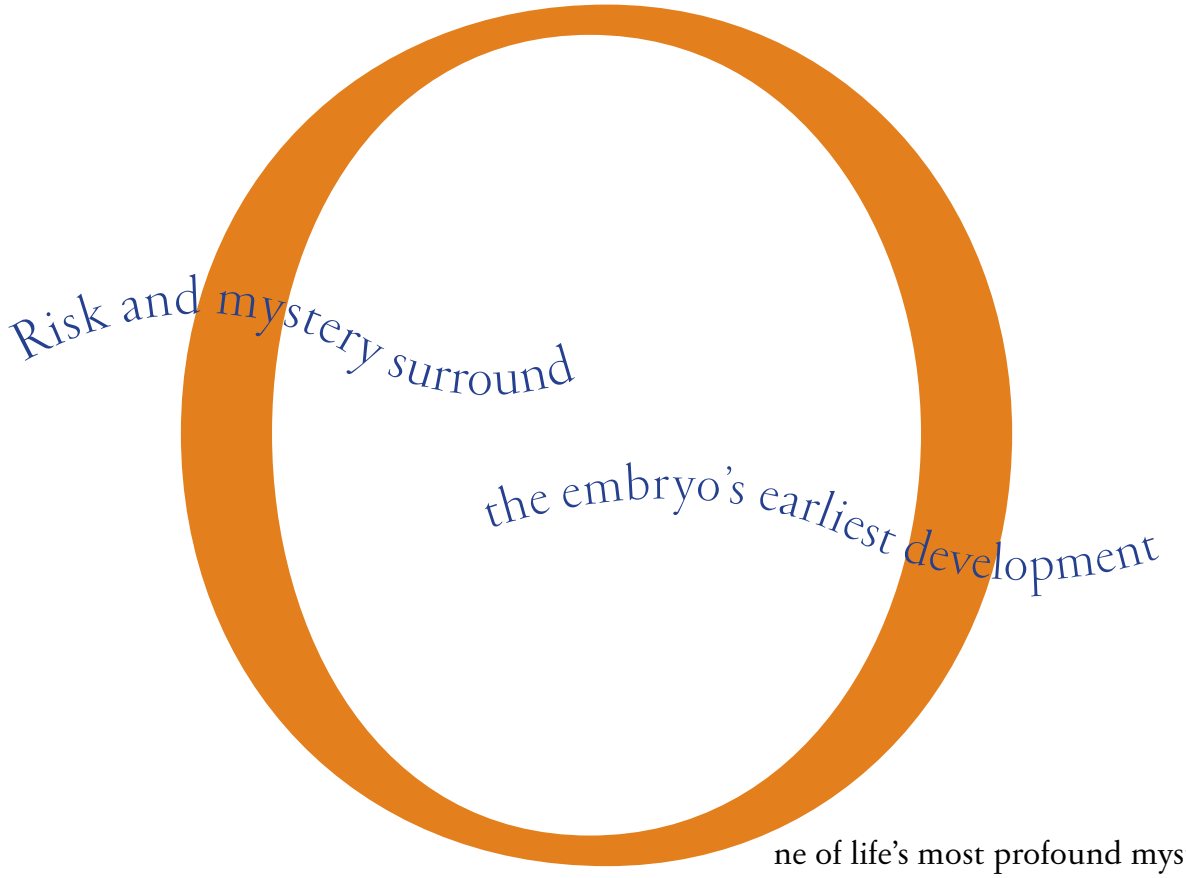
The First [21] Days

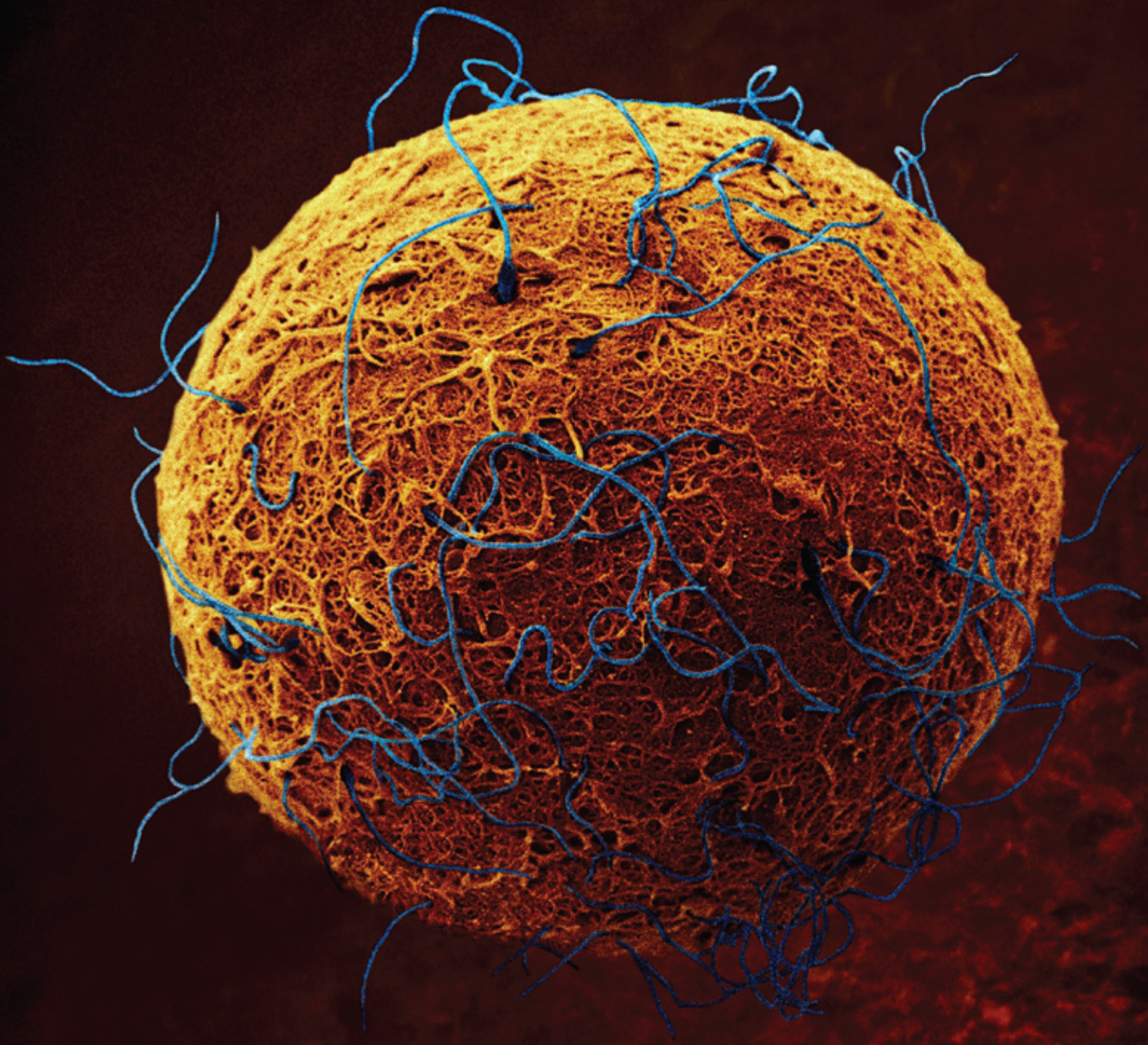


One of life's most profound mysteries — the creation of a new human being — starts with the union of egg and sperm and ends, nine months later, with a baby. It's a process so intricate and inherently risky, with pitfalls at every stage, it's amazing any of us survive long enough to be born at all. In fact, scientists estimate that about half of all human embryos die during the first two months of pregnancy when something goes wrong in those critical early stages of development.

It takes two months to form the human embryo, a process scientists call embryogenesis. After eight weeks, the embryo has all the organs and tissues found in a newborn baby — although many exist in primitive form. During the last seven months of a human pregnancy, the fetus (no longer called an embryo) continues to grow and develop, but the fundamental blueprint for the baby-to-be is established during embryogenesis.

BY SALLY POBOJEWSKI

YORGOS NIKAS



A human egg surrounded by sperm (color-enhanced)

Many of the most important and least understood stages of a human embryo's development take place during the first 21 days of pregnancy before the mother even knows she's pregnant and while the embryo is still incredibly small.

