Although in this lecture I will be talking about some clinical correlations associated with the early developmental processes discussed in previous lectures, I just want to show you this picture once again on the left of a 4 week embryo which is 5 mm in crown-rump length (that's how it's measured). And on the right is how we look at 8 weeks of development 30 mm crown-rump length, so we have grown in length six-fold, and we at least look like, at least to me, little human beings. If you were to dissect the organism on the right, it would have all of the named muscles that adults have, it would have all of the named nerves that adults have, and in fact, because by 8 weeks of age we are so similar in structure to the definitive adult form, we change the name from embryo to fetus. So the embryonic period is the first 2 months of development and the fetal period is the last 7 months of development, beginning at the age of 8 weeks old. This is not to say that there are no any additional anatomical changes that will not occur in the subsequent weeks of development, certainly there are some, but the basic body plan and the basic named structures have all been laid down by eight weeks of age.

But of course, my drawings never really look very much like what they are meant to represent. So, here again is my version of the median sagittal section of a four week embryo. We developed this in the previous lecture, but we developed it in isolation. In the next few slides, I'm going to put this structure into the context of that old friend- the cytotrophoblastic sphere - and the uterus and placenta.

This is that four-week embryo placed within the sphere of cytotrophoblast. Cytotrophoblast is this thin gray line (which is labeled as cytotrophoblast) and lined by pink stuff, which starts out as simple somatic extraembryonic mesoderm, but by this time has turned into a connective tissue. On the outer surface of cytotrophoblast is some brown stuff, and all of that brown stuff and all of the rest of the brown stuff is uterine tissue. Now I have given you the size of the embryo itself in the previous slide. It was 5mm in crown-rump length. The cytotrophoblast sphere at this stage is 20mm in diameter, so obviously I've drawn the embryo in much larger in proportion to the cytotrophoblast sphere than it really is, and furthermore, the uterus is far more than 2cm so that I have drawn the cytotrophoblast sphere in much larger proportion to the uterus than it really is. I don't care much about these sizes. I think it's probably sufficient that you know that even a 2cm diameter cytotrophoblast sphere can be seen by ultrasound. You cannot see the embryo in ultrasound when it's this small, but you can, if you do an ultrasound of the pregnant woman, see something which is identifiable as the sphere of cytotrophoblast. Just to round out my description of this picture, I've indicated syncytiotrophoblast as yellow tissue in contact with these finger-like projections of cytotrophoblast and its underlying somatic layer of extraembryonic mesoderm. I've labeled the extraembryonic coelom, and you can see now fairly clearly how it is continuous around the vitelline duct and yolk sac, through the umbilical cord and into the intraembryonic coelom. The uterus is drawn such that the uterine cervix is down and to the left, and the vagina is a black line into which the uterine cervix opens.

And now I want to change the name of something. Because, once the somatic layer of extraembryonic mesoderm that lines the inside of the cytotrophoblast turns into a connective tissue with some mechanical strength, then that connective tissue, with its outer layer of cytotrophoblast, is called the chorion. And the extraembryonic coelom changes its name to the chorionic cavity. These are only name changes; nothing magical has happened to these regions or structures in any other way, and I must tell you that I honestly don't know at what stage in development it is appropriate to make that name change, but certainly by 4 weeks it is. Those finger like projections that I referred to earlier, and you can see here sticking into the wall of the uterus, are called chorionic villi, and they have syncytiotrophoblast on their outer surfaces.

And we even go so far as to distinguish different regions of the chorion. That portion which has these finger-like projections called "villi", is said to be the villous chorion. And the part which doesn't is said to be the smooth chorion. And although syncytiotrophoblast originally formed around the whole external surface of the
cytotrophoblastic sphere, it is lost in the region of the smooth chorion and is maintained only in the region of the villous chorion, where it in fact grows quite substantially. Now you may have heard the term "chorionic villous sampling". If you need to know something about the genotype of the fetus or embryo, one way to do it is to go in and snip off a little piece of a chorionic villus. Chorionic villi are composed of cells derived from the zygote, and therefore, when you do a genetic analysis of the cells of a chorionic villus, you are in fact doing a genetic analysis of the embryonic or fetal cells, not of the mother.

