CONTEMPORARY READINGS FOR GENERAL BIOLOGY

CRANE

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JOHN W. CRANE
Washington State University

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PREFACE

New information emanating from the biological sciences affects our lives today on a scale never before imagined. Almost daily we hear of deadly diseases for which no cures exist. The AIDS virus, which breaks down the human immune system, has begun a silent invasion of the general population. Investigations continue on cancer, heart disease, and Alzheimer's disease. Although surgical, drug, and radiation therapies do aid in treatment, prevention still eludes us. But there is promise! Research in cellular biology and genetics has opened up new possibilities for treatment and prevention. Genetic engineering, encompassing the relatively new fields of genetic manufacture and genetic substitution, holds promise for preventing and curing genetic disease. In fact, as Madeline Chinnici, author of "The Promise of Gene Therapy," has suggested, "Man will have both the knowledge and the tools to do something that had been unthinkable: reengineer his own genetic composition."

New information regarding other biotic constructs is also making headlines. Ethology—the study of behavior—is beginning to offer new insights into behavioral responses of humans and other living systems. Ecologists are beginning to understand the importance of diversity—both biotic and abiotic—in the maintenance of properly functioning and viable ecosystems. They stress the importance of plant and animal system interactions and how these are important in maintaining a healthy biosphere. Much concern is being expressed regarding our continuing environmental degradation, from the threat of "nuclear winter" to the effects of "high-tech" pollution.

We also are in the process of examining older concepts, such as evolution, and attempting to refine earlier doctrines in light of modern scientific inquiry. New attempts at explaining the absence of observable continuity between species have resulted in the concept of "punctuated equilibrium"—evolution by spurts, rather than by gradual change. The continuing reexamination of Charles Darwin's hypotheses reveals that, with some modifications, his theories hold true.

The biotic condition, based in the sciences of physics and chemistry, is perhaps the most dynamic science. The quality of all life depends, in large part, on a human understanding of the intricacies of the biotic/abiotic connection. For it is we who have control.

In producing an anthology dealing with contemporary biological subjects, an attempt has been made to select articles that (a) are compatible with the better textbooks now available, such as Wadsworth's *Biology: The Unity and Diversity of Life*, Fourth Edition, by Starr and Taggart; (b) are relevant to information presented in these texts; and (c) perhaps most important, help enhance the excitement and importance of the biological sciences. ■

CROSS-REFERENCE GUIDE

to Starr and Taggart's **Biology: The Unity and Diversity of Life**, Fourth Edition

This cross-reference guide correlates selected readings in this book with units and chapters in Starr and Taggart's *Biology: The Unity and Diversity of Life*, Fourth Edition.

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CELL BIOLOGY

Human life, as does most, begins with but a single cell. In our case we each begin as a cell containing 46 chromosomes—23 from each parent. From this beginning each of us eventually matures into an individual containing an almost uncountable number of cells, many of which are far different from the original. Why and how these cells evolve from a single ancestor to widely divergent cellular components has received much investigation. In the article "The Fate of the Egg," Stephen S. Hall reports on research that has taken us to the brink of understanding how cellular differentiation occurs and what the implications of this information may be.

Cancer—cells reproducing out of control—usually leads to the death of the individual, unless surgical, radiation, and/or drug therapy works. A cure? In "Cancer: Cautious Optimism," John Langone suggests that despite all the ballyhoo about cancer treatment, a breakthrough is not at hand. But hope continues to rise as scientists discover more about cancer's biology.

Breakdown of the human immune system and its terrible consequences are examined in "AIDS: A Growing Threat." Research now suggests that inactivation of our immune system is caused by invasion of helper T cells by the AIDS virus. When infections occur, T cells no longer have the ability to recognize antigens and become factories for producing more virus—a deadly circle from which there is no escape. ■

THE FATE OF THE EGG

Life begins as a single, highly organized cell. And it unfolds with confounding precision.

BY STEPHEN S. HALL

THE BIOLOGISTS WHO investigate nature's deepest and longest-running mystery often use the term fate map to describe the startling transformations that lie in store for the fertilized egg. It is one of the more venerable terms in embryology, and one of the most appropriate, too, for destiny and geography indeed intersect within the magnificent speck of DNA and cytoplasm that is an egg on the edge of becoming a organism. In this one cell, the entire genetic bill of lading for an animal, be it fruit fly or human, is stored, waiting to unfold with miraculous precision. It is that process of life unfurling—of cells becoming brain or backbone, of genes selectively flashing on and herding cells toward their certain fates, of tissues aggregating and differentiating toward ever more specific tasks—that both confounds and as surely delights developmental biologists.

"Embryology appears to be unique among modern experimental disciplines in biology in not only still possessing but still celebrating its ancient unsolved problems," noted Rudolf Raff of Indiana University and William Jeffery of the University of Texas in 1983. "Those are still our problems," Raff says now. "We just have better ways of getting at them." Centuries of uncertainty have made embryologists a cautious lot, yet progress made in recent years has been sufficient to prompt Eric H. Davidson of the California Institute of Technology to say, "One now has a chance, for the first time, of understanding the workings of a process that has been around at least 550 million years."

