from the cell body. This dies out. Now, what this could this, automatically, if there is injury here, there is a formation of syrinx out here. So, this will not allow this neuron really to penetrate through this.

But, if we have some more, that we have some kind of molecule, which could dissolve this fluid filled cavity; dissolving this fluid filled cavity. There is a possibility, then this neuron may starts to send out, again sends out its process, that is a very debatably shown. Could there be motor neuron regeneration? There is another option which is, if by some chance, some of the surrounding inter neurons, which are very much more smaller, may get transformed.

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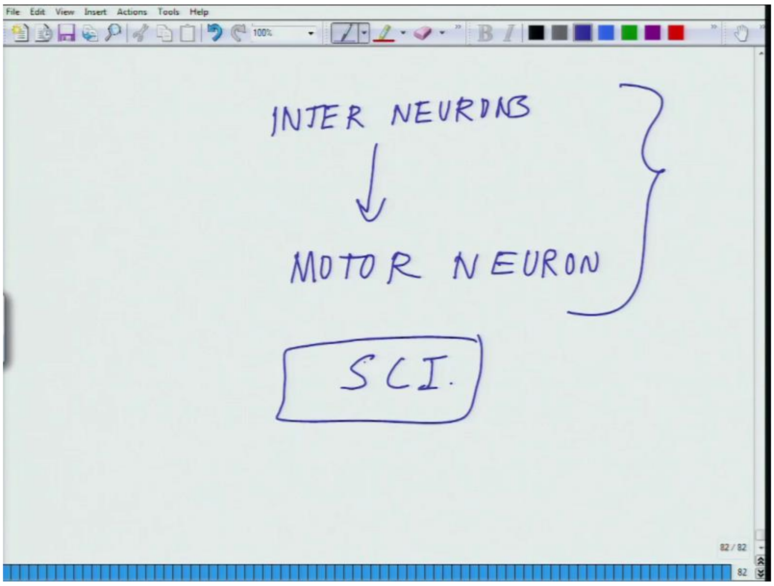

One of the next theories is, some of the inter neurons becoming motor neurons. These are very debatable topics and there is enormous amount of research, going on across the world for those people, who are working on the cellular side of spinal cord injury. They are working a lot to figure out, if there are some inter neurons, which may transform.

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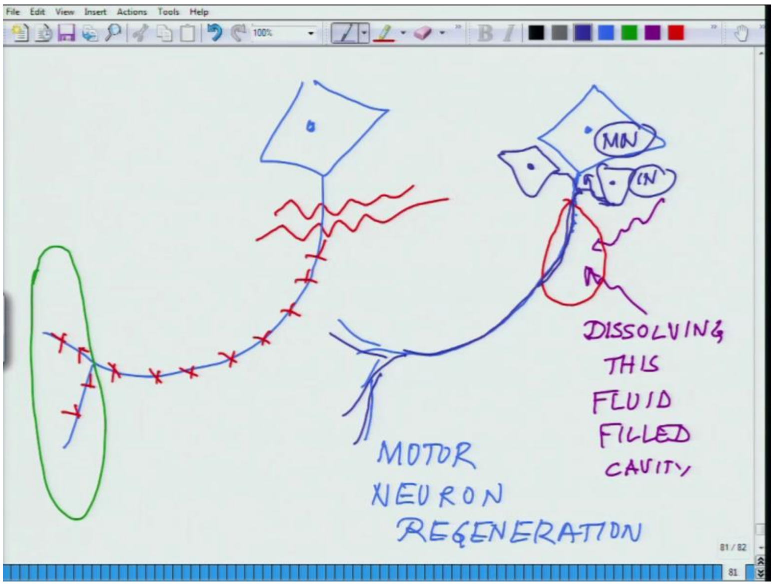

In other words, what will happen, if there is a very close by inter neuron and it can get transform into a motor neuron. This is, I represent by IN and this is, I represent by MN as a motor neuron and inter neuron. Then there is another possibility, it may, but of course, no one can guarantee that it is going to follow the same path. There is no guarantee. Neither you nor I or anyone else can give a guarantee. There is another way, that you put some form of condi tube, I will come to that the next level of therapy, which is feasible.

