Gene Segments on the Move

by Ben Patrusky

Jumping, flipping, dancing, and drifting segments of genetic material address such riddles as immunological diversity and cell differentiation.

Scientists, you might say, live in a dogma eat dogma world. Theirs is the realm of the evanescent, of the tentative, of the transient, a domain in which new observations may abruptly shatter cherished doctrine. Sometimes they lose sight of the ephemeral nature of their calling, often to their profound—if temporary—chagrin. Witness what has been happening of late in molecular genetics.

Barely a decade ago, molecular geneticists were languishing in a state of deep despair. As the 1970s loomed, many investigators felt stranded, mired in a career-impeding, intellectual cul-de-sac. The prevailing belief was that since 1953, when James Watson and Francis Crick ushered in the new era of molecular genetics with their illumination of DNA, all the fundamental principles regarding the form and function of life's master molecule had been delineated. Their research heyday was over; little was left for molecular biologists to do—except perhaps think about changing careers.

Admittedly, the new rules of genetics had been formulated from studies of very simple organisms—procaryotes, nonnucleated, single-celled organisms, especially *Escherichia coli*, the harmless intestinal bacterium. But as the 1960s drew to a close, there was little reason to assume that what was true for procaryotes would not also hold true for eucaryotes, higher organisms in which the genetic machinery is housed within a cell nucleus. As such, all that seemed to remain for the down-in-the-dumps molecular geneticists to do was to validate the universality of the procaryote-derived principles. That would undoubtedly happen soon enough, once the new technology for probing the genome—the genetic repertoire—of higher organisms became available.

The dogma at the time went something like this: A gene is a continuous segment of one of the extremely long DNA molecules in which the cell stores the organism's genetic information. The sequence of nucleotide bases along each strand of the DNA double helix represents a linear code. The information in that code directs the synthesis of specific proteins. Except for an occasional random point mutation, where one nucleotide substitutes for another and alters the code for some protein production or other, genes are generally constant, stable, and static.

But as molecular biologists acquired the wherewithal to cut, splice, clone, and otherwise manipulate DNA, their despair began to give way to a new spirit of heady optimism and adventure. For with this newly mastered power to penetrate the biological syntax of heredity more deeply, scientists were quick to ferret out some startling, dogma-devouring discoveries.

It became evident, for example, that in eucaryotes, unlike procaryotes, the genes coding for protein production did not exist as one continuous stretch of DNA. Rather, the information for protein manufacture was likely to be split into several discontinuous segments, or modules, separated by spacers called intervening sequences. Genes-in-pieces rejuvenated biologists and gave them plenty of fresh mysteries to ponder: How were the separate bits of information in these modules brought together to produce a coherent gene capable of ordering up the production of a specific protein? What was the meaning of split genes? Did they retard or speed up evolution? (See "Split Genes: More Questions Than Answers," *Mosaic*, Volume 10, Number 5.)

As if the existence of genes-in-pieces wasn't startling enough, scientists with their new techniques for delving more deeply into gene make-up and strategy were marshaling evidence that would spell doom for another well-entrenched doctrine—this having to do with the constancy of genes. What began to become clear in the 1970s was that DNA was hardly the stable molecule everyone thought. On the contrary, it seemed to be endowed with a strong streak of capriciousness. Fragments of the long molecule were found to be quite capable of changing addresses, of moving from place to place on the genome. Initially the evidence for this genetic wanderlust was delineated in procaryotes. That in itself was surprising enough. But soon there was substantial evidence to indicate that there were also jumping genes in eucaryotes.

The studies to date have already unearthed a broad spectrum of jumping styles. In the salmonella bacterium, for example, DNA segments have been seen to flip-flop end for end, to switch directions on the chromosome in a way that dramatically alters the nature of protein manufacture. In yeast the gene change, part of the organism's unconventional ritual of reproduction, has been likened to the substitution of one cassette for another in a tape recorder. A jump/splice strategy, meanwhile, explains the mammalian manufacture of disease-fighting antibodies. And an observation with important medical implications is that antibiotic resistance in microorganisms is carried within a prowling, virtually free-lance DNA fragment that can readily transfer not only from one DNA molecule to another but from one bacterium to another.

Many molecular biologists are now convinced that the discovery of movable genetic elements holds the key to the solution of several long-standing mysteries. It seems to

go a long way, for instance, toward explaining how the human body is able to synthesize a million and more different molecular antibody species, each tailor-made to grapple with a specific antigen. Movable elements may help answer the age-old question of differentiation: how a fertilized egg divides and ultimately becomes, in the course of embryonic development, many different kinds of tissue cells. Jumping genes may also provide a mechanism for satisfying scientists who have been arguing that point mutations alone were far from enough to account for the story of evolution.