For more than a century, developmental biologists have charted regions of the egg much as ancient cartographers made their first tentative interpretations of the New World. The amphibian egg, to cite a much-studied example, has been viewed as a large globe with a northern hemisphere and a southern hemisphere, north and south poles, and an equator with latent special cellular destinies. The rough outlines of egg cells like this have been known for some time. But researchers are now in a position to journey, as it were, to the center of the planet, where, it may turn out, geography *is* destiny.

Molecular biology has proven to be the vehicle of choice for this journey, opening up the interior of the egg and the embryo to a degree never before achieved. But the story begins with the egg cell itself. As a model, John C. Gerhart, a developmental biologist at the University of California at Berkeley, holds a six-inch ball of Styrofoam in his hand. It represents the unfertilized egg of *Xenopus laevis*, the African clawed toad. "There's a wonderful geometry to it," says Gerhart. "It's no mean feat to come up with one coherent fate map in a big egg like this."

The egg arrives for its zygotic rendezvous with sperm in a state of exquisite preparation. (It's sometimes hard, in fact, to view the sperm cell as having anything other than a walk-on role during fertilization.) The northern hemisphere is dappled brown with pigment granules, and the egg's southern hemisphere is pale yellow to reflect its dense inner swirl of yolk platelets. The fates of the regions have been well mapped. The northern, or animal, hemisphere is nearest to the nucleus and destined to become the nervous system and the skin. The southern,

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or vegetal, hemisphere will develop into the digestive tract, and the equatorial region gives rise to skeletal, muscle, and circulatory tissues. The question, of course, is how.

"It's thought," says Gerhart, "that this hemispheric structure, with pigmented and unpigmented hemispheres, represents a real polarity, so that inside the egg, the cytoplasm may be different in the different areas." Indeed, deep inside the egg lies perhaps the organism's most precious inheritance: molecules passed down from the mother, such as maternal proteins and maternal "messages" in the form of messenger RNAs that are waiting to be translated into protein. It is suspected that these molecules, segregated roughly into the separate hemispheres, wheel into action later on in development by tripping genes into action. Embryonic cells have genes that respond to two major cues, or determinants, as they develop: one is the influence of neighboring cells, known as induction, and the other is the influence of materials in the egg, such as maternal messages. The latter type of activation occurs in certain cells and not in others, possibly because of the localization of these signals in particular areas of the egg.

It so happens in the case of *Xenopus* that the sperm cell can only penetrate the northern hemisphere of the egg. As soon as the sperm enters, however, the fertilized egg undergoes two significant planetary tremors. First, the thin outermost layer, or cortex, of the egg separates from the cytoplasm, creating a structure roughly analogous to the Earth's crust sitting above its core. Then, more critically, the outer sphere slides over the inner one for about 30 degrees. The sloshing motion brings material from the southern hemisphere into contact with northern hemisphere material. This smear of contact, known as the gray crescent, determines no less than the dorsal side of the toad—the side that, in all vertebrates, blossoms into spinal column and brain.

No one yet knows why this exceedingly precise rotation occurs, or why the gray crescent forms 40 to 80 minutes after fertilization. But the egg is doomed to a kind of developmental decapitation if this maneuver doesn't take place. By tampering experimentally with the rotation, researchers found that anything less than the 30-degree movement results in embryonic flops. "If the movement is small, about five degrees, the embryo just has a tail," Gerhart explains. "If it is about 10 degrees, it gets a tail and a trunk. If it is 15 degrees, it gets the tail, trunk, and some hindbrain structures. At 20 degrees, it gets the midbrain structure. At 30 degrees, it gets the forebrain structure. The extent of movement sets the context for later regional gene expression." In other words, the degree of "slosh" brings elements from the two hemispheres into contact, and this commingling seems to affect later events.

One hundred minutes after fertilization, the *Xenopus* egg divides into two smaller cells called blastomeres. This event, known as cleavage, is a general feature of development that continues with successive cells until the embryo becomes a hollow sphere of cells, or blastula, and reaches a developmental stage known as gastrulation, when groups of cells begin to fork off into one of three major fates: an outer layer, the ectoderm; an inner layer, the endoderm; and an intermediate layer, the mesoderm. The endoderm ultimately gives rise to the gut and digestive tract, while the ectoderm develops into skin, sense organs, and the entire nervous system. Lying between the two, the mesoderm becomes muscle, blood, and sex glands.

Gerhart argues that many of the signals sending cells peeling off to pursue their individual fates—the nervous system here, the gut there—seem to be built into the egg. There are outside cues, but the egg seems to march to the beat of its own drummer a good deal, too. "My impression," Gerhart says, "is that there are lots of scheduled events. This egg, once it's been fertilized, has a whole series of steps that it will proceed through." Indeed, the mere puncturing of a *Xenopus* egg with a needle rather than sperm sets off the same series of events: the cortex around the egg, the rotation, the gray crescent. "The capacity is there from the very beginning. There's an enormous amount the cytoplasm can do before any gene activation actually occurs."

