Inside The Womb

What scientists have learned about those amazing first nine months — and what it means for mothers

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As the crystal probe slides across her belly, Hilda Manzo, 33, stares wide-eyed at the video monitor mounted on the wall. She can make out a head with a mouth and two eyes. She can see pairs of arms and legs that end in tiny hands and feet. She can see the curve of a backbone, the bridge of a nose. And best of all, she can see movement. The mouth of her child-to-be yawns. Its feet kick. Its hands wave. Dr. Jacques Abramowicz, director of the University of Chicago's ultrasound unit, turns up the audio so Manzo can hear the gush of blood through the umbilical cord and the fast thump, thump, thump of a miniature heart. "Oh, my!" she exclaims as he adjusts the sonic scanner to peer under her fetus' skin. "The heart is on the left side, as it should be," he says, "and it has four chambers. Look — one, two, three, four!"

Such images of life stirring in the womb — in this case, of a 17-week-old fetus no bigger than a newborn kitten — are at the forefront of a biomedical revolution that is rapidly transforming the way we think about the prenatal world. For although it takes nine months to make a baby, we now know that the most important developmental steps — including laying the foundation for such major organs as the heart, lungs and brain — occur before the end of the first three. We also know that long before a child is born its genes engage the environment of the womb in an elaborate conversation, a two-way dialogue that involves not only the air its mother breathes and the water she drinks but also what drugs she takes, what diseases she contracts and what hardships she suffers.

One reason we know this is a series of remarkable advances in MRI's, sonograms and other imaging technologies that allow us to peer into the developmental process at virtually every stage — from the fusion of sperm and egg to the emergence, some 40 weeks later, of a miniature human being. The extraordinary pictures on these pages come from a new book that captures some of the color and excitement of this research: From Conception to Birth: A Life Unfolds (Doubleday), by photographer Alexander Tsiaras and writer Barry Werth. Their computer-enhanced images are reminiscent of the remarkable fetal portraits taken by medical photographer Lennart Nilsson, which appeared in Life magazine in 1965. Like Nilsson's work, these images will probably spark controversy. Antiabortion activists may interpret them as evidence that a fetus is a viable human being earlier than generally believed, while pro-choice advocates may argue that the new technology allows doctors to detect serious fetal defects at a stage when abortion is a reasonable option.

The other reason we know so much about what goes on inside the womb is the remarkable progress researchers have made in teasing apart the sequence of chemical signals and switches that drive fetal development. Scientists can now describe at the level of individual genes and molecules many of the steps involved in building a human,

from the establishment of a head-to-tail growth axis and the budding of limbs to the sculpting of a four-chambered heart and the weaving together of trillions of neural connections. Scientists are beginning to unroll the genetic blueprint of life and identify the precise molecular tools required for assembly. Human development no longer seems impossibly complex, says Stanford University biologist Matthew Scott. "It just seems marvelous."

How is it, we are invited to wonder, that a fertilized egg — a mere speck of protoplasm and DNA encased in a spherical shell — can generate such complexity? The answers, while elusive and incomplete, are beginning to come into focus.

Only 20 years ago, most developmental biologists thought that different organisms grew according to different sets of rules, so that understanding how a fly or a worm develops — or even a vertebrate like a chicken or a fish — would do little to illuminate the process in humans. Then, in the 1980s, researchers found remarkable similarities in the molecular tool kit used by organisms that span the breadth of the animal kingdom, and those similarities have proved serendipitous beyond imagining. No matter what the species, nature uses virtually the same nails and screws, the same hammers and power tools to put an embryo together.

Among the by-products of the torrent of information pouring out of the laboratory are new prospects for treating a broad range of late-in-life diseases. Just last month, for example, three biologists won the Nobel Prize for Medicine for their work on the nematode Caenorhabditis elegans, which has a few more than 1,000 cells, compared with a human's 50 trillion. The three winners helped establish that a fundamental mechanism that C. elegans embryos employ to get rid of redundant or abnormal cells also exists in humans and may play a role in aids, heart disease and cancer. Even more exciting, if considerably more controversial, is the understanding that embryonic cells harbor untapped therapeutic potential. These cells, of course, are stem cells, and they are the progenitors of more specialized cells that make up organs and tissues. By harnessing their generative powers, medical researchers believe, it may one day be possible to repair the damage wrought by injury and disease. (That prospect suffered a political setback last week when a federal advisory committee recommended that embryos be considered the same as human subjects in clinical trials.)