Clinical Aspects of Early Embryogenesis, slide 7
The lining of the uterus is highly vascular and I've indicated that by little red dots throughout the uterine endometrium. Shortly after delivery the uterine lining will be shed and, therefore, that lining is called the decidua, which means "will be shed" just like deciduous trees shed their leaves, and it gets different names depending upon where it's located. That portion of the decidua in contact with the villous chorion is called the decidua basalis. That portion of the decidua which is in contact with the smooth chorion forms a capsule over the chorionic membrane and is called the decidua capsularis. It's much thinner than the decidua basalis, and all of the rest of the uterine decidua which is not in contact with anything embryonic is called the decidua parietalis. The decidua basalis is an important structure and it's a term I would like you to know. Decidua capsularis and decidua parietalis are terms I have included here for the sake of completeness but I don't care if you know them.

Clinical Aspects of Early Embryogenesis, slide 8
And this straightforward slide simply tells you that by definition, the placenta is the name given to the villous chorion and decidua basalis together.

Clinical Aspects of Early Embryogenesis, slide 9
Now, over the course of the next couple of months, many things are going to happen to the embryo and fetus, but let's ignore those for the moment and just concentrate on what is happening with the amnion, chorion and the uterine cavity. And what this slide shows you is that the amnion will get larger, therefore the fluid-filled amniotic cavity gets bigger. The chorion gets larger, but the space of its cavity does not In fact, it probably gets smaller as the increasingly large amnion encroaches on the chorionic cavity. The uterine cavity again becomes increasingly narrower, as the enlarging chorion encroaches on it.

Clinical Aspects of Early Embryogenesis, slide 10
This shows you a further stage in the development of the fetal membranes. I've left the actual embryo itself unchanged (but you know that isn't true). This is the way things look somewhere near the end of the second month. The amnion has grown very large and has encroached quite considerably on the chorionic cavity, making it a narrow space. Similarly, the chorion has grown quite large and encroached considerably on the uterine cavity, making it a narrow space.

Clinical Aspects of Early Embryogenesis, slide 11
And now we are early in the third month again. I've falsely left the embryo and fetus unchanged. But early in the third month, the decidua capsularis that's over the chorion contacts the decidua parietalis of the rest of the uterus, and the two fuse, and that obliterates the uterine lumen. And almost at the same time, the connective tissue that's on the outer surface of the amnion, contacts the connective tissue that's on the inner surface of the chorion, and in this way the chorionic cavity itself completely obliterated. The entire volume of the uterus, exclusive of the cervix, is filled up by the amniotic cavity. The adherent amnion and chorion are referred to as the amniochorionic membrane. In this picture, it is comprised of the grey layer, which is cytotrophoblast, a pink layer, which is the adherent connective tissue of the amnion and chorion, and then a blue layer, which is amnioblast cells. I specifically refer to connective tissue layers of the amnion and chorion as adhering, not fusing, because when these membranes are expelled from the uterus following delivery, you can strip them apart. I guess I should remind you once again, that I've allowed the embryo to be completely unchanged, but of course, early in the third month of development, it is a fetus and is very much larger than I have drawn here, and in fact will encroach upon the amniotic cavity and will make it much smaller than I have indicated.
Clinical Aspects of Early Embryogenesis, slide 12
This shows what happens at delivery. Hopefully the fetus is more developed than I have indicated here. But what happens is the amniochorionic membrane ruptures, amniotic fluid is expelled, and this is why the amniochorionic membrane is referred to colloquially as the bag of waters. Hence, prior to delivery, the bag of water ruptures, the amniotic fluid is expelled to the cervix and vagina and then sometime after that, the fetus is delivered. About 15 minutes after the baby is delivered, the amniochorionic membrane and placenta are expelled with some decidual cells adhering to their outer surfaces. And then sometimes during the next few days, the rest of the decidua comes out.

Clinical Aspects of Early Embryogenesis, slide 13
And now we'll return to consideration of what's going on with our embryo. You remember that the old prochordal plate became the oropharyngeal membrane, and that posterior to the primitive streak there was a region of adherence of endoderm and ectoderm that was called the cloacal membrane. Sometime before the end of the 4th week of development, the oropharyngeal membrane ruptures, establishing communication between the amniotic cavity and the foregut. That's shown in the next slide.