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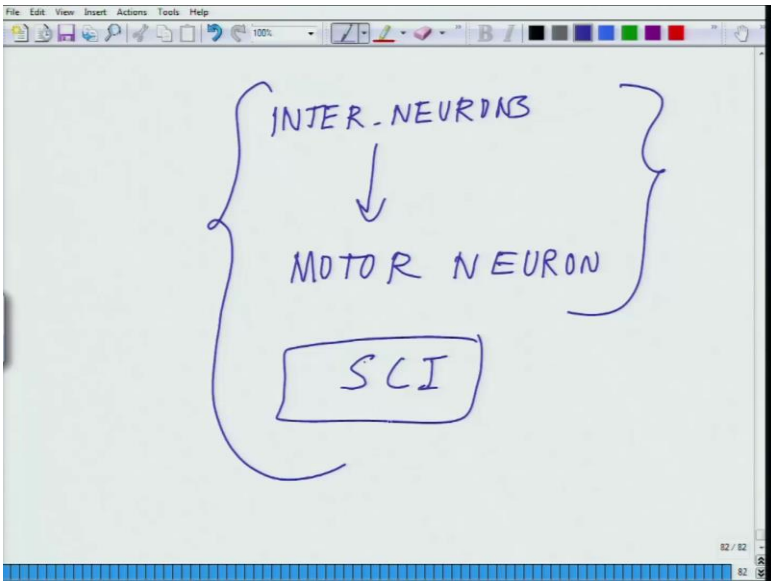

This is another option, the inter neurons concentrate on the motor neurons.

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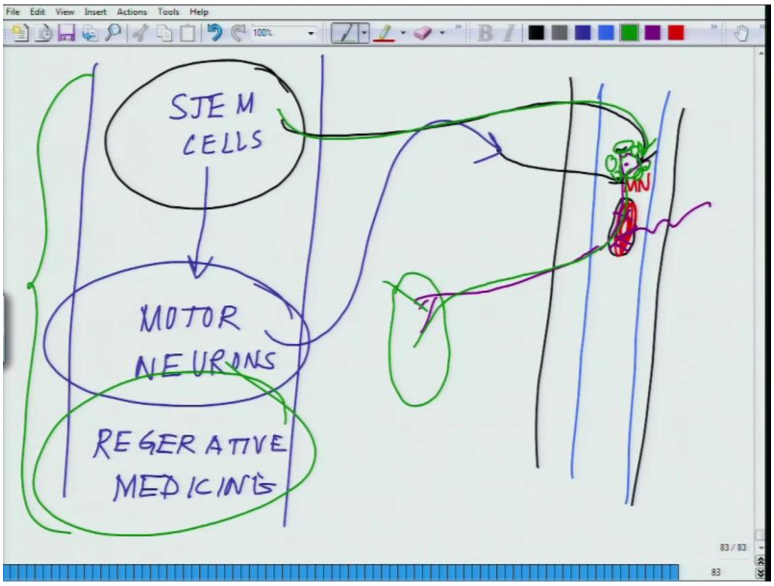

The other option is that you have a source of stem cells. These stem cells, you are transforming them into motor neurons, and then, what you do is, you take this motor neurons. This is all happening outside. This falls under the region of regenerative medicine. You take these in with the motor neuron, and you put them back out into the ventral horn, which is out here, near the dorsal horn, it takes your motor neuron and go, but again, mind it, there is a syrinx which is waiting. So, you implant your motor neuron here.

