GERALD SCHNEIDER: Today, we'll do more neuroanatomy, but it's-- we're focusing on development now, for the next four lectures. You will need to some of the things you've learned in the previous anatomy sessions. Let's just review some of the highlights of what we've been talking about. You should now know of the basic subdivisions of the central nervous system, definitions of some of the cell types.

You should be beginning to get familiar with the shape of the neural tube-- cross-sectional shape-- at various levels, at least the embryonic neural tube. If you did the dissection yet-- a few more of you will do it tonight-- you'll get a more realistic view of that. Then we went through sensory channels, or trying to simplify pathways' information takes when it comes into the nervous system.

You should know the definition of dermatomes. You should also have an idea what "diaschisis" means. It becomes very important in talking about lesion effects. And it's a neglected topic in neuroscience, and that's why I like to emphasize it, because of its importance. Functional depression of neurons after deafferentation. That is loss of inputs.

Then we talked a little bit about the evolution of neocortex, how it arose, and some of the major ascending and descending pathways to and from it. You were asked about that in today's quiz. And we did the spinal cord structure, noted the differences between different levels. We defined propriospinal system, which was a quiz question that I took off.

The components of the autonomic nervous system. Hindbrain organization. You should know what I mean by distortions of the basic plan of the hindbrain. What's the major distortion in mammals? Cerebellum, and the cerebellum which appears in the roof plate, and then what appears in the migrates from the alar plate but actually ends up at the bottom. The pons-- very enormous in humans. OK?

And we've talked about some of the cranial nerves. We've mentioned a number of them. The one we put the most emphasis on in the lectures was the fifth, the trigeminal nerve. You should review that a little bit so you know how to relate that to what we said about the spinal cord. When we went into the midbrain, I talked about the midbrain tectum, superior and inferior colliculi. You saw that in your dissections, if you came.

Often, anatomists talk about the tegmentum, below the tectum. Actually, both words have similar meanings. Tectum means the roof, and tegmentum means the covering, so I guess it's the covering of everything below the tectum. But it actually refers to all of that reticular formation and even the red nucleus down below.

OK, then the 'tween brain, the diencephalon. Two major functional subdivisions that I used actually for midbrain, also-- midbrain, diencephalon, and membrane, OK? Midbrain, 'tween brain, membrane-- the somatic and limbic portions. And then we talked the major structural parts, the two biggest ones, thalamus and hypothalamus, then the smaller ones, the epithalamus and subthalamus.

OK, and then the endbrain-- you should know the difference between cerebral hemispheres and basal forebrain. That you get some help in the dissections, also. Origins of two major pathways for descending axons. And there are some ascending axons in those pathways also. What are they?

They come from embryology-- lateral and medial forebrain bundles. The medial forebrain bundle is a commonly used term in anatomy. Lateral forebrain bundle is not. Instead, they confuse you by giving it all kinds of different names at different parts, different portions of the nervous system. OK?

I say here, other major pathways, but actually, this one is part of the lateral forebrain bundle-- corticospinal and corticopontine pathways. Corticospinal pathway actually goes to all levels of the CNS descending pathways. Officially, corticospinal, of course, is only those axons that make it all the way down to the cord.

OK, I'm going to divide development up into these stages. The text does it slightly differently, but we'll review that briefly. We've mentioned neurulation already, formation of the neural tube. But we've not talked much about the proliferation and the migration of cells. I've mentioned migration, but we'll talk about it in more detail now. And then we'll finally talk about growth of the processes. So the cells grow from their little neuroblast stage to where they look like mature neurons.

I should mention here that with differentiation, we're going to talk mainly about structural differentiation. But in fact, at the molecular level, cells become determined to be a certain cell type earlier than they actually look different, OK? And we will mention that it's called determination of the cell.

OK, this is the way the textbook and I present it just because I want you to realize there's different ways to divide up a time sequence. They start there with mitosis and neurogenesis. Well, I start a little earlier. In fact, we'll even go back one stage earlier in the next few slides so you know what happens before there's neurolation. OK, what happens to that fertilized egg? How does it get to the nervous system?

OK, so here, they start focusing on neural development. They're just starting with mitosis after the neural tube is already formed, OK? And then migration. And we're going to talk about different kinds of migration. And then what we call differentiation, they have divided up here.

They're talking just about the initial stages of growth processes. And then he has synaptogenesis, cell death, synaptic rearrangement. Now, all these things happen not in strict sequence, OK? And I will include them all as part of differentiation of the nervous system.