To be sure, the marvel of an embryo transcends the collection of genes and cells that compose it. For unlike strands of DNA floating in a test tube or stem cells dividing in a Petri dish, an embryo is capable of building not just a protein or a patch of tissue but a living entity in which every cell functions as an integrated part of the whole. "Imagine yourself as the world's tallest skyscraper, built in nine months and germinating from a single brick," suggest Tsiaras and Werth in the opening of their book. "As that brick divides, it gives rise to every other type of material needed to construct and operate the finished tower — a million tons of steel, concrete, mortar, insulation, tile, wood, granite, solvents, carpet, cable, pipe and glass as well as all furniture, phone systems, heating and cooling units, plumbing, electrical wiring, artwork and computer networks, including software."

Given the number of steps in the process, it will perhaps forever seem miraculous that life ever comes into being without a major hitch. "Whenever you look from one embryo to another," observes Columbia University developmental neurobiologist Thomas Jessell, "what strikes you is the fidelity of the process."

Sometimes, though, that fidelity is compromised, and the reasons why this happens are coming under intense scrutiny. In laboratory organisms, birth defects occur for purely genetic reasons when scientists purposely mutate or knock out specific sequences of DNA to establish their function. But when development goes off track in real life, the cause can often be traced to a lengthening list of external factors that disrupt some aspect of the genetic program. For an embryo does not develop in a vacuum but depends on the environment that surrounds it. When a human embryo is deprived of essential nutrients or exposed to a toxin, such as alcohol, tobacco or crack cocaine, the consequences can range from readily apparent abnormalities — spina bifida, fetal alcohol syndrome — to subtler metabolic defects that may not become apparent until much later.

Ironically, even as society at large continues to worry almost obsessively about the genetic origins of disease, the biologists and medical researchers who study development are mounting an impressive case for the role played by the prenatal environment. A growing body of evidence suggests that a number of serious maladies — among them, atherosclerosis, hypertension and diabetes — trace their origins to detrimental prenatal conditions. As New York University Medical School's Dr. Peter Nathanielsz puts it, "What goes on in the womb before you are born is just as important to who you are as your genes."

Most adults, not to mention most teenagers, are by now thoroughly familiar with the mechanics of how the sperm in a man's semen and the egg in a woman's oviduct connect, and it is at this point that the story of development begins. For the sperm and the egg each contain only 23 chromosomes, half the amount of DNA needed to make a human. Only when the sperm and the egg fuse their chromosomes does the tiny zygote, as a fertilized egg is called, receive its instructions to grow. And grow it does, replicating its DNA each time it divides — into two cells, then four, then eight and so on.

If cell division continued in this fashion, then nine months later the hapless mother would give birth to a tumorous ball of literally astronomical proportions. But instead of endlessly dividing, the zygote's cells progressively take form. The first striking change is apparent four days after conception, when a 32-cell clump called the morula (which means "mulberry" in Latin) gives rise to two distinct layers wrapped around a fluid-filled core. Now known as a blastocyst, this spherical mass will proceed to burrow into the wall of the uterus. A short time later, the outer layer of cells will begin turning into the placenta and amniotic sac, while the inner layer will become the embryo.

The formation of the blastocyst signals the start of a sequence of changes that are as precisely choreographed as a ballet. At the end of Week One, the inner cell layer of the blastocyst balloons into two more layers. From the first layer, known as the endoderm, will come the cells that line the gastrointestinal tract. From the second, the ectoderm, will arise the neurons that make up the brain and spinal cord along with the epithelial cells that make up the skin. At the end of Week Two, the ectoderm spins off a thin line of cells known as the primitive streak, which forms a new cell layer called the mesoderm. From it will come the cells destined to make the heart, the lungs and all the other internal organs.

At this point, the embryo resembles a stack of Lilliputian pancakes — circular, flat and horizontal. But as the mesoderm forms, it interacts with cells in the ectoderm to trigger yet another transformation. Very soon these cells will roll up to become the neural tube, a rudimentary precursor of the spinal cord and brain. Already the embryo has a distinct

cluster of cells at each end, one destined to become the mouth and the other the anus. The embryo, no larger at this point than a grain of rice, has determined the head-to-tail axis along which all its body parts will be arrayed.