THE DEVELOPMENTAL CUES sequestered in the egg's cytoplasm are what most intrigue Eric Davidson and his group at the California Institute of Technology in Pasadena, where one world view can be inferred from a poster on the wall of Davidson's basement office. "It is not birth, marriage, or death, but gastrulation which is truly the most important time in your life."

Davidson, a leather-vested cell biologist, has chosen to study the developmental cues in sea urchin eggs. One reason is that there's no shortage of raw material, as colleague Frank Calzone demonstrates by injecting potassium chloride into a fertile female *Strongylocentrotus purpuratus*. Moments after the injection, the urchin, its spines waving, disburses a soft precipitate cascade of yellow-orange eggs into a beaker filled with seawater. Within 10 minutes, there is an eighth of an inch of material at the bottom of the beaker—perhaps as many as five million eggs.

Davidson and his collaborators, notably Roy J. Britten of CalTech, have cast the problem of development in stark molecular terms: Sea urchin cells become committed to a particular fate, they believe, when particular genes switch on, so they want to know why these genes are turned on in certain cells and not in others. To that end, they have focused their attention on three cell lineages—the gut, the skeleton, and the embryonic skin—and are attempting to identify the genes that seem to nudge cells toward the formation of these tissues. They know these cells begin to fulfill their particular destinies within 26 hours of fertilization. But, again, the question is how.

Molecular biology has enabled these researchers literally to see genes turning on in the developing embryo, and consequently the fate of cells can be directly tied to the activation of specific genes, providing a degree of focus almost unimaginable five years ago. James Lee of CalTech and Robert Angerer of the University of Rochester have studied, for example, a gene known as *CyIIIa*, which codes for a protein called actin. About 15 to 20 hours after fertilization, this gene blazes into action but only in one particular cell lineage, the aboral ectoderm, which forms the skin of the sea urchin larva.

Another example concerns the cell lineage that builds the skeletal structure. Within five hours of fertilization, the sea urchin egg has subdivided four times. At

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this fourth cleavage, a cluster of four cells called micromeres form at the southern end of the embryo. After a subsequent division one hour later, there are four small micromere cells and four large ones. The four large cells are destined to form the entire skeleton of the free-swimming larva.

When the subpopulation numbers 32 cells, these so-called primary mesenchyme cells become uncoupled from ongoing cell divisions elsewhere in the embryo. Like independent creatures, they dissociate from each other and wander around on their own in the hollow interior of the spherical blastula. Finally, as the gastrulation process begins, these cells link back up. Joined together in cablelike structures, they begin to secrete a spicule protein that eventually will develop into the skeleton of the embryo.

These cells clearly run through a complicated, highly synchronized series of events. With the use of radioactive or fluorescent tracers, the appearance of specific gene products such as proteins can be detected in the developing embryo. Like a glimmer of destiny, these glowing proteins intimate the shape of things to come, even before morphological characteristics are completely clear. The appearance of new proteins, of course, means that previously mute genes have somehow cleared their throats and begun to express themselves. It is suspected that molecules inherited from the mother, either proteins or messenger RNA, play a role in activating these genes; the cytoplasmic organization in the egg suggests that some of these molecules might have been distributed to certain neighborhoods of the embryo, so that the changes they exert are local.

The next step, however, is to figure out what it is about these genes—what is intrinsic to the sequence of nucleotides, or base pairs, along a particular stretch of sea urchin DNA—that has them blinking on and off at crucial junctures of embryogenesis. That work is already underway, thanks to an ingenious use of "fused genes," which, for example, combine part of the *CyIIIa* gene for actin with another gene that makes an easily detectable bacterial protein dubbed CAT. Using micropipettes, researchers can inject this recombined DNA into unfertilized eggs. Upon fertilization, the fused gene is incorporated into the nucleus and goes along for the ride during development. When *CyIIIa* genes normally turn on—about 20 hours after fertilization—the CAT enzyme lights up in assays. The same approach will provide an extremely precise timetable for key developmental genes.

"That gives us a spectacular advantage," says Davidson. "We're going to be able to learn just what is the DNA sequence information required for this developmental specification of gene activity. If we can find out, by the introduction of cloned DNA, what regions of genes are required to get them to turn on at the right time in the right place, then we at least have a chance of determining what molecules interact with those regions and cause this event to occur."

AS POWERFUL AS IT IS, molecular biology has not cornered the market on embryological insight. Since the beginning of this century, geneticists have picked through millions of mutant fruit flies, identifying tiny genetic glitches from white eyes to misshapen wings, in an effort to understand which genes control what. In his third-floor laboratory at CalTech, amid hundreds and hundreds of stoppered flasks filled with fruit flies, working in a cluttered room where photographs of classical geneticists like Thomas Hunt Morgan and William Bateson are propped up against a blackboard, a diminutive, gentle-voiced, silver-haired biologist named E.B. Lewis set the stage for perhaps the most interesting revolution to hit developmental biology in recent years.