At 21-days-old, a human embryo is less than two millimeters long or roughly the size of the circle at the end of this sentence. •

But even at 21 days, the embryo is much more than just a simple ball of primitive cells. Its gender and basic body plan — top and bottom, front and back, left and right — are already established and the developmental future of every cell in the embryo is already set.

It's an amazing journey. And it all starts with a single cell.

DAY 1 Fertilization

IN THE BEGINNING IS THE EGG

Inside the fallopian tube, a mature human egg waits in a state of arrested development. Just released from the ovary, it is the largest cell in the human body. The egg is packed with nutrients, growth factors, enzymes and proteins — nearly everything it needs to jump start the development of a human embryo. Except for one little thing — it needs a sperm. If a sperm doesn't penetrate the egg's tough outer membrane to activate it within the next 24 hours, the egg will die.

During fertilization and the first stage of embryonic development, the egg runs the show. All a mature human egg really needs from a sperm is its DNA — the genetic code stored in 23 chromosomes inherited from the father. When combined with 23 chromosomes in the egg from the mother, the new embryo has the full complement of genetic material required to make a human being.

Much of what scientists know about fertilization and what happens during the early days of an embryo's development has come from research to help the 10 percent to 15 percent of couples who need medical assistance to have a baby. Many of these couples turn to in-vitro fertilization (IVF) or other assisted reproductive technologies. In 2004, 49,458 babies were born in the U.S. from embryos created when sperm and egg got together in a Petri dish, rather than inside a woman's body.

Gary Smith, Ph.D., is an associate professor of obstetrics/gynecology, urology and of molecular and integrative physiology. He studies mouse, cow and human embryos to learn what happens during the first few days of development. Although everything happens faster in mice than in humans, the steps involved in the process are essentially the same in both species. Studying what happens to embryos outside the body is not ideal, however, because there are big differences between how embryos develop in a culture dish and how they develop inside a living animal.

In the body, early embryos grow inside the moist, confined environment of the fallopian tube, where they are in constant contact with proteins, nutrients and other cells. But in the laboratory, most embryos start out floating in culture medium in a Petri dish — a situation that's like "a person floating out in Lake Michigan," says Smith.

To mimic conditions inside the fallopian tube where fertilization and the initial stages of development take place, Smith worked with Shuichi Takayama, Ph.D., an associate professor in the College of Engineering, to develop a device about half the size of a credit card that makes it possible to observe an embryo and monitor its biological signals during the first days of development.

Within the tight confines of narrow channels in the microchip, scientists can keep an embryo moving, maintain the flow of fresh nutrients and remove waste products. Smith calls it a dynamic culture, as opposed to the static culture currently used to grow embryos in a Petri dish. Using a dynamic culture system that simulates natural conditions, Smith and Takayama have found they get healthier mouse and cow embryos that are more like those grown inside the animal's body.

