25: EMBRYOLOGY: WEEK 1

The zygote cell is ***totipotent***. ("Toti" means "totally" and "potent" means "powerful or capable.") This cell is capable of becoming any type of human cell, even supporting cells such as the placenta or the amniotic sac. All of its DNA is open; nothing is methylated or closed. It takes an entire day for the zygote to go through mitosis. The two nuclei of the gametes must fuse together and function as one complete cell. This first division is called ***cleavage***. ("Cleave" means "split.") The two resulting cells are joining together by ***gap junctions***. A junction is a place where things are joined. Gap junctions are protein gadgets that might remind you a bit of a sewing bobbin. There are two plates with a tube in the middle. The hollow tube allows the cytosol from the cells to flow back and forth. This allows the cells to communicate. Chemicals made by one cell can flow into another, so the cells "know" what their neighbors are doing. We will see gap junctions again when we look at cardiac (heart) cells. The gap junctions allow the cells in the heart to all beat together in unison.

On day 2 the cells go through mitosis again, making 4 cells. The zona pellucida is still there, so the cells can't get larger. These four cells don't take up any more space than the one zygote did. The cells divide again, making a clump of 8 cells. This turns out to be a critical stage in development and some pre-embryos don't make it past this stage. We know this because of research done during "in vitro" fertilization where eggs and sperm are mixed in a test tube and researchers can watch this whole process happen right before their eyes. They've noticed that some pre-embryos don't develop beyond this point. They'd like to know why this happens so that they can make good choices about which pre-embryos to select for putting into the mother's uterus. But as of the writing of this text, they still have not figured it out.

When the cells divide again, there are enough of them now to make a little clump that looks a bit like a mulberry or raspberry. Since the Greek word for mulberry is "morus" the stage was named the ***morula*** stage. By the time the morula has 32 cells, the ones at the very center might be having a hard time getting enough oxygen. The cells are receiving oxygen (and getting rid of carbon dioxide) by simple diffusion. The cells on the outer edge are getting plenty of oxygen. The ones in the center are in danger of not getting enough. (No cell in our bodies is more than a very short distance from a capillary. That's how many capillaries we have!) Since there are no capillaries yet, this ball of cells must use another strategy. What happens is that it becomes hollow.

The next stage is called the ***blastula*** or ***blastocyst***. ("Blast" means "bud," those things that plants make that turn into flowers and leaves. In this case, the bud will turn into a human being.) The ball becomes hollow and filled with fluid (mostly water). The fluid can flow around and carry oxygen to all the cells.

On approximately day 6 (some charts say day 5) the blastocyst will start to grow a little lump called the ***inner cell mass***. The cells that stay in the outer ring will become a supporting structure called the chorion. These inner cells will differentiate into the placenta, several sacs, and the baby. These inner cells are ***pluripotent cells***. They have undergone a very small amount of differentiation (methylation) but almost all of their DNA is still open. They have many ("pluri") options still open. These are the cells that stem cell researchers like to harvest. ("Stem cells" are cells that have not completely differentiated into a type of body cell. More on stem cells in a future lesson.) Of course, doing this on a human pre-embryo is very controversial. Fortunately, however, the pre-embryos of other mammals (and even some invertebrates such as the sea urchin) can be used for embryology research. In fact, most of what we know about embryology comes from research on non-human embryos.

On day 6 (some charts might say 5 or 7), the embryo finally "hatches" out of the zona pellucida. The cells of the blastula secrete enzymes that soften the zona pellucida, then the blastula has a growth spurt and gets larger very quickly, popping the z.p. The blastula is now free to start growing larger.

It is interesting to note that this first week is pretty much the same for all mammals. This is amazing when you think that a mouse has a gestation period of only 3 weeks. That leaves only 2 weeks to go from the blastula to a baby mouse that has most of the same inner organs that we do! Also, it is interesting to note that some animals (including bears, kangaroos and roe deer) are able to pause gestation at this point and hold the embryo for up to several months until the right season of the year comes around.