Of course, you have to put those kind of molecules, which will ensure that you will dissolve the syrinx. With a hope, that this motor neurons eventually, go back to its original target, if this the original target, which is lost. It goes there and forms connectivity. This is all, I guess work. This is one option. The other option is, you take your motor neuron; stem cells. You directly implant the stem cells out here. We should implant the stem cells out here and then, you have some kind of drug, or some kind or growth factor releasing aspects, chemicals which transform these stem cells, here itself to motor neuron and it goes and innervates; direct stem cells implantation. So, either you could implant the motor neurons directly, which are formed through the process orl you can implant the stem cells directly, at the site. Both these approaches are being tried out. Then, there is another side of the game, which is even more tricky.

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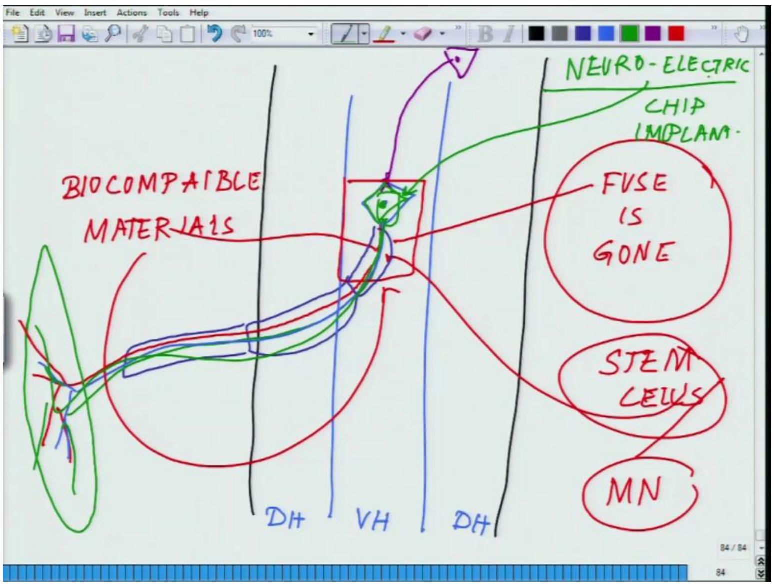

Realize the original situation before the injury taking place. Here, we have the ventral horn, sorry, the dorsal horn and here, sorry, I am just drawing it wrong. So, here we have the ventral horn, VH and dorsal horn, DH, DH. Originally, when, might be before injury, the pathway is like this; it is coming to its original position and here, is the target tissue.

Now, whenever you are implanting anything out here, say for example, I implant something out here. In other words, what you are essentially doing is this. You realize that these are also under the control of the higher motor neuron, which are coming from the brain from, somewhere from the upper motor neuron.

Whenever, this particular connectivity goes off, say for example, this one goes off, in other words, what is happening? The fuse is gone or the connectivity is gone. What you do in a real situation? You put the fuse back. In our case, the fuse is your stem cells or the motor neurons. These are other, you may have this stem cells or the motor neuron, you are implanting here.

Now, while we are doing so, we have to ensure; when you are putting the stem cells, you have to ensure, that they follow the same route by which it could go to the exact target organ. In order to do so, some people across the world are working and developing condo tubes, likewise. These are nano scale tube which ensure that the process, the newly implanted cells, the process is sent out by the newly implanted cells, follow that tube and reaches to the target organ.

There are specialized materials which are being used; very strong biocompatible material, which could be used as a implanting agents, for taking care of these injured patients. These are some of the ways by which, you can, at least we dream up, that we can hope, that some of these spinal cord injury patients could be cured. There is another way, which is a purely neuro electric way, where we believe that some of these therapy are being done. We believe that you develop, you implant some kind of neuro electric chip out there, in these sides, which will regulate the motion of these target tissue; neuro electric chip implant. These are all the futuristic technologies, what we are talking about; the regenerated medicine, neuro electrics and some of another theory, which I missed out while talking about Parkinson and all these things.