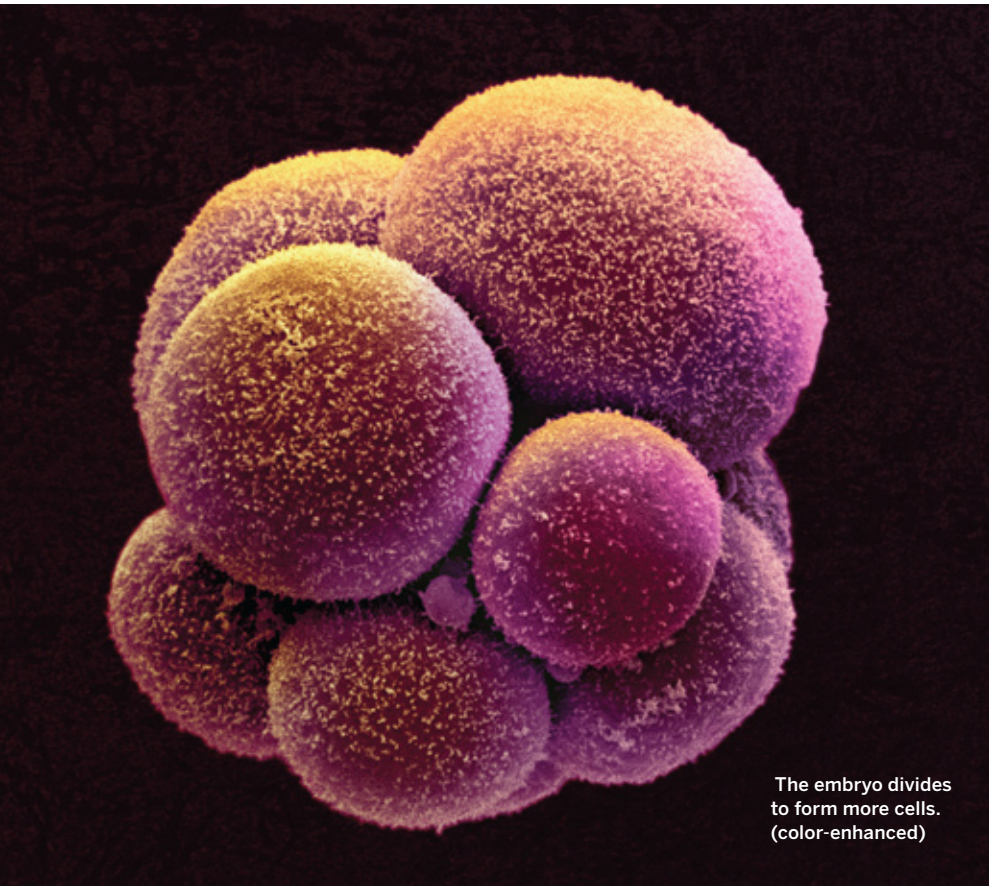
Smith's goal is to learn the body's secrets for growing a healthy embryo and use that knowledge to help more infertile couples have a healthy baby.

> AT THE EIGHT-CELL STAGE, THE EMBRYO SOMEHOW ACTIVATES ITS GENES. FROM THIS POINT ON, THE EMBRYO IS ON ITS OWN TO FOLLOW ITS UNIQUE GENETIC DESTINY.

DAY 2 TO 3 | Early Cleavage

TURNING ON THE EMBRYO'S GENES

Inside the mother's body, a fertilized egg moves through the fallopian tube, pushed toward the uterus by filaments lining the inside of the tube. Still dependent on nutrients and genetic instructions contributed by the egg, the embryo divides to form two cells, then four cells, then eight. At the eight-cell stage, through a process scientists still don't understand, the embryo somehow activates its genes. From this point on, the embryo is on its own to follow its unique genetic destiny. If anything interferes with gene activation, the embryo will die.



The embryo divides to form more cells. (color-enhanced)

YORGOS NIKAS

In the language of reproductive biology, it's called embryonic developmental competence, and it's a critical point where development often stops for reasons scientists don't understand.

"Some eggs have what it takes to support the embryo's development past the eight-cell stage and some don't," Smith explains. "Most eggs will fertilize and the embryos will start to divide normally, but when they reach the eight-cell stage, the system sometimes breaks down and development stops."

Exactly what an egg must have to make it possible for the embryo to turn on its genes, and how to tell which eggs have it, are two of the most important questions in developmental biology today, according to Smith.

"We know this developmental time point is very important for the embryo's survival and that gene activation is regulated by maternal, or egg-derived, factors, but we don't understand how the transformation works," Smith says.