Clinical Aspects of Early Embryogenesis, slide 14
This just shows a ruptured oropharyngeal membrane.

Clinical Aspects of Early Embryogenesis, slide 15
This lets you know that sometime during the 7th week the cloacal membrane ruptures. I never remember these times but I think it is only important for you to know that before the fetal stage is reached (that is, before the end of the second month) both the oropharyngeal and cloacal membranes have ruptured, establishing a complete communication from the amniotic cavity into the gut and back out the end of the gut into the amniotic cavity again.

Clinical Aspects of Early Embryogenesis, slide 16
Here I have shown that eventually some of these things up near the head end of the embryo are going to turn into something that looks a lot like a face, and I've put in an eye, and a nose, and an upper lip, and a lower lip, and I've shown that now there is a path through the fetal mouth from the amniotic cavity into the gut. Eventually the nervous system and other structures will mature to the extent that the fetus can begin to swallow. And it seems obvious that the main thing the fetus can swallow is amniotic fluid, an it swallows quite a bit of it. During the middle months of pregnancy, in fact, the fetus swallows almost the entire volume of amniotic fluid every day. What happens when anybody swallows a large amount of fluid, it gets absorbed from the gut into the blood stream. There is a second way that a significant component of amniotic fluid gets into the fetal blood stream. That is by passing across the amniochorionic membrane that covers the placenta and getting into the fetal vasculature that way. So we have a situation where, on a daily basis, quite a bit of fluid is getting into the fetal blood stream. What happens when a lot of fluid gets into your blood stream? It causes you to urinate, and the same thing happens with the fetus. An equal volume of fluid that gets into the fetal blood stream via swallowing and passage across the amniochorionic membrane is then urinated out of the fetus into the amniotic cavity. The water molecules are not the same. A lot of the water in the fetal urine is produced by metabolic processes within the fetus itself, just as a lot of the water in your urine is produced by your metabolic processes. For the sake of completeness, I'll mention that further in development, the fetus also breathes in amniotic fluid and breaths out fluid. The net effect is to contribute a small volume to the amniotic fluid every day. The bottom line is that there is a large turnover of amniotic fluid on the daily basis.

Clinical Aspects of Early Embryogenesis, slide 17
There being some mechanisms by which the volume of amniotic fluid is increased and other mechanisms by which it is decreased, but something can go wrong with these mechanisms and there can be an alteration in the volume of amniotic fluid so that it is either too great for any given stage in development, that's called polyhydramnios or hydramnios, or amniotic fluid volume may be too little for a particular stage in development, that's called oligohydramnios. Now there are causes of this that really tell you nothing about what's going on with the fetus, but there are also anomalies of fetal development that affect amniotic fluid volume and you should certainly know about these. I ask you to read about polyhydramnios and oligohydramnios in the clinical aspects document.
Floating around in the amniotic fluid is hair that has fallen off the fetus, dead skin cells that have been shed from the fetus, and so these things are swallowed along with the fluid. And this solid matter accumulates in the bowel of the fetus. Added to it are dead epithelial cells that line the bowel. And all together these things, this solid matter, makes up a fecal material of the fetus. That fecal material of the fetus is called meconium. And it is a very dark green color because it is stained by digested bile, which has been secreted by the fetal liver. The very first bowel movement of a newborn is this meconium; it's a pasty dark green substance. In the very large majority of fetuses defeation is inhibited, so there is no meconium that's ever defecated into the amniotic fluid, but in some small percentage, 10-15%, there is seen to be meconium in the amniotic fluid. It used to be thought that this was a sign of fetal distress, but in fact, no longer is it a matter of much concern. It also used to be thought that if you found meconium in the amniotic fluid, you knew that some of it had to be inhaled, because the fetus does inhale amniotic fluid, and that you would have to worry about a serious lung problem called meconium aspiration syndrome. I discuss this in the clinical aspects document. It is no longer believed that meconium all by itself, inhaled, causes any pneumonia, but that there has to be some underlying lung pathology, which then makes the lung tissue susceptible to irritation by the meconium.