How on earth does this little, barely animate cluster of cells "know" what to do? The answer is as simple as it is startling. A human embryo knows how to lay out its body axis in the same way that fruit-fly embryos know and C. elegans embryos and the embryos of myriad other creatures large and small know. In all cases, scientists have found, in charge of establishing this axis is a special set of genes, especially the so-called homeotic homeobox, or hox, genes.

hox genes were first discovered in fruit flies in the early 1980s when scientists noticed that their absence caused striking mutations. Heads, for example, grew feet instead of antennae, and thoraxes grew an extra pair of wings. hox genes have been found in virtually every type of animal, and while their number varies — fruit flies have nine, humans have 39--they are invariably arrayed along chromosomes in the order along the body in which they are supposed to turn on.

Many other genes interact with the Hox system, including the aptly named Hedgehog and Tinman genes, without which fruit flies grow a dense covering of bristles or fail to make a heart. And scientists are learning in exquisite detail what each does at various stages of the developmental process. Thus one of the three Hedgehog genes — Sonic Hedgehog, named in honor of the cartoon and video-game character — has been shown to play a role in making at least half a dozen types of spinal-cord neurons. As it happens, cells in different places in the neural tube are exposed to different levels of the protein encoded by this gene; cells drenched in significant quantities of protein mature into one type of neuron, and those that receive the barest sprinkling mature into another. Indeed, it was by using a particular concentration of Sonic Hedgehog that neurobiologist Jessell and his research team at Columbia recently coaxed stem cells from a mouse embryo to mature into seemingly functional motor neurons.

At the University of California, San Francisco, a team led by biologist Didier Stainier is working on genes important in cardiovascular formation. Removing one of them, called Miles Apart, from zebra-fish embryos results in a mutant with two nonviable hearts. Why? In all vertebrate embryos, including humans, the heart forms as twin buds. In order to function, these buds must join. The way the Miles Apart gene appears to work, says Stainier, is by detecting a chemical attractant that, like the smell of dinner cooking in the kitchen, entices the pieces to move toward each other.

The crafting of a human from a single fertilized egg is a vastly complicated affair, and at any step, something can go wrong. When the heart fails to develop properly, a baby can be born with a hole in the heart or even missing valves and chambers. When the neural tube fails to develop properly, a baby can be born with a brain not fully developed (anencephaly) or with an incompletely formed spine (spina bifida). Neural-tube defects, it has been firmly established, are often due to insufficient levels of the water-soluble B vitamin folic acid. Reason: folic acid is essential to a dividing cell's ability to replicate its DNA.

Vitamin A, which a developing embryo turns into retinoids, is another nutrient that is critical to the nervous system. But watch out, because too much vitamin A can be toxic. In another newly released book, Before Your Pregnancy (Ballantine Books), nutritionist Amy Ogle and obstetrician Dr. Lisa Mazzullo caution would-be mothers to limit foods

that are overly rich in vitamin A, especially liver and food products that contain lots of it, like foie gras and cod-liver oil. An excess of vitamin A, they note, can cause damage to the skull, eyes, brain and spinal cord of a developing fetus, probably because retinoids directly interact with DNA, affecting the activity of critical genes.

Folic acid, vitamin A and other nutrients reach developing embryos and fetuses by crossing the placenta, the remarkable temporary organ produced by the blastocyst that develops from the fertilized egg. The outer ring of cells that compose the placenta are extremely aggressive, behaving very much like tumor cells as they invade the uterine wall and tap into the pregnant woman's blood vessels. In fact, these cells actually go in and replace the maternal cells that form the lining of the uterine arteries, says Susan Fisher, a developmental biologist at the University of California, San Francisco. They trick the pregnant woman's immune system into tolerating the embryo's presence rather than rejecting it like the lump of foreign tissue it is.

In essence, says Fisher, "the placenta is a traffic cop," and its main job is to let good things in and keep bad things out. To this end, the placenta marshals platoons of natural killer cells to patrol its perimeters and engages millions of tiny molecular pumps that expel poisons before they can damage the vulnerable embryo.