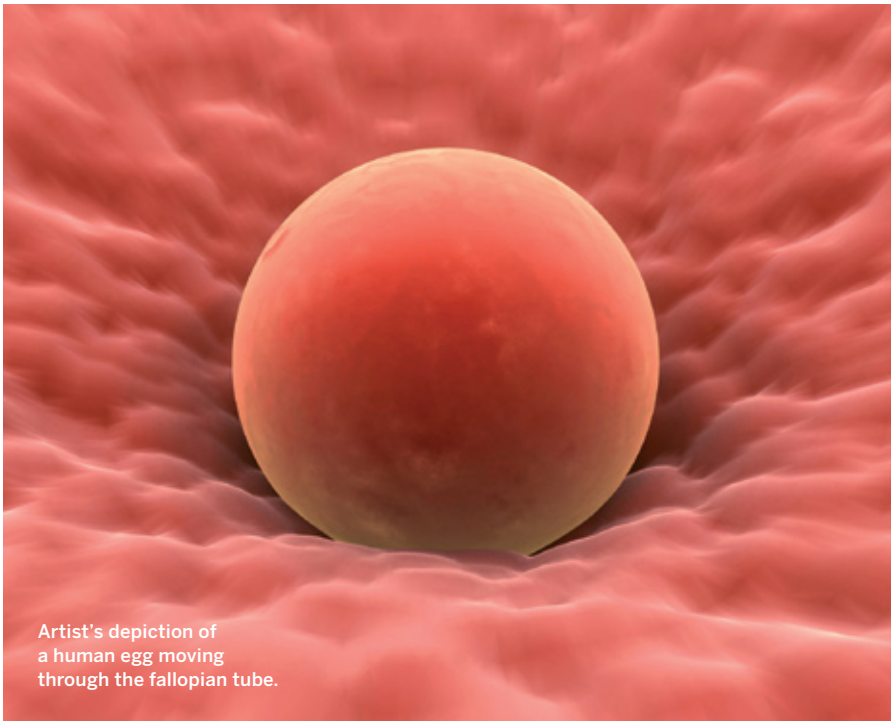
Smith believes the factors responsible for activation of the embryo's genome are programmed into the egg while it develops inside compartments in the ovary called follicles. It takes up to several hundred days for a human follicle to produce a mature egg. Before every menstrual cycle, several follicles begin to grow, but in the end, only one typically produces an egg that is primed and ready for fertilization.

"Nature has developed this journey to provide embryonic competence," Smith says. "It's naïve of us to think we can just go in [to the ovary] and pluck out eggs. They may all look the same at a microscopic level, but developmentally we know that not all eggs are created equal."

When embryos fertilized in a Petri dish during in-vitro fertilization reach the eight-cell stage, one or more are chosen to be transferred to the mother's uterus. Unfortunately, only about 20 percent of all transferred embryos will successfully implant in the wall of the uterus and continue to develop, according to Smith.

Biological tests or assays to determine in advance which eggs are capable of activating the embryo's genome, and which embryos have the greatest potential to implant, would be a big step forward in improving the odds of a successful IVF pregnancy.

"Today all we can do is look at embryos under a microscope and pick the prettiest ones with the most time-appropriate cell number," Smith says. "One of the goals of our research is developing a culture and analysis system that will allow us to produce the healthiest embryos and select the embryo with the best chance of implantation."



Artist's depiction of a human egg moving through the fallopian tube.

DAYS 3 TO 5 Blastocyst

CELLS MAKE THEIR FIRST CHOICE

By the time a three-day-old human embryo enters the uterus, it contains 16 identical cells packed together to form a sphere called a morula. As it moves into the uterus, the embryo is preparing for a major transformation. During the next 48 hours, the morula will become a blastocyst — a hollow oval with about 100 cells divided into two different types. Cells that will form the placenta make up the outer layer of the blastocyst. Nestled inside is a small inner cell mass with about 50 cells. These 50 cells will give rise to the millions of specialized cells, tissues and organs it takes to make a newborn baby.

Scientists refer to cells in the inner cell mass as being pluripotent, meaning they can become nearly any cell in the human body. But this unlimited potential lasts for just a few days. If pluripotent cells are removed from the blastocyst and cultured in the laboratory under the right conditions, they form colonies of human embryonic stem cells. Otherwise, they are quick to get on with the business of becoming the specialized cells the embryo will need as it grows and changes.

Sue O'Shea, Ph.D., a professor of cell and developmental biology who directs the Michigan Center for Human Embryonic Stem Cell Research, is trying to decipher the flood of genetic signals involved in the transformation of early embryonic cells into cells that are differentiated, or specialized to perform specific tasks. Working with mouse embryos, mouse embryonic stem cells and human embryonic stem cell lines that have been approved by the federal government for use in scientific research, O'Shea and her graduate students Nicky Slawney and Lisa DeBoer are identifying the genes and growth factors involved and learning how they work.

O'Shea is especially interested in teasing out the signals required to transform human embryonic stem cells, and cells in the early embryo, into neurons — one of the first specialized cells to develop in an embryo.