Finally, we need to know where this is happening. This whole process takes place in the tube that connects the ovary to the uterus. Ovulation is when an ovum leaves the ovary and gets picked up by the "fingers" of the ***fallopian tube***. The ovum is fertilized by sperm soon after it enters the tube. The sperm must swim all the way up the tube so that only the strongest sperm will survive. This whole first week of development happens as the zygote travels down the fallopian tube towards the uterus. Tiny hairs called ***cilia*** beat in the direction of the uterus, pushing the pre-embryo along. If the cilia are not able to do this fast enough and the pre-embryo gets stuck in the tube, this is called an ***ectopic pregnancy***. ("Ecto" means "outside," in this case meaning outside of the uterus.) This condition is very painful and is life-threatening for the mother. A surgeon must remove the pre-embryo from the tube. Most of the time, the pre-embryo travels down the tube just fine, and enters the uterus on day 5 or 6. It floats around for a while until it bumps into the lining of the uterus and sticks there. When it sticks to the lining of the uterus, it will implant there and begin a new stage of development. If the pre-embryo does not stick anywhere, it will be flushed out of the body when the woman begins to menstruate. (Menstruation is when the temporarily thickened lining dissolves and drains out.) A woman (or any mammal) is not technically pregnant until the embryo implants into the wall of the uterus.

26:   EMBRYOLOGY: WEEK 2

At the start of week 2, the pre-embryo implants into the ***endometrium*** (lining of the uterus). Once it implants, it will officially graduate to being called an embryo. The cells of the embryo need an outside source of energy by this point. They have used up most of the energy that was stored by the ovum. (Remember, the ovum had a rich supply of fats and sugar in the cytosol. Also, remember how large the ovum was. The ovum would not have had enough energy to produce hundreds of cells the same size as itself, but since these embryonic cells kept getting smaller and smaller, there was enough energy to go around.)

The embryo needs to tap into the mother's supply of nutrients. Food and oxygen are brought into the uterus by tiny capillaries in the endometrium. (The endometrium also contains glands that produce a temporary supply of nutrients for the embryo.) The mother's capillaries come very close to the embryo, but the mother's blood will never actually touch the embryo. This is good because once the embryo develops a blood supply of its own, it might not be the same blood type as the mother's. Different types of blood (A, B, AB, O and Rh factor) can have bad reactions when mixed. We will learn about blood types in a future lesson.

The side of the blastocyst that touches the endometrium starts growing cells that look like they have little fingers, called ***villi***. These villi quickly begin growing into the endometrium. We call this process ***implantation***. (If the blastocyst was a plant, the villi would be the roots.) Scientists consider implantation to be the official start of pregnancy. And to celebrate, we can stop saying "pre-embryo" and begin using the term "embryo."

The outside "shell" of the embryo is now called the ***chorion***. This word comes from Greek and means "the outer membrane that covers a baby." Since villi are structures we find in other cells of the body, we should really call these villi the ***chorionic villi***. The place where the chorionic villi come very close to the mother's capillaries will grow to become the ***placenta***. It is important to note that the placenta is a combined structure: one half is from the mother and one half is from the baby.

The chorionic villi began secreting digestive enzymes that eat away at the endometrial cells around them. They dissolve a little hole for the embryo to snuggle into, and the endometrium eventually closes in around it. This provides extra security for the tiny embryo. The mother can jog and dance and bounce up and down all she wants to and the embryo is safe.

The chorionic villi have yet another important function. These cells secrete a hormone called ***HCG*** (human chorionic gonadotropin), which acts as a chemical messenger. HCG goes to the ovaries and tells the ovarian cells to secrete a hormone that will prevent the endometrium from being flushed out as it usually is every month. (This hormone is called ***progesterone***. "Pro" means "for" and "gester" means "gestation."   <u>Pro</u>gesterone <u>pro</u>motes pregnancy by keeping the endometrium alive and well.) Most pregnancy tests are testing for the presence of HCG in the mother's blood or urine. If the level of HCG is not quite high enough at the time the mother does a pregnancy test, the result might be a "false negative." Pregnancy tests rarely give a "false positive" because if HCG is detected, it most certainly means that there are little chorionic villi producing it. (It's interesting to think that since all cells in the body have identical DNA, then every cell in the body has the information needed to produced HCG. However, as we learned, most information is permanently locked away by methylation. The information needed to make HCG is only opened by these cells at this particular time. DNA has timing mechanisms built into it!)