For virtually his entire career, the 67-year-old Lewis has studied the bithorax complex of genes, which controls the orderly development of many of the fruit fly's body segments: two thoracic and eight abdominal segments, one after the other. In the patient manner of the classical geneticists, he has created mutant flies, carefully identified the growth disorders they displayed, and began to correlate the insects' errant development with a class of "master switch" genes. Lewis embarked on this immensely complex genetic odyssey in 1946, before the structure of DNA was even known, yet recent advances in recombinant DNA technology have confirmed his predictions and created probably the hottest area of focus in developmental genetics: the homeotic genes.

Homeotic genes appear to have a kind of hierarchical control over other genes in developing fruit flies. Lewis first began by studying mutants of the bithorax complex. "It looked as though what appeared to be one large genetic unit with many controlling properties was actually a cluster of genes, and that's what they turned out to be—40 years later," he says now. "It is a cluster of perhaps 10, possibly 30, lined up in a row in the chromosome. The astonishing feature is that the genes are lined up in the same order that they seem to turn on during development, and that order is the same as the order of segments along the body axis."

Philip Beachy, a graduate student in the Stanford University laboratory of David S. Hogness, has worked out some of the molecular details of the bithorax complex and likens the function of these homeotic genes to a corporate hierarchy. "You could think of them as executive officers in a big corporation," he says. "The vice president in charge of the third leg may be in charge of a whole slew of other functions." This control appears to be exerted because homeotic genes make regulatory proteins that in turn switch on other genes, initiating the cascade of genetic activity that each distinct fly body segment undergoes, just as an executive is responsible for everything from policy to clerical functions within a particular department.

When homeotic genes fail to flip their switches, major disruption ensues. Legs may grow out of the insect's head where the antennae should be, or a second set of wings may sprout where none should be. "If you delete *all* the genes of the bithorax complex," explains Beachy, "what you see is that all the segments of the fly develop as if they were the second thoracic segment." In other words, development gets stuck on the very first of the 10 body segments under bithorax control, and this segment is reiterated again and again because the embryo doesn't have the genetic know-how to develop the next nine posterior segments. Most of these mutations never see the light of day because mutant *Drosophila* embryos are doomed not to hatch, but since the fly wears its skeleton on the

outside, its rigid larval skin, or cuticle, faithfully registers all these odd developments, making them easy to spot.

Lewis predicted the developmental role of these bithorax homeotic genes in 1978. By 1983, a team of molecular biologists led by Welcome Bender of Harvard had isolated and cloned this gene complex. In the meantime, a second homeotic complex in the fruit fly has been identified by Thomas C. Kaufman's group at Indiana University. It is called the *Antp* (or *Antennapedia*) complex, and it seems to control the development of the head.

Once this executive suite of developmental control was breached in fruit flies, researchers obtained a kind of molecular skeleton key that opened up other homeotic sites and provided startling surprises. In 1984, the laboratories of Walter Gehring in Basel and Matthew Scott at the University of Colorado independently reported the existence of several mysterious but much ballyhooed patches of DNA in the neighborhood of the fruit fly's homeotic genes. This strip of DNA has come to be called a homeo box. No one is quite sure what it does, but it is beginning to appear with surprising ubiquity up and down the phylogenetic ladder. Three popped up in the bithorax complex of fruit flies, and two turned up in *Xenopus*. Now, according to recent work by William McGinnis and Frank Ruddle of Yale and Michael Levine of Columbia, virtually the same strip of DNA also occurs in the chromosomes of mammals like mice and humans. The segment is short, measuring only 180 base pairs of DNA, but the odds against an identical segment of that length turning up in more than one species are astronomically high. Needless to say, all the firepower of molecular biology is being trained at the homeo box in an effort to explain its enigmatic role, which many believe has to do with coding for a protein that controls other genes. The idea that so particular a segment of DNA could be preserved and duplicated in such a wide range of species suggests that it derives from an ancestral gene that was so successful in orchestrating development that evolution appropriated it for more widespread use. "Generally, you only have one chance in evolution," notes E.B. Lewis. "You don't have a chance of evolving whole new systems without somehow making use of some common ancestral genes to do it with." The homeo box, he suggests, may be an ancient mechanism for regulating the constellation of genes involved in making diversified tissues in higher organisms.

LURKING IN THE BACKGROUND of all this work is the question of how genes determine the fate of a cell, and implicit in that question is an even more fundamental one: How does the switch get flipped? What are the genetic mechanisms that account for the founding of an entire population of cells, and later, tissues?

Explaining how genes switch on and off, of course, would be of fundamental consequence for all of biology. It would go a long way toward explaining how genes become "hard wired"—permanently activated, like the globin gene in red blood cells, or permanently repressed, like the same globin gene in a brain neuron cell. The theater of activity for such inquiry tends to be the cell, and it hinges on the complex affinities of molecules floating around in the cytoplasm for certain patches of DNA in the nucleus. How do these mechanisms work?