You knew enough about development to understand the basis for twinning much earlier in this series of taped lectures, but I thought you should delay reading about it until now because one of the problems associated with twinning involves an understanding of oligohydramnios and hydramnios. So at your convenience read that part of the clinical aspects document that deals with twinning.

Now I want to move on to clinical aspects of neural tube formation, for which I have some slides. But first I want to simply remind you that during 3rd week, there are these two longitudinal neural folds that form. That green stuff which runs from the crest of one fold to the crest of the other is called the neural plate.

During the third week folding progresses. The crests of the neural folds get very close to one another.

And as you know, beginning on day 22, the folds fuse and seal off a neural tube and a column of neural crest on either side, which column eventually turns into clumps of neural crest on either side, and that this sealing off of the neural tube really occurs during the fourth week of development, simultaneously with embryonic folding.

Then, shortly thereafter, sclerotomes, derived from somites, organize themselves into vertebrae, and here I've shown the early stage of a vertebra with a separate centrum and neural arch.

This is a schematic representation, in terms of the kinds of drawings I present, of what would happen if the crests of the neural folds don't actually meet one another and fuse. If this occurs in the region of the trunk, you get an abortive development of the spinal cord. No normal spinal cord forms, and you get exposure of this peculiar neural tissue to the external environment, in this case the amniotic fluid. Such a condition is called myelomeningocele, and since the two halves of the vertebrae cannot meet one other dorsal to the neural tube, you have a split vertebrae which is called spina bifida. Myelomeningocele is a kind of spina bifida. There are other conditions as well in which the two halves of the vertebrae cannot meet dorsal to the neural tube. Myelomeningocele is also referred to as an open neural tube defect. I think that's fairly obvious why. It mainly occurs in the lumbar region or the adjacent part of the vertebral column - low thoracic or upper sacral. And obviously the more extensive is the myelomeningocele the more vertebrae are split down the middle so the longer is the spina bifida.
Clinical Aspects of Early Embryogenesis, slide 25
Here is what a genuine myelomeningocele looks like. It's a fluid-filled cyst, and that little dark patch in the middle is actually exposed neural plate. The next slide shows you a drawing, created by someone else, which gives you a better idea of why it has this cystic nature.

Clinical Aspects of Early Embryogenesis, slide 26
In this drawing we see the exposed neural tissue. It's called neural placode by this author, but it's the same thing as we call neural plate. And we see that the fluid is actually cerebrospinal fluid that's accumulated in the subarachnoid space and pushed this neural plate upward. Myelomeningocele is often considered one of the cystic spinal bifidas for obvious reasons. It's very important to realize that in the region of failed neural tube closure, there is complete absence of normal spinal cord development, so that individuals with myelomeningocele are completely paralyzed in all segments of the body caudal to the region of the lesion, and also they are insensate - they cannot feel anything from any part of the body caudal to the lesion. And in this condition, where embryonic or fetal tissue that is normally sealed off from amniotic fluid by skin is exposed to the amniotic fluid, we find that there is a leakage of a molecule called alpha fetoprotein into the amniotic fluid. You can take a sample of amniotic fluid and find alpha fetoprotein in it, or after a while the concentration builds up enough that it gets into the maternal blood stream and you can measure what is called maternal serum alpha fetoprotein. And when that reaches a high level you have to be worried that there is some exposure of fetal tissue to amniotic fluid that should not be happening. To be honest, the importance of measuring alpha fetoprotein in order to detect an open neural tube defect has declined very considerably in the last few years, because ultrasound has now become so good that you can actually make the diagnosis better with a good ultrasound image.

Clinical Aspects of Early Embryogenesis, slide 27
This is another kind of spina bifida, one which also arises from imperfect fusion of the neural folds in development of the spinal cord, but not nearly of as severe a nature as we saw in myelomeningocele. The most obvious part of the defect here is that there is a ballooning out of the dura and the arachnoid between the unfused vertebral arches, and that pushes out a bulge of skin ahead of them and because the subarachnoid space has cerebrospinal fluid, this is another kind of cystic spina bifida. It's called a meningocele because the only thing that is protruding is meninges, and even though the spinal cord is largely normal in development, its dorsal aspect is always tethered to this protruding sac of dura and arachnoid by a connective tissue band. Meningocele is the second most common type of neural tube defect in the region of the developing spinal cord. More often than not, meningocele is asymptomatic at birth, sometimes the defect in the spinal cord is severe enough to produce symptoms, but as I have said, usually not. Regardless, meningocele should be treated surgically as soon as is possible, not only because it is cosmetically unacceptable, but this tethering band will sooner or later interfere with proper growth of the spinal cord.

