Nova – How Babies are Made

(bright music) -

[Narrator] Tonight on NOVA. During the nine months that this baby was inside her mother's womb, a remarkable series of events unfolded. Weighing seven pounds now, this child started as a single cell, smaller than the head of a pin. Inside that cell were the instructions for the making of this unique individual. How can you get a whole baby from one single cell? The study of this microscopic worm and of this tiny fly might provide keys to unlock the mystery of how a living creature is created. The stakes are very high. This research might lead to a better understanding of why much later in life some cells become cancerous and why sometimes things go wrong during pregnancy. Tonight on NOVA, How Babies Get Made. (dramatic orchestral music) (ethereal music) Major funding for NOVA is provided by this station and other public television stations nationwide. Additional funding was provided by the Johnson & Johnson Family of Companies, supplying healthcare products worldwide. And by Allied Signal, a technology leader in aerospace, electronics, automotive products and engineered materials. (light electronic music) (triumphant music) A newborn baby, perfect and complete. (peaceful music) Virtually all of the body's complexity is present, seen in the details of the hands, of the face, in fact, in all of the body's organs. What lies ahead is growth and modification. But the detailed patterns of the body are already permanently set in place. Just how all of this develops from a single fertilized egg is the central puzzle of modern biology. When solved, it will describe not just how human babies are made but all living creatures. If you trace back the development of the human baby, most of the body's complexity is apparent as early as seven months before birth. The key aspects of development all took place in the first two months as an embryo. That order emerged from a ball of thousands of cells which in turn developed from just one. In the earliest stages, all vertebrate animals, those with a backbone, begin their development like this. The first cells divide and divide, producing a hollow ball of thousands of cells. Then, as if on cue, part of the ball buckles inwards and cells pour to the middle to start forming the internal parts. The surface layer of the embryo rolls up into a tube, creating the spinal cord and brain. Inside internal organs form. A heart beats, blood flows. In this case after a few weeks a newt has been made. (twinkling music) In fact, in the very earliest stages all vertebrate embryos look strikingly the same. These four embryos are from quite different animals. As they develop, only one will become a human fetus. Their differences show as they get further along in their development towards becoming a fish, a salamander, a chicken, or a human. That completely different animals start out as almost identical looking embryos suggest that they may not be so different after all. Nature makes creatures that are varied in form and size. Yet different as they are as adult animals, they all must pass through very similar stages in their earliest growth. But more surprising, given the exquisite precision that's required for the task, is the fact that development works at all. - There seem to be two important aspects to development and one is the extraordinary success rate and precision of the process. The other is the flexibility of the process. The flexibility is most easily demonstrated by experiments where you do what seems to be enormous damage to the embryo and yet it's able to repair that damage and still develop, in many cases, into a fairly normal adult organism. -

[Narrator] This flexibility is clearly helpful for an early embryo's survival. The cells of the earliest embryonic stages can withstand an incredible range of harsh conditions. Here under the microscope, a mouse embryo made up of two cells, is actually being pulled in half. Each half of the embryo will recover and identical twin mice will form. Sometimes this happens spontaneously in nature producing identical twins or even triplets like these. The embryo in their mothers will split into three pieces. Since this happened early enough, each separate cluster of cells retain the ability to go on. They develop normally, emerging as precisely identical looking human beings. In another case, up to 90% of an early mouse embryo can be destroyed, and yet recover, and develop to produce a perfectly normal mouse. (mouse squeaking) Instead of destroying cells more can be added. One of these embryos would've become a black mouse. The other, a white a mouse. But when fused, the resulting ball of cells develops normally producing a hybrid mouse called a chimera. Its whole body is a mixture of black and white cells, not just in the skin but everywhere. This mouse has four parents instead of two. Embryos survive other kinds of harsh treatment. As the temperature drops to 31 degrees below zero, ice crystals envelop this embryo. (light ethereal music) This baby boy, born in 1985, was once deep frozen. As am embryo, he was stored at minus 320 degrees Fahrenheit in liquid nitrogen, thawed out, and then planted into his mother's womb. (birds chirping) Even more remarkably, some animals have their own methods of storing an embryo but at body temperature. A kangaroo usually gets pregnant again immediately after giving birth. While its baby nurses, a new embryo starts to grow. But then as if by magic the embryo is stopped in its tracks. This normally rapidly dividing ball of cells is restrained for months while the baby feeds. Once the baby is weened, the new embryo starts to grow again. One month later, another baby kangaroo is born. (soft music) Embryos can even survive within a foreign species. This horse has just given birth to a zebra. (camera clicks) As an embryo, the zebra colt had been successfully implanted into its surrogate mother. Despite being made of foreign tissue, it was not rejected. (people chattering) In fact, all of us were once foreign tissue in our mother's womb. Even an embryo developing in a mother of its own species like this human when in the uterine tube is made of partly foreign tissue. The cells of the embryo originate from both father and mother. So in a sense, it is an alien residing in the womb. Yet the mother's body does not reject it. In pregnancy the immune system of both mother and baby are specially modified to survive the experience. An early embryo can be damaged, split, frozen, and thawed, and get recovered. But in the long journey that lies ahead it will have to give up this flexibility forever. About one week after conception, the cells of the human embryo begin to specialize. - What one wants to know is how one goes from the egg, the fertilized egg which is one cell, to something, someone like yourself which is millions and millions of cells. Different kinds of cells and they're all arranged in a rather well defined pattern. -