Donald Brown, a researcher at the Carnegie Institution of Washington in Baltimore, Maryland, has balanced these huge questions atop a single, tiny, cellular building block known as 5S ribosomal RNA. Ribosomes, which are partly made of RNA, are the factories in each cell where proteins are assembled. Most genes code for protein products and use messenger RNA to translate their messages at the ribosome. But ribosomal 5S RNA genes code for a structural RNA that is actually part of the ribosome.

It is a complex story but truly at the heart of development's conundrums. In the developing *Xenopus* egg cell, the 5S gene comes in two families. There are nearly 80,000 5S genes active in the oocyte. About 1,600 other 5S genes, called somatic 5S genes, are also active, but, unlike oocyte genes, they remain active throughout the life of the organism. The oocyte and somatic 5S genes make very similar 5S RNA molecules, and they both work flat out, making huge amounts. Then, after the egg cell is fertilized, a dramatic change occurs. The oocyte genes mysteriously shut down. The genes are there but inactive. Only the somatic 5S RNA genes continue to work. "That's the developmental control that we have to explain," says Brown. "Why is the oocyte gene family turned on in oocytes, and why is it off in somatic cells?"

The 5S gene, it appears, turns on when at least three distinct protein molecules, which fit together like a biochemical jigsaw puzzle, sit smack dab in the middle of the 5S gene on a patch of DNA about 50 base pairs long, a patch that Brown calls the internal control region. This superstructure of proteins clamped on the DNA sticks out like a landmark and is recognizable to an enzyme known as RNA polymerase III, which cruises around in the nucleus. This superstructure not only functions as a landmark but somehow manages to guide and align polymerase with the 5S gene so precisely that the enzyme copies—or transcribes—the genetic information for making 5S RNA with great fidelity. Only one of the three protein or factor molecules has been identified. Known as A, it was recently described by Robert Roeder while at Washington University in St. Louis. Factors B and C are being investigated now.

The interaction of these factors with the 5S genes also appears to account for the remarkable shutdown of the oocyte gene family. Brown's group has determined that there is a staggering excess of Factor A in the egg cell: about 10 million molecules for *each* 5S gene. Brown's group has also discovered that the key difference in the control region of the oocyte 5S gene and its somatic cousin is the sequence of a mere three nucleotides of DNA. That infinitesimally small discrepancy, in fact, is sufficient to give somatic genes a huge competitive edge over the more numerous oocyte genes: Evidence suggests they grip Factor A many times more tightly.

That advantage doesn't make much difference in the egg cell, saturated as it is with millions of Factor A molecules. But after fertilization, the concentration of Factor A molecules falls precipitously until there is only one molecule for every four or five 5S genes. In this situation, the somatic genes have a distinct advantage. Without Factor A, the oocyte 5S genes in a sense lose their landmark sta-

tus—the enzymes can't "see" them, and the genes remain unread.

In somatic 5S RNA genes, however, this transcriptional superstructure somehow manages to remain visible to the enzyme. And by late development, the smaller family of 5S RNA genes is stably turned on while the larger family is stably turned off. This strange superstructure is still ill-defined, but preliminary descriptions suggest the molecular interactions involved in turning certain genes on and off. Is it possible, asks Brown, that these stable, transcribing complexes provide a kind of memory effect that establishes the destiny of a cell? Gene determination, Brown believes, is "probably the most important next question to be answered about developmental phenomena."

WHAT HAPPENS *after* a cell has become committed to a general fate, such as becoming a blood cell or a liver cell? How does this kind of cell acquire the more specialized traits associated with particular body tissues? This movement toward increasing specialization is called differentiation, and it, too, seems to evolve as a particular ensemble of genes gradually becomes active in the descendants of an early cell.

An incisive attack on this problem has been mounted by Beatrice Mintz, a scientist at the Fox Chase Cancer Center in Philadelphia, who has focused her work on mammals. More specifically, Mintz is trying to find out how a mouse embryo manages to establish its population of various blood cells, known collectively as the hematopoietic system, with only a few founder cells.

All the different cell types of this system, from red blood cells to various specialized white blood cells, derive from a small number of ancestral cells with the imtimidating name of totipotent hematopoietic stem cells. These stem cells appear to arise in the liver when it begins forming, on the 10th day of fetal development. In the liver, the cells continue to divide and gradually yield more differentiated cells, which enter the circulation of the fetus. Then, around birth, some stem cells reach the bone marrow, where blood cells are manufactured for the duration of the animal's life. Through a complicated series of maneuvers, including the injection of healthy stem cells into the placentas of mouse fetuses with defective stem cells, Mintz has recently shown that these genetically disabled fetuses could be "rescued" by the transplanted cells, which yield normal blood cells. It has also been determined that the entire blood system of the surviving mice can develop from a single normal stem cell.