Now the inner cell mass begins to change. It organizes into two layers called the ***epiblast*** and the ***hypoblast***. (This is called the ***bilaminar disc***.) A cavity begins to grow next to the epiblast and becomes the ***amniotic cavity***, which will eventually give rise to the amniotic sac. On the other side of the hypoblast, another cavity forms, which we call the ***yolk sac***. Obviously, since newborn babies don't have yolk sacs, this structure will be temporary.

A big change comes when the 2-layer disc turns into a 3-layer disc. This process is not shown in the drawing, but is discussed in the video. The cells in the middle of the epiblast begin dividing quickly and then moving (yes, moving) into the space between the two layers, creating a third middle layer.

A space also begins to open up just inside the outer layer, creating a cavity all around what used to be the blastocyst. We call this the ***chorionic cavity***. This is also a temporary structure that will not be seen by the time the baby is born.

The three layers are often called the ***germ layers***. ("Germ," in this sense, means "seed." These are the little "seeds" that will grow into a complete human body.) These layers are like a little stack of pancakes. The top pancake is called the ***ectoderm*** and it will grow into the outer layer of skin (epidermis), hair, nails, and the entire nervous system including the brain. The middle layer is called the ***mesoderm*** and it will become muscles, bones, connective tissue, blood, kidneys, bladder, gonads, heart, lymph system, spleen, and the bottom layer of skin (dermis). The bottom layer is the ***endoderm*** and it will become the inner lining of the digestive tract, the lining of the lungs, the liver and pancreas, and many glands including the thyroid and thymus. (We'll meet the thymus when we study white blood cells in lesson 44.)   The formation of the 3-layer germ disc is often referred to as ***gastrulation***.

In the middle of the mesoderm there is a little dot that represents something called the ***notochord***. We will learn more about the notochord in the next lesson.

Cancers are often classified as sarcomas or carcinomas. ***Sarcomas*** occur in body parts that can be traced back to the mesoderm. Most childhood cancers fall into the sarcoma category. ***Carcinomas*** are cancers in tissues that came from the ectoderm or the endoderm. Adults are more likely to get carcinomas. Tumors and other cancers are caused by cells that don't know when to stop dividing. Cancer cells keep dividing and dividing and dividing, and body parts begin to malfunction as a result.

27: EMBRYOLOGY: WEEK 3

In this drawing, we will focus only on the 3-layer "germ" disc. The disc is still inside the chorion (formerly blastocyst) but it will be too complicated to draw the chorion in all of these drawings. This is typical of embryology drawings, though. They often show just the 3 layers developing. So your drawings will match many of those you might see in a text or on the Internet.

First, let's take a took at the disc from the top. The ectoderm (in blue) is defined as the top layer and the endoderm is then the bottom layer. The bottom layer will eventually curl around to be inside. If the germ disc was already a person, it would be lying on its stomach. The blue layer would be the back (***dorsal*** side), and the yellow endoderm would be the stomach (***ventral***) side. Dorsal and ventral are good words to know when studying anatomy. (The word *dorsal* comes from the Latin "dorsum" meaning "back," and the word *ventral* comes from the Latin word "venter" meaning "belly.") Not only do we need top and bottom, we also need to determine left and right, and head and feet.

A little streak begins to form at one end of the disc. This is called the ***primitive streak*** and it is the very beginning of determining the general body plan. (Sometimes they say this already begins while the disc is still in the 2-stage layer.) At the top of the streak is a little place called the ***primitive pit*** and above that is a place called the ***primitive node***. The side with the primitive streak will be the side that eventually turns into the legs and feet. Above the primitive steak is the end that will become the head. And since we now have head and feet, back and stomach, we can imagine the baby lying on its stomach with its head toward the top of the page, so the left and right sides of the body correspond to the left and right sides of the paper. We will now imagine that we have cut a cross section through the disc and we will look at the inside.