[Narrator] This dividing ball of cells is approaching the first major step in which cells specialize and form patterns. The hollow ball buckles in a specific place. This will become the tail of the animal. Cells stream into the interior, Where they contact the opposite side, a mouth will eventually form. This rearrangement of cells is critical process for embryos. It's called gastrulation. - The embryos have been vaginated, it's a hollow ball. It's as if you were to push your fists in through the ball and so the edges of the ball close around your wrist. So the embryo actually sort of turns itself almost inside out. In doing that, it creates a new layer of cells inside and a hole which, well, called the blastopore. That large scale tissue movement yields a sort of multilayered embryo. Once that's happened, each layer of the embryo then has a different fate. -

[Narrator] Gastrulation divides the embryo into three distinct layers. The outer layer, the ectoderm, is fated to become the nervous system and the surface of the animal. The middle layer, the mesoderm, will make the tissues that connect the outside to the inside. (light music) The inner layer, the endoderm, gives rise to most of the internal organs. In the human embryo, gastrulation happens at about two weeks. Over 1/3 of human embryos never reach gastrulation or undergo it incorrectly. It's a precise and delicate process, a crucial event for the success of all embryos. If gastrulation happens in more than one place, a double embryo is made, and Siamese twins, joined or even sharing internal organs, may result. - It's not birth's death or marriage which is the most important event in your life but gastrulation. It is a very important event in early development because you get enormous changes in the location of cells in the early embryo so they get put in the right place so that organs can then really begin to develop. -

[Narrator] With gastrulation, cells rapidly lose their flexibility. They begin to differentiate to become committed to specific fates. - These are early frog embryos. About five hours or so ago they were single fertilized eggs and in that period they've divided until there's about 1,000 cells here. Now they look all the same from the top here. If you turn them over, you can see that in fact some of the cells at the bottom are white and the top cells have pigment in them. Under normal circumstances if you leave these embryos alone, the cells at the bottom, underneath here, the white ones, will develop into part of the gut only. But what if I move individual white cells like these to another region of the embryo and place them amongst cells that are destined to become other organs such as brain? Will this white cell still become gut or will it now change into brain? It all depends when it's done. At this stage, the white cell is changed by its new environment. It now becomes brain and other tissues. But just three hours later, this white cell is now committed to being gut only. Moving it to its new location has no effect because it actually finds its way back to the correct place in the embryo and develops into gut. (soft music) -

[Narrator] Organs develop according to a precise schedule. After gastrulation, the outer layer, the ectoderm, rolls up to produce a tube, the neural tube, which makes the brain and spinal cord. The middle layer, the mesoderm, goes on to produce little blocks of muscle which start to twitch. Now cells are visibly different. Specialized muscle cells in the heart pump specialized blood cells. The ancestors of these cells were capable of generating any kind of cell even a founding a whole embryo. Now the cells that go into making a structure like the eye seem to have made irreversible choices. In the frog embryo, these developmental choices are made over the course of a few days. -

[Chris] This is what the embryos will become in three or four days. These are the early swimming tadpoles of the frog. One looked at from the side and one looked at from underneath. We can see in this one the developing gut which is all curled up inside the abdomen, and the eye. The one looked at from the side, you can see the brain and the spinal cord which is this grey line running down here. Now if I increase the magnification we can see many differentiated cell types. These black things here are pigment cells in the skin. We can see the developing heart which is this muscular pump. So there are obviously very many differentiated cell types present at these later stages of embryogenesis. -