"Nobody has actually seen a hematopoietic stem cell or figured out a way to get a potful of them," Mintz cautions. Nonetheless, the work done so far has allowed Mintz to develop a hypothesis that might explain how, from a single set of founder cells, the entire blood cell population can branch out and yet constantly renew itself. It appears that the founder cells and some of their progeny have an extensive capacity to renew themselves, slowly but with great persistence over the lifetime of the organism, so that there are always stem cells in the system. At the same time, this cell has the ability to produce daughter cells that, although still stem cells, have slight differences: they have a shorter self-renewal capacity. Within this hierarchy of stem cells, successive generations of stem cells differ ever so slightly until ultimately progenitors to the specialized cells typical of the blood system population are produced. This model might well apply to other developing tissues as they undergo differentiation, and the Mintz group hopes soon to examine the genes that may be influencing the process.

"I doubt it's a simple one-step process, whether these stem cells are precursors of blood, skin, or whatever," says Mintz. "Going from the most primitive cells that have made the commitment to be a certain class of cell to much more specialized cells surely has to involve a lot of different genes. The idea that all the old ones turn off in concert and all the new ones would turn on in concert is extremely unlikely. Differentiation is not a single-step process but involves step-wise commitments."

A more molecular view of what may be going on in differentiated cells has emerged from the enterprising work of Keith Yamamoto and his group at the University of California, San Francisco. They have focused on genetic elements called enhancers, which appear to be two or more stretches of nucleotides adjacent to and sometimes within genes. As their name implies, they seem to enhance the efficiency with which a gene churns out its designated protein product.

For 10 years, Yamamoto's group has explored this problem as it pertains to a class of steroid hormones called glucocorticoids, which selectively collaborate with specific genes in, say, liver cells—a classic example of differentiation. What makes these particular genes so receptive to these hormones? When a hormone molecule attaches to a liver cell, for example, it combines with special proteins known as receptors that, in Yamamoto's words, "cruise around areas near the cell membrane." Once they meet, the hormone changes the shape of the receptors and confers on them a unique "go-between" quality that allows them to insinuate their way into the nucleus, seize onto the enhancer patches of DNA, and thereby influence nearby gene activity.

Yamamoto, however, has taken the role of enhancers one step further—at least theoretically. His group and others have suggested that enhancers might have a kind of dual role in cell differentiation. In a trigger role, enhancers would accomplish a one-time, irreversible activation of a gene. Thus, they would hardwire the function of a cell. This could occur when a protein plops down on or near the enhancer. Once it lands, this agent, a transcription factor, doesn't budge, and the gene is permanently on.

In a modulator role, on the other hand, enhancers would control the waxing and waning gene activity, consistent with the periodic appearance of hormones. When hormone-unleashed proteins meet up with a triggered gene, they could form short-lived but powerful interactions that would take a turned-on gene and dramatically boost output. An untriggered gene, by contrast, could never be influenced by these regulatory proteins. To view it another way, Yamamoto's model views enhancers as functioning something like a dimmer switch on a lamp—the trigger enhancers would behave like a basic on-off switch, and the "modulator" enhancers would act like adjustable controls, so that the output of protein, like the output of light, could be made higher or lower or turned off, depending on circumstances.

Molecular biology has shown that genes are the entities that control the

synthesis of proteins, but developmental biology is beginning to reveal a surprising and provocative new function. Changes in genes active during development may drive evolution itself. This is one of the most exciting new domains of the discipline.

Evidence for this dramatic new function is beginning to accumulate, thanks to a tiny nematode named *Caenorhabditis elegans*. These faint, white, wiggling burghers of wormdom graze in the soil of probably every backyard from Bangor to Honolulu. They measure about one millimeter in length, dine on bacteria, and complete their developmental journey, from embryo through four larval stages to adulthood, in about 63 hours. Each adult hermaphrodite contains exactly 959 cells, not counting germ cells, and the origin and fate of each and every one of those cells has been painstakingly mapped, which prompts Massachusetts Institute of Technology biologist H. Robert Horvitz to boast, "We know this animal inside and out."

On the wall in Horvitz's office is the fate map of *C. elegans*, resembling a kind of schematic rendering of a railroad switching yard. The resemblance is apt, for *C. elegans* researchers have been able to identify key developmental genes that, like the homeotic genes in fruit flies, play major switching functions. In the classic manner of genetic research, these genes have been revealed by mutation—the time-honored strategy of breaking or altering a gene and then seeing what changes, if any, pop up in the organism.

In just such a manner, researchers identified so-called lineage or *lin* genes. These genes act like binary switches, meaning that they route a cell's progeny toward one destiny, Fate A, when the gene is on, or toward Fate B if the gene is off. For example, a gene known as *lin-14* exercises powerful control over the type of cuticle, or outer skeletal structure, formed at various times during development. Horvitz's lab has shown that when the *lin-14* gene is on in early development, the so-called seam cells form cuticles typical of the larval stage. When *lin-14* shuts down, the seam cells switch to adult cuticle formation. Many other developmental events are similarly affected by *lin-14*. The most interesting wrinkles occur, however, when mutations disturb this delicate timing. If the *lin-14* gene fails to shut off when it is supposed to, certain cells are unable to escape the larval stage, even if the rest of the organism is maturing around it. If *lin-14* fails to turn on, conversely, certain cells are, in a sense, born adult, completely bypassing the characteristics of the first larval stage and out of sync with the rest of the developing larva. In an organism with so few cells, such mutations can dramatically change the worm's overall structure.