Clinical Aspects of Early Embryogenesis, slide 28
This represents the least common type of cystic spina bifida; it's called a myelocystocele. There is an outpocketing of dura and arachnoid with cerebrospinal fluid, but within that outpocketing of dura and arachnoid is also an outpocketing of an epithelial layer that represents the dorsal aspect of the poorly developed spinal cord. The term "myelo" refers to the spinal cord and since this cyst has a part of the spinal cord in it that's why we get the name myelocystocele. Myelocystocele may or may not be associated with neurologic defects at birth, but even if you treat the child surgically, later in life you might be able to detect some minor neurological deficit.

Clinical Aspects of Early Embryogenesis, slide 29
Now this doesn't look at all like a problem with neural tube closure. By the way, problems with neural tube closure in the spinal cord region are called spinal dysraphisms. So this doesn't look like any sort of spinal dysraphism. The cord itself is normal, but is usually considered to be caused by some problem with neural tube closure and so is included in this category. The only sign is a pit in the skin over the presumed site of the problem. The vertebral arches are formed normally, so this is not a kind of a spina bifida. The name of this condition is spinal dermal sinus, and if this pit occurs in the region between your buttocks, then it is almost always of no consequence whatsoever. The reason that such pits occurring superior to the intergluteal fold might be problematic is shown in the next slide.
And that's because pits located superior to the intergluteal fold are often associated with an open tract that leads to the subarachnoid space or spinal cord. Such an open channel, which is often very narrow, still provides the opportunity for infection to travel down to the subarachnoid space or spinal cord. And even if no infection does develop, if this tract connects to the spinal cord, it tethers that structure to the skin, and will lead to neurologic symptoms as it affects the growth of the spinal cord when the child gets older. Consequently, if you see such a pit superior to the intergluteal folds, that should be investigated with MRI or ultrasound to see if, in fact, there really is a narrow channel associated with it. If there is, the proper name for this condition is called a spinal dermal sinus tract or spinal dermal fistula, and it must be treated.

Here is a condition more common than all of the other neural tube closure problems I have talked about, it's called spina bifida occulta, and it is characterized simply by failure of the right and left halves of the neural arch to meet in the midline dorsal to the neural tube. There may be absolutely no indication that a person has spina bifida occulta except by palpation or X-ray. Sometimes there's a little tuft of hair over the zone of failed vertebral arch fusion. The cause of spina bifida occulta is not known for certain, and one is inclined not even to view this as a spinal dysraphism - it might be due to some problem with vertebral arch formation - except that very rarely people with spina bifida occulta do have some kind of neurological defect, which makes you think that maybe it should be a spinal dysraphism after all.

If the neural tubes fail to close properly in the region of the developing brain, you don't get a spinal dysraphism but you get a similar type of problem in the head region. Even more common than myelomeningocele is the condition illustrated in the left two images here, which is called anencephaly, which is failure of neural tube closure in the developing brain region. This is invariably a fatal condition, with one exception mentioned in the clinical aspects of the document. The image to the right shows the head's equivalent of myelocystocele; it's called encephalocele. It is also possible for there to be a craniomeningocele. The failure of skull development over the defect would be called a cranium bifidum but this is a term not often used. You may have deduced that anencephaly is another open neural tube defect and will be associated with alpha fetoprotein in the amniotic fluid and the maternal blood serum.

And now on to a different problem entirely; a little reminder that there are these things called pleuropericardial membranes that are going to seal off pericardioperitoneal canals from the future pericardial sac.

And in this previously seen drawing, I just show the completed pleuropericardial membranes and separation of pleural cavities from pericardial cavity. And I also show the two lung buds growing out of the laryngotracheal diverticulum.