[Narrator] The process of specialization takes the frog embryo only a short time. In a human embryo it is a matter of weeks and months. This is a human embryo after five days. It is a compact cluster of cells no bigger than the original egg. After about 10 days, the embryo is firmly implanted in the lining of the uterus, still barely visible to the naked eye. Soon afterwards gastrulation will begin. After two weeks, the embryo is elongated. (ethereal music) At the top is the structure which will become its head and brain. At four weeks, the embryo has arm butts. It has the beginnings of eyes. At seven weeks the internal organs are visible. The embryo has clearly defined fingers that move. Less than one quarter of the way through its developmental journey, the embryo has already come far from one fertilized egg cell to millions of specialized cells. What creates this variety of cell types? How does one cell become different from another? This is one of the central questions that intrigues biologists studying development. The trick has been to find an animal simple enough to let scientists watch each step in the process. - If you ask how many cells do you and I have, the answer is something on the order of a million million. To begin to think of describing all of these cells, let alone studying them in some detail, is almost unimaginable. Whereas if we take an animal that has fewer than 1,000 cells, we can really look at it in great detail. We actually study a worm, it's a very small worm. It's a microscopic animal, it's only one millimeter in length. The features of this worm are very much like the features of the larger animals that we're used to. It has many of these different cell types, a nervous system, a musculature, gut, gonad, and so on. But it has only very few cells within its body. -

[Narrator] These circles mark individual intestinal cells of the immature C. elegans worm. The ability to watch these and the other cells of the worm develop allows biologists a unique opportunity. - The simplicity in the number of cells and the fact that the animal is transparent has allowed us to look inside it while it develops and follow this development from one cell to two to four and so on, all the way up to the 959 in the adult. -

[Narrator] Biologists, during five years of painstakingly careful research, simply watched worm after worm grow. They observed and recorded what happened to each cell from the initial fertilized egg through the larval stages and on to the adult form. Since the entire process is the same from one worm to the next, researchers were able to put together a developmental map. Like a family tree, the map shows the division of each cell into two, tracing the series of divisions from one generation to the next until all of the cells have reached their final stage of development. For example, this branch originated as a single cell. Following the map, it can be shown that a few of its descendants became adult muscle cells. Others took on a variety of different specialized functions. Through this research, the C. elegans worm has become one of the best understood living structures in the world. - We know this animal inside and out. We know every cell in its body. We know where it's come from, we know where it's going. We've been able, in fact, to determine the entire history of every single cell in this animal. What that makes possible now is the study of the factors that influence what these cells do, what each cell does, at different times during development. -

[Narrator] Studies of the C. elegans worm have shown how it is that cells develop to become different from one another. There appear to be three general mechanisms. The first involves a single cell that contains different components that are unevenly distributed. When it divides, its two daughter cells, because of their components, are then different from each other. The second mechanism involves a set of identical cells. They communicate with each other, probably through chemical signals as they compete to develop into one of the few potential types. The third mechanism involves a group of similar cells that are influenced by a cell of a different type which is sending out a signal. That signal determines the developmental fate of these cells. - So we see really three different kinds of mechanisms. We see single cells dividing and what's in them is what makes them different. We see cells in a sense fighting it out amongst alternative potentials to decide which will do one thing and which will do another. We see cells sitting, and waiting, and listening to other cells which will tell them what to do. (light music) -

[Narrator] But understanding how cells form different types doesn't explain how a baby emerges from that initial ball of undifferentiated cells. The embryo also must organize its cells into the patterns that make up organs and body parts. - Even if you know how cells become different it doesn't tell you how you get patterns. For example, if you think of your arm, and you think of your leg, it's the same cell types in each. The muscle, cartilage, bone, the cells that make up the skin, and yet your arm's quite different to your leg. That's a problem of pattern formation, that's a problem of spacial organization of cell differentiation. I think one can see there's quite clearly, when I compare myself to a chimpanzee, as far as I know there's no cell type that I have that the chimpanzee doesn't have. There's no cell type that the chimpanzee has that I don't have and yet I came to be very different from a chimpanzee. I think that's about spacial organization rather than cell types. -