Those disproportionately significant changes are what excite Horvitz and colleague Victor Ambros of Harvard University the most. They believe that genes that act like *lin-14* may play a decisive role in species variation because simple changes in timing can produce profound developmental and morphological changes. "The characteristics of all these genes, the so-called heterochronic genes that affect timing decisions, are *precisely* those characteristics that some evolutionary biologists have been looking for," says Horvitz. Mutations in genes that disrupt the timing of developmental events could be the little engines driving major evolutionary changes.

MOST RESEARCHERS AGREE that it will be a combination of astute genetics, powerful molecular biology, and good old-fashioned cell biology that, in concert, will move us closer to understanding how cells make their crucial decisions and an organism's fate map thus unfolds. "The excitement at the moment," says Robert Horvitz, "is that progress is being made on all fronts. We hope that all of those things can be unified and tied together in a way that will make sense and perhaps even be aesthetically pleasing."

No one promises instant answers. After all, the mystery also puzzled Aristotle. A fitting reminder of the difficulty is suggested by a print on the wall above John Gerhart's desk in Berkeley. It shows an Egyptian mosaic populated by a splendid array of crocodiles, hippopotamuses, storks, and snakes. The goal that developmental scientists seek is nothing less than to explain how a single monochromatic tile called the fertilized egg becomes the vast, extravagantly hued, multiplicitous mosaic that is life. ■

THOUGHT EVOKERS

- We all begin life as a single cell. Explain what is currently known regarding a cell's ability to differentiate into widely divergent cell types.
- Discuss the recent advances dealing with cellular differentiation. What concepts are now thought to help explain cellular differentiation?

CANCER

CAUTIOUS OPTIMISM

Despite the interleukin-2 ballyhoo, a breakthrough isn't at hand. But hope is, in findings about cancer's basic biology

BY JOHN LANGONE

When, in early December, the nation's newspapers, magazines, and television networks trumpeted the news of an experimental treatment that could transform the body's disease-fighting white blood cells into killers of cancer, the cure for the deadly disease seemed finally at hand. The information seized upon so eagerly by the media had appeared in the *New England Journal of Medicine* under the names of members of a research team at the National Cancer Institute (NCI) led by Dr. Steven Rosenberg, the comforting spokesman for the surgeons who operated on President Reagan for colon cancer last summer. The NCI report was indeed heartening: in eleven of 25 severely ill cancer patients who underwent the new treatment, tumors shrank by about 50 per cent or more. In one patient the tumor regressed completely. Interleukin-2, a naturally occurring immune-system activator that plays a key role in the experimental therapy, briefly became a household word. Thousands of cancer victims phoned NCI and the American Cancer Society with the same request: How and when could they get it?

The callers were told that the number of patients who could be given the experimental treatment was strictly limited. Rosenberg's group is able to treat only four to eight patients a month. Moreover, it was soon made clear that interleukin-2, despite the remarkable early results, would require years of further testing before it could become—if it ever does—a standard treatment. It's complicated, time-consuming, and expensive. There are toxic side effects: chiefly fluid retention, which can cause a weight gain of as much as 30 pounds during the first few weeks of therapy; breathing difficulties; and kidney and liver dysfunction. Indeed, one patient in Rosenberg's ongoing study died after the treatment. "This is a promising first step in a new direction, but it's not a cancer cure in 1985," Rosenberg warned. "It's a toxic treatment which can be severe, and one of the major challenges we face is an attempt to reduce the toxicity."

Interleukin-2 may be cause for what researchers like to call cautious optimism, or it may be just another example of media hype, amplified by the researchers themselves and by the cancer charities that thrive on such promising reports. The interleukin-2 story also underlines several important facts about cancer research: the progress that has been made in unraveling the basic mechanisms of the disease may eventually unlock the secret of how to prevent it, but until that glorious day, we would do well to take the precautions known to be effective in preventing various cancers *(see table at right,* et seq.), because researchers still have a long way to go before uncovering therapies that can significantly increase the longevity of cancer victims.

A case in point: a recent issue of the journal *Cancer Treatment Reports* carried several of the sort of sobering research papers that, because they're devoid of hope, of any mention of the word cure,

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are rarely cited by the mass media. One of the reports dealt with the efficacy of an anti-cancer drug, tamoxifen, when it's used as part of a three-drug regimen. "It can be concluded," said the paper, "that the addition of tamoxifen does not statistically improve either the time to disease progression or survival in women with metastatic breast cancer." Another report painted an equally bleak picture: "The results are disappointing. It is concluded that trilostane alone is not a useful agent in the treatment of advanced breast cancer."