Alas, the placenta's defenses are sometimes breached — by microbes like rubella and cytomegalovirus, by drugs like thalidomide and alcohol, by heavy metals like lead and mercury, and by organic pollutants like dioxin and PCBs. Pathogens and poisons contained in certain foods are also able to cross the placenta, which may explain why placental tissues secrete a nausea-inducing hormone that has been tentatively linked to morning sickness. One provocative if unproved hypothesis says morning sickness may simply be nature's crude way of making sure that potentially harmful substances do not reach the womb, particularly during the critical first trimester of development.

Timing is decisive where toxins are concerned. Air pollutants like carbon monoxide and ozone, for example, have been linked to heart defects when exposure coincided with the second month of pregnancy, the window of time during which the heart forms. Similarly, the nervous system is particularly vulnerable to damage while neurons are migrating from the part of the brain where they are made to the area where they will ultimately reside. "A tiny, tiny exposure at a key moment when a certain process is beginning to unfold can have an effect that is not only quantitatively larger but qualitatively different than it would be on an adult whose body has finished forming," observes Sandra Steingraber, an ecologist at Cornell University.

Among the substances Steingraber is most worried about are environmentally persistent neurotoxins like mercury and lead (which directly interfere with the migration of neurons formed during the first trimester) and PCBs (which, some evidence suggests, block the activity of thyroid hormone). "Thyroid hormone plays a noble role in the fetus," says Steingraber. "It actually goes into the fetal brain and serves as kind of a conductor of the orchestra."

PCBs are no longer manufactured in the U.S., but other chemicals potentially harmful to developing embryos and fetuses are. Theo Colborn, director of the World Wildlife Fund's contaminants program, says at least 150 chemicals pose possible risks for fetal development, and some of them can interfere with the naturally occurring sex hormones critical to the development of a fetus. Antiandrogens, for example, are widely found in fungicides and plastics. One in particular — DDE, a breakdown product of DDT — has

been shown to cause hypospadias in laboratory mice, a birth defect in which the urethra fails to extend to the end of the penis. In humans, however, notes Dr. Allen Wilcox, editor of the journal Epidemiology, the link between hormone-like chemicals and birth defects remains elusive.

The list of potential threats to embryonic life is long. It includes not only what the mother eats, drinks or inhales, explains N.Y.U.'s Nathanielsz, but also the hormones that surge through her body. Pregnant rats with high blood-glucose levels (chemically induced by wiping out their insulin) give birth to female offspring that are unusually susceptible to developing gestational diabetes. These daughter rats are able to produce enough insulin to keep their blood glucose in check, says Nathanielsz, but only until they become pregnant. At that point, their glucose level soars, because their pancreases were damaged by prenatal exposure to their mother's sugar-spiked blood. The next generation of daughters is, in turn, more susceptible to gestational diabetes, and the transgenerational chain goes on.

In similar fashion, atherosclerosis may sometimes develop because of prenatal exposure to chronically high cholesterol levels. According to Dr. Wulf Palinski, an endocrinologist at the University of California at San Diego, there appears to be a kind of metabolic memory of prenatal life that is permanently retained. In genetically similar groups of rabbits and kittens, at least, those born to mothers on fatty diets were far more likely to develop arterial plaques than those whose mothers ate lean.

But of all the long-term health threats, maternal undernourishment — which stunts growth even when babies are born full term — may top the list. "People who are small at birth have, for life, fewer kidney cells, and so they are more likely to go into renal failure when they get sick," observes Dr. David Barker, director of the environmental epidemiology unit at England's University of Southampton. The same is true of insulin-producing cells in the pancreas, so that low-birth-weight babies stand a higher chance of developing diabetes later in life because their pancreases — where insulin is produced — have to work that much harder. Barker, whose research has linked low birth weight to heart disease, points out that undernourishment can trigger lifelong metabolic changes. In adulthood, for example, obesity may become a problem because food scarcity in prenatal life causes the body to shift the rate at which calories are turned into glucose for immediate use or stored as reservoirs of fat.

But just how does undernourishment reprogram metabolism? Does it perhaps prevent certain genes from turning on, or does it turn on those that should stay silent? Scientists are racing to answer those questions, along with a host of others. If they succeed, many more infants will find safe passage through the critical first months of prenatal development. Indeed, our expanding knowledge about the interplay between genes and the prenatal environment is cause for both concern and hope. Concern because maternal and prenatal health care often ranks last on the political agenda. Hope because by changing our priorities, we might be able to reduce the incidence of both birth defects and serious adult diseases.