[Narrator] In fact, all higher vertebrates share basically the same types of specialized cells. For example, blood cells, skin cells or nerve cells. It's the arrangement of those cells that distinguishes one animal from another. But how do those patterns of cells form? (monkey cries) (growling) This is the sea animal, hydra. Its ability to maintain body pattern is so strong that it can be completely mashed up into a pulp. (ethereal music) Yet, given sufficient time, the cells will reassemble themselves and restore the correct pattern. In the normal development of higher vertebrates like the chick, cells also know where they belong. For example, at a certain point cells commit to being part of a wing or a leg. But which part the cell will specialize further. - Cells remember that they belong to the leg as distinct from the arm. So for example, if you take cells from the very early leg bud and put them into the wing bud in the chick, they behave according to the position that you put them into the wing bud nut remember themselves as leg. So if you take cells that would normally give rise to the thigh and graph them to the tip of the developing wing, then they now develop as a toe because they take on a new position that is at the tip of the limb but they remember that they are leg. So they develop as a toe. (light music) -

[Narrator] So first a cell is committed to being part of a leg. Its next decision is whether to become thigh versus toe and that depends on where the cell is along the limb. But how does the cell know where it is? - One way of thinking about it is in terms of what one might call position information. That is that you can make a very wide variety of patterns using the following principle. First of all you tell the cells where they are or the cells learn where they are rather as a coordinates system or for example if you imagine people in a stand. You know, there's flash card patterns you see before match of the day or you've seen before the Olympics. Each person knows what to do with the particular position because they know their position and what they've gotta do in that position. -

[Narrator] An enormous number of nature's patterns might be built with such a simple principle. (crowd applauds) Like these performers, the cells in a developing limb need to know where they are and behave in an appropriate way to become part of an elbow or a toe. But how do cells determine their position? (twinkling music) One way for a cell to measure its position is by a chemical signal. The block at the lower left is exuding an invisible but powerful chemical attractant. These single cells are clustering towards the signal from all directions. (ethereal music) In fact, these primitive single cell creatures also find each other chemically attractive and swarm together to form a slime mold. Such spectacular feats of one of nature's most simple forms of life can provide clues about how cells might build more complex patterns in higher animals. In multicellular animals, like the worm C. elegans, there's also evidence that cells are communicating with each other. We have seen that one kind of cell, sending out a signal, probably chemical, can affect the development of other cells. This same mechanism could also create patterns. For example, when the signal from the top cell reaches the group of identical cells, the strength of the signal will be felt differently by each of them. Since each cell feels the signal to a different degree based on its position, it will become one of three different cell types. This grated signal has set up a pattern among the cells. - So in a sense what we're seeing is a single cell controlling spatial patterning. One cell sends a grated signal and that grated signal results in three different fates in different positions in the animal. -

[Narrator] In theory at least in the limb of the developing vertebrate there may also be a chemical gradient to which cells could respond, telling them whether to become thigh or toe. Certainly some chemicals have a spectacular effect. The salamander has an unusual ability to regenerate some body parts. This makes possible intriguing studies of the effects on chemicals on limb development. Normally if the hand is cut off, the remaining cells will regenerate the missing part. However if the salamander receives a dose of the chemical vitamin A, the cells of the growing limb get confused and replace more than was missing, a whole new arm instead of the hand. In the development of a human being, the formation of body patterns is vulnerable as well to the presence of chemicals. In the normal uterine environment, the developing embryo must be protected from chemical disturbances which lead to deformity. The most vulnerable time is between 15 and 60 days of gestation as body patterns and organs begin to form and when many women don't even know they're pregnant. Drugs, in rare instances, even over the counter drugs can affect the embryo during this time. One dramatic example was thalidomide, a mild sedative taken by some pregnant women in the early 1960s. Their babies were born with severe deformities. Clearly chemicals affect how cells fall into patterns. After the first two months of development, the major patterns of the human form have been established. Even after birth, the body continues to grow. Somehow it manages to maintain correct proportions of the arms for example. - I'm always amazed by that, that our arms do end up the same length because they start off very small. They're quite independent, one from the other, and it's really like sending up two projectiles, two rockets, and they reach exactly the same heights, well very nearly the same heights after, what, 15 years or 20 years. I think it's astonishing that growth turns out to be that precise. (rapid whooshing) -