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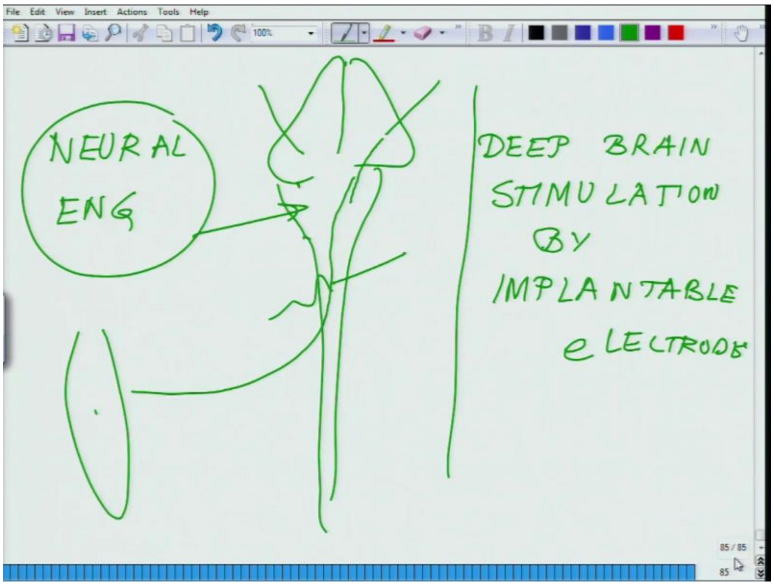

All those diseases, that there are different deep brain stimulations using electrodes. That is another way of approaching. That falls under the regime, neural engineering, where basically, deep brain stimulation by implantable electrode; electrodes neural engineering. This is where, this whole domain falls, where you implant different kind of neuro electric devices, chips or like, electrodes, which will stimulate that specific circuit. It is just like an electric circuit. You replace it with another electronic component, which will stimulate the specific target organ.

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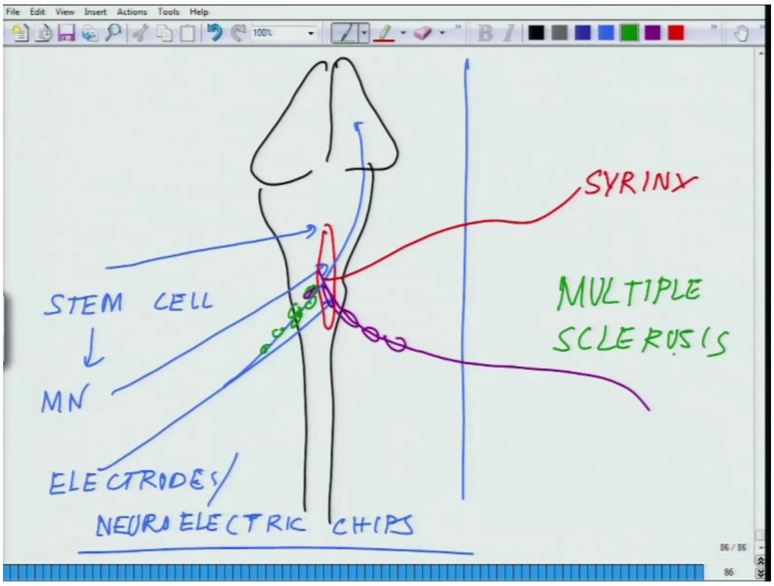

If I have to summarize what are the different things, we have just now talked about, is one of the option is that in the circuit, talking about what all we have just now talked about as you could have this stem cell therapy, which falls under the regenetic medicine. You could have directly stem cells transformed into motor neurons, which could be implanted. You could have electrodes, which could be implanted at both; at this level, as well as, the higher brain regions. You could have neuro electric chips to ensure, that this circuit works. So, no one therapy, and above all, we have to ensure that the syrinx could be dissolved first of all. Then, you have different condi tubes, which I was mentioning, which will allow these molecules; these stem cells processes and motor neuron processes to move to the target organ.