OK, now you remember this picture? Because it's fun to look at, we'll look at it again. Before there's even a neural plate, OK, we talk about the gastrula. And we're going to look at gastrulation. But after the gastrula is formed, OK, by an invagination of the blastula, the gastrula forms, and then the neural plate appears. You can't really see it here, but now you can begin to see it on the dorsal part of this one, from there to there. And then we see it form the neural tube and then fold, OK?

OK, so now, we're going to go back to the stage before-- the stage just before neurolation, just so you know what's going on. These are diagrammatic, but they're showing you how you can-- cells have already become determined much earlier. So what happens? You get one cell first. It becomes fertilized, then it starts dividing. Then it's two, four, eight, and so forth. That's the moral-- it's a raspberry, OK? It's a clump of cells.

OK, but then, the blastula forms. It develops a hollow center, fluid-filled center, OK? That eventually becomes the-- will be incorporated as fluid of the ventricles of the CNS, as well as other things. OK, but so now we have here the hollow ball, and it has become determined that different parts of that surface will become different things. OK? This part here will become nervous system.

It's starting to invaginate right there. And here is the invagination. And what happens is the cells flow in to the interior, OK, and you get them the formation of the germ layers with gastrulation. OK, so you get the surface ectoderm layer, the mesodermal layer, where you get the notochord forming, and then the endoderm in the inside. And then we've already looked at what happens to the gastrula when the nervous system starts to form with the neurolation. And this is the way they're diagramming it. We've looked at that already.

So how does that happen? It has been known a long time that the notochord region, and even earlier-- the part of that gastrula that will form the notichord-- if you manipulate it in the developing embryo, you will alter the development of the nervous system. You can even get two nervous systems to form. If you take part of it and put it at the other end, you'll get two nervous systems.

And the reason is the nervous system is induced by the notochord region. And Tom Jessell and co-workers at Columbia discovered some of the inducing molecules involved, and then others were discovered, too, to play a role in later determination of the cells of the neural tube, OK?

So these are the terms you should already know-- formation of the neural plate, the thickening of the ectoderm above the notochord, and then we talk about the neural groove before the invagination is complete. And it forms the tube. And then you should also know the term neural crest, OK?

So what we want to talk about now is-- let me get my pen back here. We want to talk about molecules that come from the notochord here that are influencing the overlying structure, OK? And that continues to happen at this later stage.

And finally, after the neural tube is formed-- so that we call that induction. It's an influence of these molecules. The molecule is called sonic hedgehog. It's the most important one. At the later stages, that starts to be secreted also not only by the notochord here but by the floor plate. This is going to become the floor plate, these cells here. They're the ones closest to the notochord. So the concentration of those molecules seems to make a difference.

OK, this is the name of the protein that was discovered to play a key role in that process, since that time. It's been discovered to play other roles in development as well. It often happens. And it was discovered that it has later effects. It not only induces the formation of the nervous system, so neurolation results, but it also affects the later differentiation of the basal plate cells.

And then they discovered other factors, and these are a couple of them, the most important ones BMP-4 and -7-- bone morphogenetic protein because they were discovered to play a role in bone development, but they play a role in nervous system too. And they're active dermal factors.

So if we look at this again, first of all, look up here. Which part is going to from the alar plate, and which part's going to form the basal plate? Well, it's pretty clear if you look here. Here's the division, somewhere in here, between ectoderm out here and CNS. OK? If this is going to become the alar plate here, the part that's not neural crest-- we'll color it green here-- that's how it develops.

OK, so it started out right out here as the part of that neural plate that's nearest the ectoderm, OK? So BMP 4 and 7 are molecules that come from the ectoderm here and diffuse into the adjacent part of the neural tube, and the adjacent part was the alar plate region, OK?

And that influences what cells are going to become, whereas sonic hedgehog-- remember, and now at this stage, is being secreted by the floor plate cells. And those molecules are diffusing this way, and they're influencing the differentiation of the basal plate. And where it's most concentrated, you get motor neurons. Where it's less concentrated, you get interneurons. At least, that's the theory, OK?

So look at this one again, too, just so I can explain a little more of that. Here it is. Oops. OK, so just look up here in the upper right. So here you see, while this is all going on, these inducing molecules are exerting their influence. The BMP 4 and 7 are flowing into this, and sonic hedgehog is influencing this by now.

The neural tube is closing, and the floor plate is starting to secrete, well this-- so that's all happening before the neural tube is closed. You see here, it's not closed yet at the caudal end and at the rostral end. All these kinds of things are happening at all these levels, but they happen slightly different times. The earliest part of the nervous system to develop is this region, which corresponds to the cervical spinal cord, OK?

That's the earliest part of the nervous system to develop. And then it develops successively more caudally and more rostrally, OK? The last part of the neural tube to close is up here in the brain region but almost at the same time it closes at the caudal end.