[Narrator] Precision isn't just a matter of cells growing correctly. Cells also have to die or stop growing on cue. In adults, red blood cells are dying and being replaced at an enormous rate. Two and half million cells every second. In the embryo, blocks of cell in limb buds die on schedule so that fingers and toes won't be webbed. In the course of an embryo's development, a number of events must be regulated in concert in order for cells to grow, die, specialize and form patterns. Of all the stages an animal goes through, it is this one which requires the most precise control over cell growth and specialization. The extent of this control has been demonstrated in one striking experiment. These innocent looking cells are in fact a potentially deadly kind of cancer cell called teratoma that cause bizarre tumors made up of bone cells, skin cells, hair cells, in fact of all cells at once. They're completely unruly. In this experiment, these cancer cells are being ejected into the middle of a mouse embryo. (soft music) But the embryo doesn't die. It develops normally and produces a perfectly healthy mouse. A mouse which doesn't have cancer and yet those cancer cells have clearly played their part in making the mouse. All the black parts of the mouse in the skin, hair and organs are descendants of those cancer cells, even one of the two eyes. But they are no longer cancer cells. Instead they've been tamed, and forced to specialized, and to become part of patterns in the developing organism. The diseased cells have been brought under control to their surroundings of other normal embryonic cells. Time after time, skirting disaster after disaster, a single fertilized cell grows into a fully developed organism. As they develop, these four embryos will share many things. They will all cleave and go through gastrulation. But one becomes a fish, one a frog, one a mouse, and one a man. Science must explain not only why they are similar but why they are different. The explanation for that must lie in the genes. - The fact that embryo after embryo does develop precisely in the right way suggests that we're not dealing with some sort of serendipitous environmental factor, that there has to be something built into the genes themselves which ensure the realization of the right program time after time at the level of the cell. (light music) -

[Narrator] As a human egg erupts from the ovary, it's already carrying genes from the mother. The genes of the father are contained in the sperm. At the moment of fertilization, they merge to form the unique nucleus of the first embryonic cell. In humans, this nucleus contains 46 chromosomes. 23 from the mother and 23 from the father all of which must be copied every time a cell divides. Each chromosome contains thousands of genes. Genes which instruct the embryo to become a man and not a mouse, a frog and not a fish. As cells of an embryo divide and eventually become specialized, they lose the ability to become any kind of cell. Is there a change in the chromosomes of these cells? Are genes being lost? In plants it's easy to show the genes are not being lost. These are fully grown potato plants. Yet by taking a bit of the leaf, and separating it into individual cells, and growing the cells in culture, one specialized leaf cell can produce a whole potato plant. So each cell must retain all the plant's genes. It's more difficult to prove this in animals. But the British scientist, John Gurdon, show that animal cells keep all their genes throughout development. In a classic series of experiments in the 1960s he took a fully specialized intestine cell from a white tadpole, broke it open, removed the nucleus from that cell, and inserted this package of genes into a newly fertilized green frog's egg whose own nucleus had been gilled. The green frog's egg now had the nucleus. The instructional genes of a white tadpole's intestine cell. If that set of genes was complete it should be able to instruct the embryo to become a white tadpole rather than a green tadpole. But if in the process of development the original white tadpole nucleus had lost genes, it would go disastrously wrong. The experiment was done hundreds of times and in a few cases it worked, producing white tadpoles which then grew up into white frogs. Gurdon had proved that a specialized cell in the tadpole's body still had all of the original genes locked up in its nucleus. One cell could provide the genetic blueprint for the entire animal. (water splashing) - Several experiments over the past 10 and 20 years have indicated most likely that all the cells contain identical genetic information. So it's not so much qualitatively what bits and pieces of chromosome they have but it's what genes are on and off. -

[Narrator] Among the genes laid out on each chromosome, appropriate genes turn on to make proteins that the cell needs at the time. Each gene codes for one type of protein and the amino acids that make up that protein are strung together only when the gene gets turned on. Active genes can be seen at work on these chromosomes. The puffed areas are the active genes, genes which are making proteins. The other parts are shut down. It is the switching on and off of its genes that determines how a cell behaves. These are cancer cells magnified several thousand times. It is now thought that in cancer cells genes which should be off have in fact been switched back on. For example, normal cells know when to stop growing. But when cells turn cancerous like these, they don't. It's not that they grow particularly fast but they don't stop growing when they should. In cancer cells, the genes which control cell division should be turned off but are not. Similarly there may be genes switched on in some cancer cells which enable the cancer to move throughout the body. This ability to move is also seen in embryonic cells like the primitive sex cells. At a critical time of development, their genes for movement switch on. - All of a sudden they galvanized into action, and start to crawl, and they leave the gut, and they crawl up the piece of tissue connecting to the rest of the body. As they do so, they crawl through the tissues of the embryo. So it pushed the other cells out of the way. They behave very much like tumor cells do when they become malignant. Then they crawl around a corner and then they stop. Something also tells them to stop in the right place where they gonad will form and where the gametes, the sex cells of the adult, will eventually differentiate. So then some cell types in the embryo exhibit properties which are very similar to malignant tumor cells in the adult. So the hypothesis is that in a tumor, as a tumor grows, some of the cells in that tumor suddenly accidentally reawaken these genes. If those genes accidentally reawakened, that cell will become motile in the adult. But out of control because there's no target. -