Essentially, what it means is this. There cannot be a single modus operandi, by which we can take care of a spinal cord injury patients. There has to be multiple roots, multiple approaches and a very inter disciplinary approach, which takes into account, I except is from material science, by materials, nervous system, development biology, cell biology, electronics, and then only, we can approach such tricky problems of nervous system damage. This is one of the pathologies, we talked about, which takes into account, the injury to the motor neurons. Think of it, how the milenation and all these things, will proceed in these neurons. Those are even, much more challenging thing, or think of situation like, multiple sclerusis. What happens in multiple sclerusis is, MS, your glial cells start dying.

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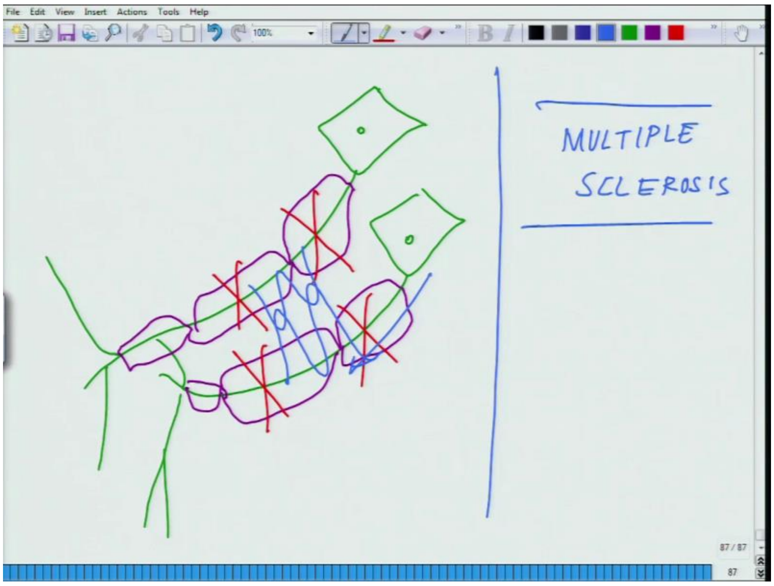

When the glial cells start dying, in other words, what is happening? If these are your neurons and which are milenated. There two kinds of neurons, either they will be milenated or they will be non milenated. In case, there are milenated neuron and say for example, these are milenated neuron, likewise. These are all the milenations, you see, say for example, these milenation are lost. The very moment this milenation is lost, what is happening is, that electrical impulses which are getting generated here, start getting short, from the electrical impulses, which are generated here. In other words, the signals do not reach to their target properly. There is improper transmission of the signal and this is very terrible situation, which happens in multiple sclerusis, because of the death of the glial cells. As of now, there is no such cure for multiple sclerosis.

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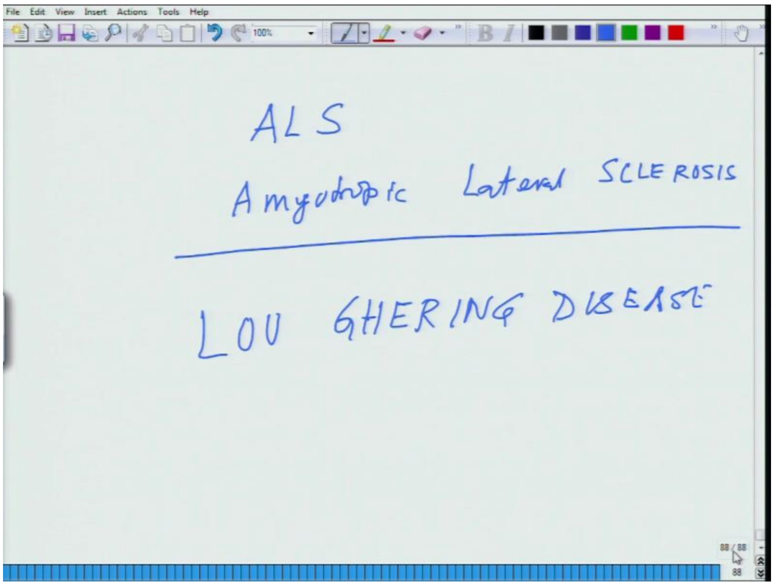

The third form of pathology is something called ALS, which full form is Amyotropic Lateral Sclerusous. This is also called Lou Ghering disease.