Before its time

The story of the discovery of jumping genes actually began in the late 1940s. Barbara McClintock of the Carnegie Institution of Washington's Department of Genetics, headquartered at Cold Spring Harbor Laboratory in New York, was studying various inherited characteristics, including color and distribution of pigmentation, of *Zea mays*, the common corn plant. Her long, painstaking and ultimately trailblazing investigation led her to conclude that certain patterns of variegation could be attributable only to something she termed "movable controllable elements." McClintock proposed that these ill-defined, prowling genetic entities could insert themselves into chromosomes at a variety of sites and, acting as biological regulatory switches, serve to turn nearby genes on and off.

At the time, McClintock's seminal discovery had virtually no impact on the scientific community. It was simply the case of an idea whose time had not yet come. Like Gregor Mendel, she worked for many years without recognition. "I simply gave up trying to publish," she recalls. "My colleagues either didn't know what I was talking about or they didn't see any reason to listen to my story."

On reflection, it shouldn't be surprising that the significance of McClintock's accomplishment was overlooked by her contemporaries. After all, her work—and her far-reaching conclusions—anteceded by several years the identification by James Watson and Francis Crick of DNA as the master molecule of heredity. Thus, with no real handle on just what a gene was, it was difficult for her confreres to envisage just what meaning to give to McClintock's movable genetic elements.

The first clear-cut evidence of DNA mobility came nearly two decades later. Working with *E. coli*, Michael Malamy, now at Tufts University, discovered an unusual kind of gene repression. It was unusual in that it could not be explained in terms of what has come to be called the lac operon principle. According to this general principle, the gene (or operon) is kept silent by a repressor protein that acts to cover the DNA site, called the promoter, at which a gene begins. With the promoter site masked, the orders for protein synthesis encoded on the adjacent gene do not get transcribed; the message does not get out to the protein factories of the cell. In Malamy's studies, moreover, not one but whole blocks of genes were found to be repressed. And no known mechanism was at hand to account for it.

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Mulling over Malamy's observations and following some experiments of his own, James A. Shapiro of the University of Cambridge (now at the University of Chicago) came up with the notion that this perplexing genetic behavior might be attributed to the insertion of alien DNA fragments into the *E. coli* chromosome. These fragments, he suggested, were acting to turn off gene expression. About the same time, Peter Starlinger and his associates at the University of Cologne succeeded in identifying several such DNA fragments, subsequently dubbed insertion sequences, or IS elements. To date, a total of five have been isolated. And what is now evident is that these fragments carry no demonstrably functional genes of their own; they have the capacity only to intrude upon the operation of other genes. Moreover, these elements can insert themselves at a large number of sites on the bacterial chromosome or, for that matter, into the DNA of viruses that infect bacteria, or into plasmids, the small, ring-shaped, self-replicating units of DNA that reside in the bacterial cell.

Transposons

Initially, detection of these mobile units of DNA didn't create much of a stir; scientists tended to regard them as intriguing curiosities. But matters changed precipitously when movable genetic elements were indicted in an outbreak of infectious disease. That happened in 1974 when R. W. Hedges and A. E. Jacob of London's Hammersmith Hospital published a historic report on the transfer of antibiotic-resistant genes from one DNA molecule to another. What they had found, in effect, was a natural occurrence of DNA recombination. They had produced the first direct evidence that, by a process akin to the insertion of IS elements, an active gene capable of neutralizing the bacteria-killing effect of the antibiotic ampicillin could be transposed from one plasmid to another.

Various studies in numerous laboratories since then have led to the identification of about ten such discrete, gene-bearing translocation units. Mostly, each of these roving units, called transposons, directs the production of a protein that neutralizes one of several antibiotics. But there are also transposons that carry genes for other traits: the synthesis of bacterial toxins, and of resistance to toxic compounds, for instance. Readily transferable from bacterium to bacterium—by hitching a ride on a plasmid or virus—just such transposons are now known to account for the recent outbreak in the United States of ampicillin-resistant *Hemophilus influenzae*, a cause of severe ear infection and other diseases in children, and of penicillin-resistant *Neisseria gonorrhea*.

Transposons, albeit more complex, carry a striking resemblance to IS elements. At the ends of several transposons, for instance, investigators have found nucleotide sequences identical to those seen in IS elements. These flanking sequences take the form of inverted repeats, nucleotide sequences that are complementary to each other, but backward; their order of nucleotide "letters" is reversed.

Studies by Dennis J. Kopecko and Stanley Cohen, of the Stanford University School of Medicine, first brought this inverted sequence arrangement to light. The investigators had separated the DNA strands of a plasmid carrying a transposon for ampicillin resistance. They then allowed each of the strands to self-anneal—to mate with complementary sequences along its own length. The result, as demonstrated by electron microscopy, was the formation of a stem-and-loop structure, the stem double stranded and produced by the matching of the complementary inverted repeats. The guess now is that these inverted repeats serve as recognition sites for enzymes involved in transposition.

The discovery of transposons represented a major advance for investigators seeking to understand the behavior of DNA inserts. For unlike the movements of IS elements, which produce no directly discernible change in an organism, those of transposons can be tracked simply by monitoring for the appearance of newly developed and readily discernible antibiotic resistance in the bacteria under study.