[Narrator] Turning on the right genes at the right time is the basis for the normal development of the embryo. This is what creates each cell's particular characteristics. - There must be a control mechanism for turning on certain sets of genes in certain parts of the organism and turning off other sets of genes in the organism. That's the mechanism we're trying to understand because that mechanism is involved in all of the special characteristics of cells. Turning on certain genes in blood cells means blood cells will have the red pigment hemoglobin in them. Turning on other genes in skin cells will make them produce hair or whatever. The whole process has to be coordinated in a very precise way. -

[Narrator] Researchers study the chromosomes in order to understand how such a process is coordinated. They can isolate genes and try to discover what each one does. So far a relatively small proportion of human genes has been analyzed in this way. - The genetic system in a human has on the order of 100,000 genes in it. These genes form some incredibly complicated circuitry in which genes turn one another on and off. We want to understand that system. Now no scientist has ever understood a system with 100,000 components turning one another on and off. -

[Narrator] So instead scientists turn to simpler organisms. In this case, a fly. - You want a organism that's small and you can see that these flies are not like your house flies. These are little guys. In this cage alone we have probably on the order of 10 to 20,000 flies sitting on those plates, laying eggs, and wallowing in the food. The food is a simple mixture of molasses and a little yeast. In a few hours on those plates you're likely to find as many as between 10,000 and 100,000 embryos. -

[Narrator] The fly is the fruit fly, drosophila. Geneticists love it because it has relatively few genes, perhaps as few as 5,000. Because its life cycle is so short that they can monitor thousands of generations for genetic changes. Some of these genetic alterations can make enormous differences. For example, changes in head shape. - Well the beginning people simply collected every strange looking fly they saw and started keeping notes on what they had collected. These were things with changed eye color, changed pattern of bristles on the cuticle, or changed wing structure, whatever it might be. Hundreds and eventually thousands of different such flies were found. In most cases these changes in the appearance of the fly were due to mutations which were inherited by all of that fly's progeny. In fact there were stock centers where thousands of different kinds of flies, all of the same species but with these little changes in their structure, these mutations, are stored. -

[Narrator] This room is full of bottles of different drosophila mutants. They all differ in some small characteristic. Eye color, wing shape, and so on. The fact that they pass a particular trait onto their offspring proves that the trait is written into the fly's genes. The next question is which genes produce which structures? - Suppose you're interested in how a wing is made in the fly. It is possible to mutagenize, induce mutations, in flies, and find out well what genes are involved in making that wing by looking for mutations that disrupt the formation of that wing. -

[Narrator] A small change in the wing can be the result of a mutation of a single gene, of a single small piece of the gene. This is the stuff that all genes are made of, it's DNA. It provides the basic instructions for the making of proteins and it's proteins that determine what each cell does. The letters on the top line the building blocks of DNA. They code for the amino acids written below them, which strung together, make up one long protein. There may be a 1,000 building blocks in this one gene. A change in just one of them can ruin the protein and cause a mutation. It could be devastating to the fruit fly. It could be lethal. Studies of the drosophila chromosomes that have undergone gene mutations show that most of the 5,000 genes have routine functions general to all cells. - There are genes that encode functions that in the field are usually called housekeeping functions. These are genes required for cells to sort of live, and breathe, and eat, and metabolize, and do all their normal everyday things. Usually it appears that these genes are not the genes that control the development processes. In fact, there appear to be certain genes that are sort of high in some hierarchy we could construct that are central regulatory switches of some sort that control what part of the developing organism develops into what. -