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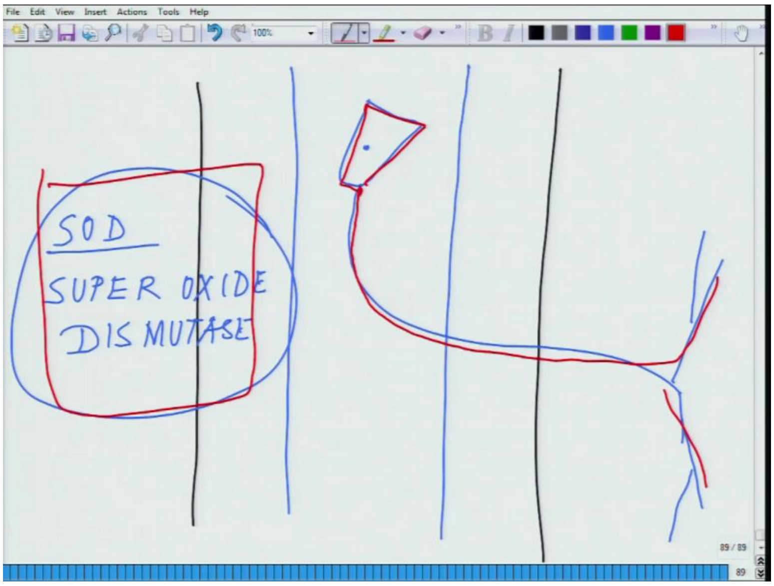

What this disease all about? This is against spinal cord disease. Again, go back to the ventral horn and here, are the dorsal horn and ventral horn. Here is the huge cell body of the motor neurons sitting. What happens in Lou Ghering disease, is very similar to what happens in alzhiemers, that these cells started to die, and the reasons are not known except, on very small cases where, there is an enzyme, which is called SOD; super oxide dismutase. This is a very small proportion of a super oxide dismutase. Just to tell you, where the origin of the SOD. The body has three specific enzymes, which helps us to safeguard our cell from oxidative damage. One is glutothin puroxidates, the another one is catleys and third one is SOD; super oxide dismutase. So, any compromise with these enzymes, can lead to oxidative damage in our body.

Super oxide dismutase is one such important enzyme in our body. A very small, say for example, out of hundred, one or two patients, or may be three, are being seen with a mutation in this particular gene of super oxide dismutase. In other words, they are unable to produce proper super oxide dismutase. Under that situation, these neurons are in continuous stress; from continues oxidative stress. But, this is a very small proportion of it. I am repeatedly telling; this is a very small proportion of it, which are in the SOD compromise situation and under that situation, what happens? What is being seen? In both the situations the symptoms are the same.