(1) This picture shows the three layers with the ***notochord*** dot in the middle of the mesoderm. The notochord area will be the "foreman" of the body building process and will tell the other cells where to go and what to become. The notochord secretes a protein called ***SHH*** that acts as a chemical messenger telling the other cells what to do. ***SHH*** stands for ***Sonic HedgeHog***. Yes, the cartoon character. When this protein was first discovered, they collected some of it and then put it into a fruit fly embryo to see what would happen. The fly ended up being covered with long spikes, like a hedgehog. The cartoon character called Sonic the Hedgehog happened to be popular at that time, so the scientists couldn't resist using the name. Then they found other similar proteins, and classified all of them as "hedgehog" proteins. There's Desert HH, and Indian HH, named after species of real hedgehogs.

(2) The SHH tells cells in the primitive streak to form a groove (the ***primitive groove)***. This is often called the ***neural groove*** because it will become the ***neural tube***.

(3) The neural groove deepens and begins rolling into a tube. The process of forming the neural tube is called ***neurulation***.
(So we've got blastulation, then gastrulation, then neurulation.)

(4) The ***neural tube*** separates from the top layer so that it is embedded in the mesoderm. The cells that were in the top of the fold, (the "crest" of the fold) now migrate down toward the neural tube and are called the ***neural crest cells***. They will develop into various type of cells, but mainly they will become nerves and nerve bundles (***ganglia***) in places such as between the spinal vertebrae, in the digestive system, around the heart, and in the head and face. Some of these cells will turn into connective tissues and bones in and around these nerve centers, including the tiny bones of the inner ear. Oddly enough, a few neural crest cells will decide not to become nerves at all and will become ***melanocytes***, pigment-producing cells in the bottom layer of the skin. A ***neural plate*** now becomes visible on the top of the ectoderm. This is the area where the spine forms.

If the neural tube does not close up all the way, but remains open at some point, (like in picture 3), various birth defects will occur. The most well-known of these defects is ***spina bifida***. Part of the soft spinal cord never gets covered with protective bone, so the baby is born with what looks like a soft lump on its back. Corrective surgery can be done to try to correct this problem, but the child can still have lasting health issues due to this defect. We know that a lack of ***folic acid*** (in the B vitamin family) can cause this birth defect. Pregnant women are encouraged to take vitamin supplements that have a high level of folic acid.

(5) Bumps called ***somites*** begin to appear and the neural plate continues to grow. The somites have areas that will differentiate into the dermis, muscle, and bone of the spine and rib cage. We also see the beginnings of the heart tubes. The heart begins as two tubes that eventually join together. The ends of these tubes will become the large blood vessels on the top and bottom of the heart.

(6) The ends of the mesoderm begin to split, with the top part destined to become an outer "bag" around the organs (made of connective tissue and called the peritoneum), and also appendages (arms and legs). The bottom part becomes all the connective tissues "bags" that will surround the organs in the body cavity.

(7) The disc begins to curl (***embryonic folding***), with the yellow endoderm layer forming the ***gut tube*** (which will turn into the inner layer of the digestive system). The inside of the yolk sac begins to grow little clumps of cells called blood islands. Each island will turn into a piece of blood vessel, complete with blood cells already inside them. Then the tiny pieces will join up to form a network. The network will grow and then spread into the embryo, joining with other blood vessels that are starting to develop in and around the heart and kidneys. The yolk sac will eventually shrink and disappear.

28: EMBRYOLOGY: WEEK 4

We have two different types of cross sections in this drawing. A ***saggital cross section*** is a lengthwise view, as if we are cutting the body down the midline from the head to feet, separating it into a left and right side. A ***transverse cross section*** is like the infamous "magician saws a woman in half" trick. (Or like chopping a carrot on a chopping board.) It is what we usually think of when we talk about cutting something in half. A transverse section of the body could be at any point--head, neck, upper chest, abdomen, or even a leg-- so we need to specify where it is. In our saggital view you'll see a dashed line. This is where our cut is for the transverse section. We will only see what is along that line. Therefore, in our transverse view we will not see the head or the brain or the lower (posterior) region.