WEEK 2 Implantation

AT HOME IN THE UTERINE WALL

When the human embryo is around six days old, it starts making a nest in the wall of the mother's uterus. Cells in the outer layer of the blastocyst stick to the uterine wall and grow long projections into it — the first step in developing a placenta with blood vessels linking mother and embryo. From now on, the embryo will depend on oxygen and nutrients from the mother's bloodstream to survive. As the placenta grows and embeds itself within the uterine wall, the inner cell mass divides to form the amniotic cavity and a flat disc with two layers of cells that is the embryo.

Once the embryo is embedded in the wall of the uterus, it starts preparing for a transformation called gastrulation that takes place during the third week of development. During this process, every cell in the flat disc will migrate to a new location and morph into one of three new cell types to form

SEBASTIAN KAULITZKI/DREAMSTIME.COM

the inner, middle and outer layers of the 21-day-old embryo. This intricate cellular choreography is regulated by growth factors turned on and off at specific times and locations in response to signals from the embryo's genes.

"The embryo uses the same seven growth factor signaling pathways over and over," O'Shea says. "But by varying signal strength, turning cell receptors on or off, or turning growth factors on or off at specific locations in the embryo, the process allows for a great deal of precision and complexity."

Directed by the node, cells move down and through the streak to be reborn on the other side as either endoderm (the inner layer of the embryo) or mesoderm (the middle layer). Once the two inner layers of the embryo are formed, the node sends a different signal to the remaining cells. Instead of going through the streak, these cells will fan out to form the outer layer of the embryo called the ectoderm.

Once cells have passed through the primitive streak and gastrulation is complete, there is no turning back.

TO MIMIC CONDITIONS INSIDE THE FALLOPIAN TUBE, RESEARCHERS IN THE SMITH AND TAKAYAMA LABORATORIES DEVELOPED A DEVICE THAT MAKES IT POSSIBLE TO OBSERVE THE EMBRYO AND MONITOR ITS BIOLOGICAL SIGNALS DURING THE FIRST DAYS OF DEVELOPMENT.

WEEK 3 Gastrulation

THREE CELL LAYERS AND A BODY PLAN

During its third week, the human embryo goes through a developmental milestone. Gastrulation establishes the embryo's basic body plan and seals the fate of its cells. Once the process is complete, the embryo will have three distinct layers with a defined top and bottom, front and back, left and right. At no other time in its development will the embryo undergo such a radical transformation.

Gastrulation begins with an indentation called the primitive streak, which forms on top of the flat disc when the embryo is about 15 days old. At the top of the streak is a small structure called the node that churns out growth factors signaling cells to break free from their neighbors, multiply and move toward the streak.

Cells in the gastrulating embryo are exquisitely sensitive to the strength of growth factors from the node. Embryonic cells closest to the node receive the strongest signal, inducing them to turn on genes that cause them to become one kind of cell. Cells on the edge of the embryo receive a weaker signal and this causes them to express different genes and become a different kind of cell.

"Just being a couple cell diameters away can mean a big difference in gene expression," O'Shea says.

Each embryonic cell is now destined to follow a specific developmental pathway. Endoderm cells will go on to form the liver, pancreas and gastrointestinal tract. Cells in the mesoderm are fated to develop into the heart and blood vessels, bone, muscle and kidneys. The ectoderm will become the central and peripheral nervous systems, sensory organs, skin and hair.

Because the blueprint for all the body's organs is established during gastrulation, it's the beginning of a time when exposure to alcohol, drugs, viruses and toxic chemicals can have a catastrophic effect on the embryo. From the third week to the eighth week while organs are still forming, the embryo will remain vulnerable to damage. Even if it's not lethal, the result can be a lifetime of disability for a child born with fetal alcohol syndrome or spina bifida.

Knowing more about what happens to a human embryo during its perilous journey from fertilization to gastrulation could help researchers learn what causes birth defects and perhaps even find ways to prevent or correct them.

Research to understand how embryos develop could benefit the health of adults, as well. Scientists are only starting to understand how mistakes during embryogenesis can have life-long consequences in the form of diseases and disorders like cancer, congenital heart defects, and Down syndrome that begin when something goes wrong during the embryo's first 21 days.

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