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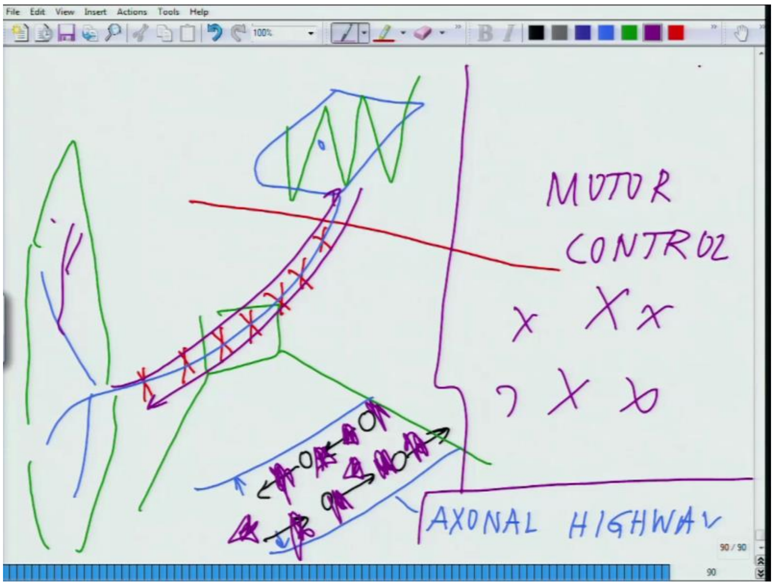

These spinal cord motor neuron starts to, their processes start to die out, likewise, and eventually, they are not getting the target tissue. Once, they do not get the target tissue eventually, these cells start dying. The causes are not known, but what is believed is something, very similar to what is being believed in or what is current the literature is indicating is, that there is a traffic ring problem. In other words, if this the highway through which, I have to blow this up, and if this is the highway of the axonal highway; called this axonal highway, the molecules which are travelling along these axonal highway; I am represent the molecules by say, black; the one which are moving towards the end of the axon and the one, which I am moving towards the cell body. This transmission is being obstructed by formation of abnormal protein along it.

The transmission process is all over, being obstructed and that, leads to improper transport of molecules, which helps this long process or the condi tube or the axonal highway, to communicate with its target organ. This is one possible situation of what is happening. As of now, there is no cure and like, those of you are aware of Stiffin Hawkin; one of the very another genius of our time, he suffered from Lou Ghering disease. This disease is more prominent among the Japanese and few other places. It is slightly higher as compared to places like India, where it is likely lesser. The cases are not that very prominent. So, what are the possibilities? These cells start dying. Automatically, this person loses all the possible motor controls. Motor control is being completely compromised. In this situation, though it can receive the signals from the cortical motor neurons source. From the cortical motor neurons, signals are coming. But at this zone, these cells are dying.

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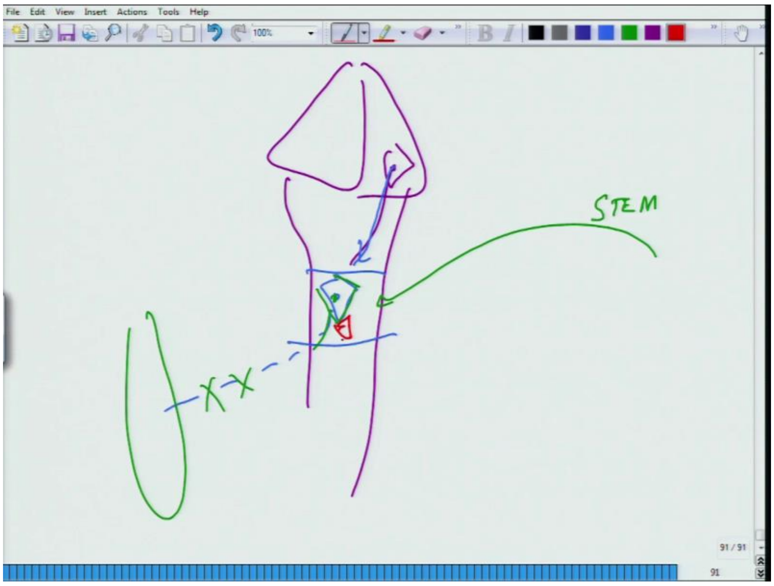

So, there is no use of this signal because the second level, at this spinal cord, this signal cannot be transmitted. In this situation, again the options come back. Could you have stem cells therapy or could you know exactly, that these cells will be destined? And then, there is one more interesting feature here. This particular disease, this ALS does not affect the surrounding inter neurons. It only affects the motor neurons and these are much unsolved mystery, unresolved mystery, and unsolved problems of neuro signs. That, why is that at specific site, only a specific cell type gets effected, whereas, not the other ones.