OK, so now we're going to talk about proliferation. We've got the nervous sys-- the basic form of the nervous system now. Of all the chordates, we've got a neural tube. It's one cell thick. But it's the tube, and it is now separate from all the periphery, OK?

So now what happens to it? Well, the neural tube is going to get thicker. The walls are going to get thicker. You've seen that in the pictures of the developing spinal cord. The mitoses always happen, in the spinal cord, at least, adjacent to the ventricle. That's not true for all parts of the CNS. But actually, in all parts, there are always mitoses adjacent to the ventricle. It's just that there's other, more specialized regions where it also takes place. And we'll talk about some of those, OK?

And because of that, we call the ventricular layer the matrix layer, OK? This term, the matrix, which means womb or mother, OK? But in fact, the terms ventricular layer, intermediate layer, and marginal layer weren't the initial terms used in embryology. But then there was too much of a proliferation of terms, and in about 1970, a group met, a group of embryologists, and tried to simplify it. But some of the old terms are still very useful because they're very descriptive.

OK, so when mitoses occur, we talk about two kinds of cell division, symmetric cell division and asymmetric cell division. Symmetric cell division is when two daughter cells are formed, but they both stay stem cells. They're both still going to undergo mitosis, OK? Whereas in asymmetric cell division, one of them becomes post mitotic and migrates away, OK? The other one remains a stem cell, OK?

Now let's look at some Cajal pictures. He was looking at Golgi stands at the wall of the neural tube in those early stages, where the neural tube was just starting to thicken, OK? He saw something very interesting. He saw that all the cells, or most of them-- not all of them-- many of them were like these three cells here. They were attached to ventricular layer and to the pia layer, OK?

Here's the pia. Here's the ventricle, OK? So we're looking at the wall of the tube. And many, many cells have these attachments. So here, we're outside the brain, and we're above the pia. That's where you would have-- the brain would be surrounded by cerebrospinal fluid. And here, you're in the ventricle, where you have cerebrospinal fluid.

Why is it the same? Because the cerebrospinal fluid is made by-- some of you were at the dissections. What makes the cerebrospinal fluid? Any of you remember? Remember that dark stuff that was found in the ventricles? The choroid plexus. A few of you were starting to say it, OK? A specialized ventricular layer of cells that make the choroid plexus.

And that also gets out through special openings at the level of the cerebellum in the roof plate in the cerebellar region, and it surrounds the brain. It flows underneath the arachnoid and part-- it's actually all subdural, in or among the arachnoid membranes, OK?

Let's look at-- this neural tube is one cell thick, but the cell bodies can be located at various places, OK? We will have some cells that are attached here, and the cell body will be out here, OK? But then it's still attached here. Other cells, cell body will be here. It's still attached here. Now some of them, like these here, have an attachment only to the ventricular layer. Either they're differentiating and becoming ventricular cells, or-- and most of them, this is true for-- they're undergoing mitosis, OK? They're in the proliferative stage, OK?

So because it's still one cell pick, we call it a pseudostratified epithelium because you can see layers in it. Many more of the cells are bunched up towards the ventricle, a few cells in the outside cell bodies. But in fact, the cells-- most of them stretch between the two margins of the nervous system.

So the cell nucleus is moving within that elongated cell. These cells that Cajal saw as frozen, because he was looking at Golgi, we know now that that nucleus can move. The fact that he saw two here doesn't mean too much. He might have been staining two together and he couldn't differentiate them. Most of them, in fact, have only one nucleus. But that nucleus can move, OK?

And it moves during the steps of cell division, OK? During mitoses. But then it moves more, further away from the ventricle, when you get migration. But it's still moving within that process-- that elongated process. And that's what we called migration.

So the first type of migration is simply translocation of the nucleus. And that seems to be the major type in the spinal cord. But we know, in other parts of the nervous system, migration can lose the attachments to the ventricular layer and the pia layer and be guided along processes that haven't lost them. So in other words, if we go back to the Cajal picture, when you get to the-- up in the cortex, this cell here might be a glial cell, but then there's little neurons moving along it. There might be many of them moving along the same line, OK?

In every one, you see the nucleus. Sorry, I hit the button there and erased it. And these cells are moving this way, OK? That's glial guidance. It doesn't happen much in the spinal cords, OK? But in every case, the nucleus is still moving through a process. But in the case of the migrating cells in the cortex, the process is extending up towards the surface, and it's withdrawing its process behind, and then the nucleus is moving.