In the 21 DAY saggital cross section we again see the embryo in the lining of the uterus. As soon as there is enough of an umbilical cord to hold it securely, the embryo will tear free of the lining and simply be in the uterus itself. The maternal capillaries create a "pool" of blood around the chorion, so that the chorionic villi are surrounded by the maternal blood supply. The baby's blood and the mother's blood will never actually touch, as indicated in this picture. Notice that the embryo is beginning to curl in the head-to-foot direction. This is a very simple picture of the embryo and does not show the somites, the neural tube, the notochord, etc. The main point of this diagram is to show how the embryo is still embedded in the endometrium and its placement inside the chorion and the amnion.

We do see the three germ layers here, and we see that the endoderm has turned into the gut tube, the yolk sac, and a new feature called the ***allantois*** (al-an-TOE-is). (This word is Greek for "sausage," which the allantois was thought to resemble.) The allantois (number 7) acts as a garbage bag, collecting waste products produced by the cells. When the embryo has its excretory systems up and running (kidneys, bladder, liver) and when the placenta is fully formed, the allantois will no longer be necessary. (However, a tiny remnant of it will remain as a piece of fibrous tissue sitting on top of the mature bladder.)

The 21 DAY transverse cross section is an imaginary cut along the dashed line. The main focus of this diagram is the rearrangement of cells in the three layers, especially in the mesoderm. We see that the somites have differentiated into muscle, dermis and bone tissues. Part of the somites turned into what will become vertebrae. We can't properly call these new vertebrae "bones" because they have not turned into bone yet. They are still made of soft cartilage. As the months go by, cartilage will begin absorbing minerals and turning into hard bone. The middle part of the somites has turned into muscle tissue. These will be the muscles of your back, neck and stomach areas. Lastly, the outer parts of the somites have turned into dermis, the bottom layer of skin.

The ectoderm (blue) has now fully separated into epidermis (the top layer of skin) and the nervous system. The epidermis is now covering the whole embryo, and is joining with the dermis. The neural crest cells (those blue blobs above the neural tube) have turned into nerves that connect the muscles to the spinal cord. The neural tube is in the process of turning into a spinal cord. The notochord is still present, too.

The mesoderm is busy creating kidneys, blood vessels and the heart. Here the heart still looks like two tubes. The tubes will join together in the next few days and begin growing into a heart. Though we don't show it in this picture, a lot of what is going on in the mesoderm areas we colored light red is formation of blood vessels that will connect all the organs. The ends of the mesoderm that we saw splitting in the last lesson are now turning into the ***visceral peritoneum*** and the ***parietal peritoneum***. ("Viscus" was the Greek word for any internal organ. The plural, "viscera" was to the Greeks like saying "guts.") The visceral peritoneum will become all the "bags" that surround each organ. The parietal peritoneum will become the outer bag, which can also be thought of as the inner lining of your skin. (Think of a formal jacket with a silky lining. The fabric of the jacket is your skin and the lining is the parietal peritoneum.) These membranes keep all the organs in place so they don't slosh around, and they also provide a surface to which blood vessels and nerves can be attached. The fact that there are multiple membranes (bags within bags) allows for movement and flexibility of this support system.

The yolk sac has a thin layer of mesoderm around it. The mesoderm produces the blood islands that then produce many tiny sections of blood vessel. The tiny sections join together to become a complicated network of capillaries.

The 26-28 DAY illustration shows the blood vessel development that is going on during week 4. If all the details of embryology were shown in one drawing, it would be too confusing, so here we focus on just the developing vascular system. In this picture, the heart tubes have fused together and are starting to grow into a heart. We don't have any chambers yet, just a bulging tube. However, even at this early stage, the cells begin to contract together in rhythm, the way they will for the rest of this embryo's life. There are some very large vessels above the heart, the ***dorsal aorta*** and the ***cardinal vein***. These will change and grow a lot over the next few weeks. We don't have any lungs yet, so the arrangement of these vessels is temporary. As the vascular system develops, some vessels will grow and enlarge while others will shrink and disappear. Very often, diagrams of the vascular system make the vessels going away from the heart red ("arteries") and vessels going toward the heart blue ("veins"). In the chorionic villi and in the yolk sac, the vessels change from going to/from the heart. Often this can indicate a chemical change, such as picking up oxygen or getting rid of carbon dioxide. In the yolk sac we also have nutrients going into the blood. The yolk sac provides a small amount of nutrition while the placenta is still forming. (The yolk sac will never grow larger than the size of a pea and will eventually be discarded, often getting trapped between the amnion and the chorion.)