We really do not know; we do not have an answer to these very challenging problems. What are our options for those kind of patients, who suffers from Lou Ghering disease or or Amiotropic latlaris chlorosis. One of the options lies is, what I have already discussed with you, that we may have stem cell therapy, or some way or the other, that we know that we could stop the progress of the disease, by some pharmacological intervention, which will prevent the further death of the neurons. Because, the way it works is that.

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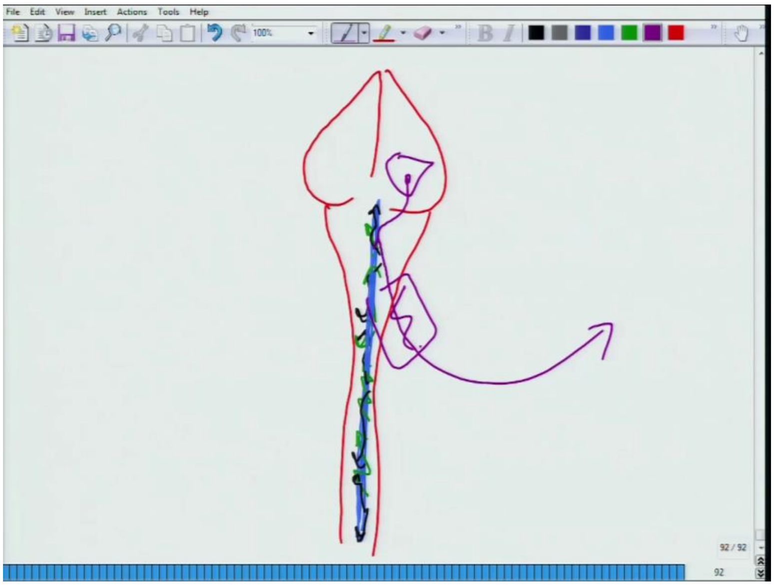

Along this spinal cord, if you look at it, the way it progresses; it starts at one point. If this is the spinal cord and this is the ventral horn. It starts progressing from one end and it moves on. There is no way to, it could start from here; it could move like this, whichever way, it does not matter. Eventually, this person becomes completely paralyzed and eventually, dies out. Because, this person cannot do anything because all the motor controls are completely compromised.

As of now, we do not have any cure for all these things. It is just, it gets diagnosed and then, you pretty much live a very much compromised life and it is very sad. One of the options is that, there could be a pharmacological intervention or in regenerative medicine, we may have a stem cell therapy, which may be able to take care of like, produce motor neurons outside the system and implanted back, or we may have some kind of neuro electronic interfacing. In other words, what will happen, is that the signals which are being sent from the higher motor neuron, they will completely by-pass this and will go to the target tissue, using some form of neuro electric amplifier, or something or other.

We really do not know, I mean, we are all just trying out several things across the world, that what is the best option or best alternative, but as of now these are the challenges of the future of the spinal cord injury or degenerative diseases of the spinal cord or diseases like Alzhiemers, Parkinson, short term dementia and all these things. We really do not know, or epilepsy, as a matter of fact.

These are the frontier areas, where we are now mankind is now heading towards to understand this very tricky diseases. I mean and I hope that in a distant feature, we have therapies for all these different things. So, with this, I will close on this lecture. Next, what we will be moving on will be the sympathetic and parasympathetic system. That is time, what I promised you, I will come back to the control mechanism of the heart and all those things. I told you that I will come back. I will remember this and I will come back to the parasympathetic and sympathetic control of the heart and other tissues, we will come back to that.

Thanks a lot for your attention.