And now the lungs are growing bigger, and in order to accommodate their increased size, the parietal pleura invades the body wall ventrally and increases therefore the size of the pleural sacs. I've retained a darker pink color for the pleuropericardial membranes, so we'll be better able to trace their positions in future slides.

This cross-section represents the completed development of the lungs and pleural sacs, and it shows that the pleuropericardial membranes are represented by mediastinal connective tissue between the lateral aspects of the parietal pericardium and the mediastinal pleura.

Here's what things would look like if the left pleuropericardial membrane never formed. You would have complete continuity between the pericardial cavity and in this case the left pleural cavity. Obviously, if the right membrane hadn't formed, the continuity would be between the pericardial cavity and the right pleural cavity, and if neither
formed, you can guess what would happen. Regardless, these conditions are asymptomatic unless you develop a pleuritis, which would then become a pericarditis, or you first develop a pericarditis, which would then become a pleuritis. But without these types of diseases, you are not going to know whether you had failure to form one or both pleuropericardial membranes.

Clinical Aspects of Early Embryogenesis, slide 38
Now I remind you that the pericardioperitoneal canals will eventually be separated off from the definitive peritoneal cavity by something that will grow down and join the cranial part of the septum transversum that will become the central tendon of the diaphragm.

Clinical Aspects of Early Embryogenesis, slide 39
The structures that do grow down and separate off pleural cavities from peritoneal cavity are the pleuroperitoneal membranes, one on either side.

Clinical Aspects of Early Embryogenesis, slide 40
The sequence of slides from here to slide 46 just show the development of the pleuroperitoneal membranes; it rehashes stuff we did in a previous lecture. The next narration occurs at slide 47.

Clinical Aspects of Early Embryogenesis, slides 41-47
No narration.

Clinical Aspects of Early Embryogenesis, slide 48
Now the central tendon of the diaphragm has been formed by a portion of the septum transversum and the two pleuroperitoneal membranes. Furthermore, the pleural sacks have invaded the lateral body wall to increase the size of the diaphragm and create a region that will be invaded by dermomyotome cells from the third through fifth cervical segments. Those dermomyotome cells will become the muscle of the diaphragm.

Clinical Aspects of Early Embryogenesis, slide 49
This shows you what the central tendon of the diaphragm will look like if the pleuroperitoneal membrane on one side fails to form. This usually occurs on the left side, so that's where I've drawn it, and on that side there will be an open, fluid-filled communication between the pleural cavity and the peritoneal cavity. Such a hole is called a Bochdalek foramen, and it will be through the posterior portion of the central tendon of the diaphragm, but may expand in size as certain things push through it.

Clinical Aspects of Early Embryogenesis, slide 50
This just shows you how a left sided Bochdalek foramen would appear on that front view that we had been looking at from time to time, and it makes clear that there is an open communication between the left pleural cavity and the peritoneal cavity. Such a communication represents a real threat to the fetus because it enables abdominal contents, largely bowel, to herniate through the Bochdalek foramen into the left pleural cavity, and there occupy space that the lung needs to develop, and in fact if the herniation of bowel contents is great enough, not only may it affect development of the left lung, but it may affect development of the right lung as well. And, underdevelopment of the lungs is called pulmonary hypoplasia, which is often fatal to the newborn.

Clinical Aspects of Early Embryogenesis, slide 51
And finally I want to consider one other anomaly of development. This slide shows a median sagittal section of a 4-week embryo, incorrectly modified to show a ruptured cloacal membrane. I say incorrectly, because, whereas it’s true that the oropharyngeal membrane ruptures by the end of the 4th week, the cloacal membrane doesn’t rupture until the 7th week of development. But I allow this pictorial error because I want to show where your anus will be formed in relation to the cloacal membrane. It’s possible for some of the pluripotent cells of the caudal eminence to fail to differentiate into the structures for which they are intended, but rather to become some other kind of tissue entirely. And when that happens, the fetus can develop a tumor here that is called a sacrococcygeal teratoma. It’s located posterior and adjacent to the anus. It may be benign, in which case it might contain well formed teeth, or hair, or muscle, or liver, or anything, because these caudal eminence cells can become anything they want. Even worse, sometimes they don't differentiate at all, and then they become undifferentiated malignant cells, which represent a grave threat to the fetus.