Notice that the actual sizes of the embryos on this page are 1-2 millimeters. That's small!

29:   EMBRYOLOGY: WEEK 5

We have two very different types of drawings here. The first one is very symbolic, with blue, red and yellow representing our three layers and what they are turning into. The second drawing will be more realistic, showing the three-dimensional shape of the embryo, similar to what you would see in a photograph.

We have two blue layers in this first drawing: the epidermis and the neural tube. The neural tube can't really be called by this name anymore, however. It is turning into the central nervous system and four distinct areas can be labeled: the spinal cord, the ***forebrain***, ***midbrain*** and ***hindbrain***. The forebrain will turn into the ***cerebrum***, which is the gray wrinkly part we envision when we think of a brain. The cerebrum is the part that does "thinking." The midbrain will turn into many inner parts, such as the thalamus, the hypothalamus, and the hippocampus. These middle parts are important for regulating things such as appetite, body temperature, and blood pressure, and also for storing memories. The hindbrain will become the lower parts such as the cerebellum and the brain stem. These control basic function such as balance, reflexes, breathing, and the waking and sleeping cycles. The lower part of the neural tube turns into the spinal cord.

The endoderm has differentiated into areas that will become the digestive system and the lungs. Right where the throat branches off into both the esophagus leading to the stomach and the trachea leading to the lungs, there will be a flap called the ***epiglottis*** that can close over the tube that leads to the lungs while food is being swallowed. The endoderm also contributes to organs and glands that are associate with the digestive system such as the liver and pancreas. In the throat area the endoderm will contribute to the structure of the thyroid and other glands. (NOTE: The endoderm alone does not form all these systems. It becomes the <u>inside</u> layer of all of these. The mesoderm will form the outer part.)

The opening at the end of the gut tube is called the ***cloacal*** (*klo-AK-al*) ***opening***. If you've studied birds, you might recognize the word ***cloaca***. A cloaca is an opening that expels both urine and feces. Bird droppings are a mixture of urine and feces. The cloacal opening in a human embryo is a temporary structure and will eventually change into the anal opening. Right now the embryo is not expelling either urine or feces, and the wastes are being collected partially by the allantois. Some molecular wastes are also beginning to go out through the developing placenta. At this stage, both the mouth opening and the cloacal opening are not really open, but are covered with a membrane. In a few weeks the membranes will rupture and then openings will actually be open. The allantois will shrink and retreat to the inside of the embryo, helping to form the top part of the urinary bladder. (A remnant of the allantois will always remain on top of the bladder., but it will not have any function.) The yolk sac is also still visible and functioning at this stage.

We can also see the area where the heart is developing. Although not nearly fully formed yet, the cells are already beginning to contract in rhythm. Remember, these cells are joined by gap junctions so that they can communicate very well with each other. This diagram does not show the many blood vessels that have already formed. We saw them in the last drawing lesson.

The second drawing shows us a more realistic view of the embryo. We can see the bumpy somites, and we can see lumps that are the growing heart and liver. A tiny eye spot and ear spot are just barely visible. By the end of week 5 there are little bumps, or "buds," that are the beginnings of arms and legs. The end of the embryo is sometimes called the "tail bud," though it is not a tail. It will shrink as the legs grow. The amnion now looks more like a sac. Notice that the yolk sac is outside of the amniotic sac.

(NOTE: If you look at 5-6 week embryo pictures on the Internet, be aware that many of them will not show you the yolk sac, even though it is definitely still present at this stage.)