[Narrator] Not all genes then are equal. There are master genes which when activated have far reaching effects. By mechanisms now being explored, they seem to be able to turn on banks of lower genes and coordinate their activity. - We really are looking at a program that's occurring on a level of a single cell. So you could really look at these master genes as programming chips. These are instructing that single cell. It's setting up a genetic program whereby the single cell is going to realize, what we call, a cascade of gene expression. -

[Narrator] This cascade of gene expression multiplied over many cells determines what kind of tissue they will form. These small stabilizers behind the fly's wings are the result of a cascade caused by a master control gene. But if that gene is mutated, a different cascade takes place. Instead of stabilizers, wings are formed. A tiny change in this master control gene completely alters the body pattern of the fly. Master genes that control body pattern are called homeotic genes. - If you mutate the homeotic gene you are likely to transform the tissues of one body segment located at one place in the fly into the tissues of another body segment normally located elsewhere. That is, in homeotic mutations, you often times make the right structure in the wrong place. -

[Narrator] For example, this is a normal fruit fly. Where normally the head sprouts a tiny pair of antennae, this mutant has a pair of legs growing. Changing a homeotic gene has transformed what would have been antennae into legs. - Now there's a number of things to notice about homeotic mutants immediately that are, besides the genetics, they're just astonishing. One thing is that the two ends of the fly are far apart, the head and the genitalia are at the opposite ends of the fly and you don't have to be much of a biologist to realize that. Yet there is a mutant called tumorous head which changes the head and the antenna into genital structures, making a quite embarrassing, quite embarrassing fly. -

[Narrator] Mutations have been found in other organisms such as the tiny worm, C. elegans. These mutations not only control where features develop but also when they develop. - As in the fruit fly, there are mutants in C. elegans that result in homeotic changes that cause one body part to be produced in addition to where it normally would be produced someplace else. But what's remarkable is that in the nematode, in C. elegans, we have been able to identify mutants that not only cause changes in position in body parts, but changes in the time in which the body parts are generated. For example, there are mutants that affect the timing of expression of what essentially is the outermost layer, the cuticle of the animal. Normally an adult animal has an adult cuticle and a larval animal has a larval cuticle. But we have mutants in which a larval animal will have an adult cuticle. We have other mutants in which an adult animal will have a larval cuticle. So what this shows is that you can control different aspects of timing independently and have different body parts developing at different rates. So just as we have genes that have been seen in both flies and worms that control the spatial positioning of certain kinds and parts of the body, we see that there are genes that control timing of particular aspects of development. -

[Narrator] In humans, the search is on for master control genes like those found in flies and worms. Genes which control the timing of development and body patterns. Minor changes in body patterns such as extra fingers or extra toes are fairly common birth disorders. Although partially genetic in nature, they appear to be influenced by environmental factors as well. As in the case of harelip, these appear to be small deviations from the developmental plan. Fortunately some of these disorders can be corrected with surgery. The developmental plan for a human face involves countless thousands of genes. But as in flies, are there a handful of master genes which dictate the basic pattern? How do we find them? There are no obvious homeotic mutants to guide us. We just do not see people with a nose in place of an ear, or a mouth instead of an eye. - Why we don't seem them in vertebrates and man is just not clear. Maybe they're lethal, maybe that they're slightly more complicated or they have to act in concert so that you have to mutate two or three or them to get the effect. The answer is we don't know but in time we will find out. -

[Narrator] At the level of body pattern, humans and fruit flies may be too far apart to bear a comparison. But perhaps the clues that link them are written in the genes. Modern molecular biologists can analyze genes to determine their DNA sequence, to look for patterns in the building blocks that make up specific genes. It's the master homeotic genes that really interest them. Genes powerful enough to turn an antenna into a leg. - As molecular biologists began working on these genes, we were of course looking for things that these genes had in common with each other. Even though the affect of a mutation, one of the genes might be to turn antennae into legs, and in another one of the genes to make an extra set of wings on the fly. Yet the basic idea of what these genes were doing was so similar in the two cases and many other cases that we really were looking for something in common between the molecular structures of these various genes. In fact we found such a thing which is now called the homoeo box. -

[Narrator] In the fly, the homoeo box was a small distinctive sequence of DNA which coded for a unique part of a protein. This sequence was found only in homeotic genes and not in ordinary genes. Was it critical for genetic control? - If the homoeo box was not some sort of a critical component of genetic control, you would expect it to be associated with genes that simply did not have a particularly interesting function in the cell. So far, at least in the fly, that has not been the case. -