With cancer drugs, it seems that disheartening results come with the territory. Every year between 1955 and 1975 thousands of agents of potential use against cancer cells were tested. But of the 30 or so drugs currently available, most came out of laboratories between 1940 and 1965—and of those 30 or so, only a handful are considered mainstays in fighting cancer. And these drugs are hardly unmitigated blessings; certainly when they're good at arresting cancer, they can bring about dramatic results, but when they're bad, as they so frequently are, their side effects are devastating.

Chemotherapy has worked well against acute lymphocytic leukemia, markedly increasing the cure rate among children. It has also recently chalked up a few successes in some tumors that are hard to treat, like lung and (when combined with radiotherapy) pancreatic cancers. In the past year, reviews of breast cancer studies have shown that chemotherapy and hormonal therapy can be effective in reducing the numbers of deaths from that disease. Early drug treatment has had some effect on rectal, head, and neck cancers, too.

However, drugs are still inefficient in treating carcinomas, the tumors that constitute 80 to 90 per cent of all malignancies and that originate in the epithelial tissue, which makes up the skin and lines all "hollow" organs of the respiratory, digestive, and urinary systems. And drugs can be highly toxic; they kill healthy cells as well as cancerous ones. Shooting through the body in scatter-gun fashion, they can destroy the cells in the delicate lining of the stomach and intestines, causing nausea and vomiting, and damage the follicles of the hair, causing it to fall out in clumps. Doxorubicin, the most widely used and broadly active drug, has proved effective against breast cancer and soft-tissue sarcomas when combined with other drugs. Unfortunately, it can also injure heart muscle cells. Five per cent of patients who've been treated successfully with drugs or radiation for Hodgkin's disease and lymphoma eventually develop leukemia as a result of their therapy. But perhaps the most alarming fact about cancer drugs is that certain cancer cells seem to develop a sort of biological "intuition" and become resistant to them. "Not much chemotherapy that looks promising has come out of NCI in the last eight to ten years," says pharmacologist Joseph Sinkule of the Michael Reese Hospital and Medical Center in Chicago. "The number of new effective drugs with tolerable side effects has plateaued."

Much the same could be said for radiation and surgery, the other conventional forms of cancer treatment. There have been refinements in non-drug procedures: doctors now treat many victims of bone cancer by removing and replacing a section of bone rather than by amputating; improvements in surgical techniques have reduced the need for permanent colostomies; powerful laser beams can be sent through an endoscope to vaporize cancerous tissue in the esophagus; local tumor removal appears to be as effective as total breast removal for many women with early-stage breast cancer; for patients undergoing radiation therapy, CT scanning helps therapists zero in on a tumor, thus sparing normal tissue; hyperthermia, the use of heat, combined with drugs is having some success against advanced localized head and neck tumors.

Still, some researchers question whether these refinements will yield long-term benefits. Permanent colostomies may be a relic of a cruder form of surgery, but survival rates for colon cancer haven't improved significantly. The same might be said for breast cancer: the newer operations are less disfiguring, but they cure no more patients than radical procedures. Lasers have revolutionized surgery, but in the case of, say, esophageal cancer, doctors who use them emphasize that the treatment doesn't lead to a cure. The tumor almost always grows back.

In sum, cancer treatment may be buying a bit more time and comfort for some patients, but the improvement in survival rates (i.e., the proportion of victims who live for at least five years after their cancer has been detected) for the main forms of the disease may be the result of better diagnostic techniques and earlier diagnosis, not of better treatment. Lung cancer, the nation's leading

THE FACTS ON 10 OF THE MOST DANGEROUS CANCERS

LUNG

Incidence: 144,000 (all figures are National Cancer Institute estimates) new cases in the U.S. in 1985. Accounts for 15 per cent of cancers. In late 1985 NCI had good news and bad news: from 1982 to 1983, lung cancer rates fell among white males for the first time in more than half a century, but they continued to increase among black men and among women of all races.

Mortality: 126,000 deaths in 1985, or 23 per cent of cancer fatalities. Has surpassed breast cancer as the number one cancer killer of women.

Risk Factors: Cigarette smoking, industrial exposure to asbestos (especially in those who smoke), or arsenic (a by-product of copper refining), radioactive gas present in uranium mines, and diets deficient in vitamin A (again, particularly when combined with heavy smoking); air pollution suspected.

Warning Signs: Persistent cough, sputum streaked with blood, chest pain, recurring attacks of pneumonia or bronchitis.

Detection: Begins as a tiny spot, usually on the inner lining of a bronchial tube, and is very difficult to detect in early stages; symptoms generally don't occur until cancer has spread considerably. Diagnosis is aided by chest x-ray, sputum cytology test, and flexible fiber-optic bronchoscopy.

Treatment: Surgery, radiation to control tumors that can't be removed surgically, chemotherapy when the disease has become widespread, combinations of the three. ➤➤

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