So the actual mechanics of movement are pretty similar, OK? In some cases, there's other kinds of migration. Like in the formation of the cerebellum, cells can move laterally. Also, they generally move along some guiding substrate. Usually glial cells form that substrate, OK?

So here, now let's just to look at a few of these stages of Cajal's picture. He calls it the epithelium. Well, it's part of the surface layer of the body. It's an epithelial layer. We know the nervous system form that way. Now we call it the epithelium. It's still one cell thick.

Almost every cell he's drawn here have the connection. But you see here, for example, the cell body is way out. Here, the cell bodies next to the ventricle. And you see how different they look at the floor plate and north plate, OK?

But now, in other-- remember, the Golgi stain is somewhat selective, and you can't always predict how it will stain. So in other [? checks, ?] day three, he saw this. He saw that, already, when all the cells seem to have the-- be elongated like this, some of them were also differentiating further, OK? Most interesting was that some of the ones in the basal plate region here were sending axons out, OK? They were becoming motor neurons, OK?

So differentiation can start when the cell still has those primitive connections to the pia and to the ventricular surface. He's also showing a few axons growing in from the dorsal root ganglion there and others that are simply extending processes within the cord, OK? Those would be interneurons in the cord. They would be growing in other parts of the spinal cord.

For example, here's one. This is the growth column. The cell body's way up here someplace, and it's grown towards the midline there on the floor plate. It's going to cross over to the other side. So that might be a developing spinothalamic tract axon.

OK so now, as it's getting thicker and thicker-- here's another two days later. This would take a little longer in a human being. It would take even less time if it were a hamster because he develops very rapidly. We still have elongated cells. They get very long, OK? And here we are from human somewhat later. And yet, the cells are simply even longer. Some of them are more complex.

Now, some of these may be glial cells. Some of them may be neurons. In fact, it's very difficult to tell the difference in these early stages, OK, unless we have a immunohistochemical procedure, where we can look at specific molecules that can identify them, OK?

So what I'm going to do here, and I can review this next time, also-- just to-- there was a lot of argument about nuclear translocation, whether it's a valid type-- can we really think of migration happening that way? The man who argued most for it, Kent Morest in-- that's this man. The other scientist, [INAUDIBLE] an MIT graduate student that worked with Morest after she left [INAUDIBLE] lab here.

They argued that it happened not only in the spinal cord but in the brain as well. In fact, Morest originally argued it happened everywhere, that other people had the wrong idea. Now we know there's multiple types of migration, OK? But to prove that it happened in the CN-- in the brain, as well as in the spinal cord-- they were able to give a very nice demonstration, in one type of brain cell that I'll describe.

It's important because it argues about the basic mechanisms of development and shows the variety. So here, at the left here, I'm showing his drawing. I guess I have to keep my-- OK.

This is the cell body that-- of a cell that is-- it originally, just before this stage, looked like this. It has attachments at the ventricle and at the pia, and its cell body was down here. It's recently undergone mitosis, OK? And it's reextended its process after mitosis, all the way out to the pia. And then just after that-- look what's happening-- it's starting to grow on axon. This is actually meant to be a growth cone here.

And it grows in a characteristic way, and that caught the attention of [INAUDIBLE] and Morest because they knew about a cell type in the adult tectum that always had an axon that had this crook in it at the beginning. And so it was called a shepherd's crook cell because of that.

So actually, stage four here is where their study started. They started with the mature cells with that peculiar axon, and then they went back to earlier and earlier stages to see if they could see the same cell. And they could identify the cell by the shape of the axon because it's the only cell type that has that in the tectal layers, superficial layers, the midbrain tectum. OK?

So if they went back a little bit, they found the axon, and they found the cell body, but they saw that it was still connected also to the pia up here. But it had lost the connection to the ventricle, OK? This is now being withdrawn, that process, OK? And they verified that by going a little earlier. And there, they found the shepherd's crook axon. They saw the connection to the pia.

But now, the cell body wasn't up there by the axon. The cell body was way down here, and the connection to the ventricular surface was still there. So they knew then, putting this together, that the cell must be migrating, like that. And in fact, if they went to the earlier stages, they saw it clear down here, OK?

See, they're going back in time. That was the way they reconstructed the developmental sequence, because they couldn't see this in tissue culture. There's only-- very recently, have investigators been able to see migration happening in culture. Culture methods weren't developed enough for that earlier.

OK, so initially, this was all worked out from static pictures but looking at closely-spaced time series. And in this case, they went backwards in time in order to reconstruct the path of that cell. So now we know nuclear translocation happens in the spinal cord. It happens in the midbrain tectum, OK? And it does happen elsewhere, too, but then other mechanisms were discovered, and that's where we're going to start next time.