[Narrator] Surprisingly this critical sequence started to turn up in other animals. Virtually identically homoeo box protein sequences were found in frogs, they were found in mice. In 1984 they were found in humans as well. For an almost identical protein sequence to be found in so many species suggests it has a unique and possibly universal function. It is an awesome notion, perhaps throughout a large part of the animal kingdom the homoeo box is always the telltale sign of a master control gene. (light music) - This proposal is based on a very simple premise and that is that complicated processes of development are solved once in evolution. You don't just randomly solve these very integrate processes of development more than once. That makes some sense. We're talking about the coordination of many thousands of genes in a developmental circuit. In order to do that you have to somehow evolve a class of controlling genes so we believe. If that's the case, you just don't expect to separately and independently evolve that kind of mechanism on many, many occasions. -

[Narrator] Insects like the fruit fly drosophila and the animals which led to us diverged 500 million years ago. For the homoeo box to be handed down unchanged throughout such a long period of evolutionary time suggests that it's doing something useful. But is it doing the same thing in vertebrates as in fruit flies? That's the important question. We still don't have an answer. If the homoeo box is a component of master control genes that lay down body patterns, then it will be found working at critical times like these. During development, cells must be told where to go and what to become. (ethereal music) From these cells, the spinal cord and vertebrae of a human being will form. If the homoeo box genes are controlling the process, they might be expected to turn up here. Ever since molecular biologists found the homoeo box in a number of human genes, they've been trying to understand the precise role of the homoeo box in human development. At the same time, comparisons with other animals have uncovered another surprising similarity between genes of two very different species. Humans and the C. elegans worm. A master control gene in the worm produces a protein involved in the communication between cells necessary for proper development. - This gene has been studied at the level of molecules for much the same reasons that the homeotic genes and flies have been studied at the levels of molecules. When the DNA sequence of this gene was examined, what was found was that it was similar to the sequence of other genes that have been seen before in animals like ourselves. -

[Narrator] This is part of the protein in the worm coded for by the master control gene that's involved in communication between cells. These are parts of proteins produced by human genes which play a similar role. Some components in both sets of proteins form a pattern, evidence of an underlying structural similarity. These kinds of similarities between human genes and a worm's master control gene encourage researchers to look throughout nature for mechanisms of development that are basic to all life. - So what we hope is that by continuing the detailed studies that are possible of this gene in the worm, we'll be able to understand how genes like this function in people, and also perhaps how genes like this may disfunction in people to lead to certain human disorders. -

[Narrator] The study of simple organisms like the worm has led to startling discoveries about the way that cells develop and the roles genes and their protein products play in cell communication. The molecular study of the master control genes in fruit flies that allow drastic mutations has led researchers to find genes of a similar structure in a wide variety of organisms including humans. But the understanding of the human chromosome and its 100,000 genes is only just beginning, and even when understood, will not reveal all the secrets of human development. - Genetics, our genetic makeup, clearly is defining to a great extent what we can develop into. We're not gonna become penguins or redwood trees. We're clearly all gonna become people. Yet at the same time, the genetics really lays out a blueprint. We know from a variety of studies, for example work on the nervous system, that the way in which we have experienced certain things during our lives can affect certain aspects of the development of the nervous system. We don't yet really know enough about development in detail, particularly in people to know to what extent environmental influences will affect development. But it seems perfectly clear that superimposed upon that basic blueprint of the genes will be environmental influences. -

[Narrator] Science, through observation and experimentation, has uncovered a host of intriguing clues about the nature of embryos in development. That these clues come from so many forms of life shows how fundamental the questions are that we are trying to answer. (soft music) But as our understanding increases, our wonder is not diminished. It is a common occurrence and yet an awesome fact that a human being is formed from a single fertilized egg cell. That even before being born, a baby has traveled a complex and mysterious journey. It is a journey science is striving to understand. But even when understood, it will remain a miracle how babies get made. (mid-tempo light music) For a transcript of this program, send $4 to NOVA Box 322 Boston, Massachusetts 02134. Please be sure to include the show title. To purchase film or video copies of this program for educational use, call toll free 1-800-621-2131. In Illinois or Alaska, call collect, 312-940-1260. (ethereal music) Major funding for NOVA is provided by this station and other public television stations nationwide. And by Allied Signal, a technology leader in aerospace, electronics, automotive products and engineered materials. And the Johnson & Johnson Family of Companies supplying healthcare products worldwide. (light orchestral music) (audience applauds)