Patrusky contributes frequently to Mosaic *on a range of scientific subjects.*

Chromosome modules

Recently, transposons have been found to carry the wherewithal to effect their own transfer. In a series of studies begun at the University of Washington with Craig Reubens and Stanley Falkow, and subsequently continued at the University of California at San Francisco, Frederick L. Heffron (now at Cold Spring Harbor Laboratory) succeeded in working out the complete nucleotide sequence and mapping the functional components of a specific transposon.

Heffron's map reveals that the transposon capable of imparting resistance to ampicillin comprises at least four distinct regions: (1) inverted-repeat ends, (2) a gene for the production of the enzyme beta-lactamase, which acts to neutralize ampicillin, (3) a gene carrying the blueprint for the manufacture of transposase, an enzyme required for transposition, and (4) a gene for the synthesis of a repressor protein to regulate the ability of the DNA segment to undergo transposition.

Transposons can insert themselves at many sites within a recipient DNA molecule, but as is the case for IS elements, their insertion is not random. Experiments by Stanford's David Tu and Stanley Cohen have shown insertion to take place at locations on the recipient molecule where the nucleotide sequences complement the sequences of the transposon's inverted-repeat ends. The transposase, the enzyme required for transposition, can apparently recognize and cleave these DNA regions to facilitate transposon insertion.

Needless to say, the discovery of gene inserts has led to considerable speculation on why and how they came into being. Says A. I. Bukhari of Cold Spring Harbor Laboratory: "Transposable elements have brought into focus the principle that DNA can be arranged rapidly during evolution. Thus, evolution does not have to depend upon the painstaking accumulation of mutations in chromosomes. Complex genomes can be built by simply joining together separate blocks or modules of information.... In this light, the IS elements can be thought of as joints or connectors for the modular construction of chromosomes.... Such a reassortment function would obviously offer selective advantage to organisms like bacteria which are subject to rapid changes in environmental pressures." In speculating on how transposons may have evolved, San Francisco's Frederick Heffron considers it likely that two IS sequences that inserted themselves on either side of a useful gene subsequently scooted off with their catch to form an advantageous—and permanent—union as a movable entity.

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An end-for-end flip

Transposition—the movement of so-called free-lance fragments from one location on the DNA molecule to another—is hardly the only brand of jumping gene uncovered in procaryotes. Recently Melvin Simon and his colleagues Michael Silverman, Janine Zieg, and Marcia Hilmen at the University of California at San Diego discovered a genetic shuffle they called a flip-flop. It was found in salmonella, a disease-causing bacterium that invades the human gastrointestinal tract. The flip-flop, or 180-degree reorientation, of a nucleotide sequence on the salmonella chromosome explains the phenomenon of phase variation in the organism.

Salmonella, it seems, propel themselves with hairlike rotors called flagella and apparently have the capacity to produce either of two kinds, or phases, of flagella. Each kind evokes a different kind of immunological response from the organism under attack. The phases, designated H1 and H2, are determined by separate genes located on opposite sides of the salmonella genome. Simon and his co-workers have established just what it is that determines which of the two genes will be expressed. By isolating the genes and cloning them in *E. coli*, the investigators found that phase is dependent on the orientation of a small DNA switching segment adjacent to the H2 gene. When this switch is in the off position, H1 is expressed; when it flips to the on position, it calls up products that suppress the H1 gene, and the H2 flagellum is synthesized.

Simon says this capacity to change phase appears to be an evolutionary outgrowth that has accrued to salmonella's advantage. He believes phase inversion enables the salmonella to fool its host into mounting an immunological attack against only one type of flagellum, allowing the other phase to persist. As Simon puts it: "Phase variation introduces a relatively stable change in gene expression into a small fraction of the population.... For salmonella, the ability to express an alternate flagellar antigen might ensure survival of a fraction of the population after the host organism mounts an immune response to the primary antigen."

In recent work, Simon and his colleagues have found that the segment of DNA that inverts contains a gene that mediates the inversion event. Further, this gene is similar to one of the genes that Heffron found to be part of the transposon. This suggests to Simon that there is at least a "loose unity" in the way these systems operate.

Genetic cassettes

And so it is that within a matter of just a few years—abetted by a newly expanded technological arsenal for the penetration of the master molecule of heredity—investigators have consigned another well-entrenched dogma to the scrap heap. The work on procaryotes clearly demonstrated that DNA was far less of a stay-at-home molecule than had once been assumed. Not surprisingly, this soon led investigators to wonder about the eucaryotic (nucleus-bearing) cells of higher organisms. Presumably eucaryotes also indulged in some form of genetic musical chairs; McClintock's seminal work on corn, since rescued from obscurity, intimated as much. Now it behooved scientists to explore the explicit molecular nature of gene choreography in nucleated cells.

One novel example surfaced in 1977, in studies by Ira Herskowitz, James Hicks and Jeffrey Strathern at the University of Oregon. The investigators were seeking to make genetic sense out of the unconventional sex life of *Saccharomyces cerevisiae*, baker's yeast.

Yeast comes in two mating types—designated *a* and *alpha*—even though mating is not essential for yeast reproduction; yeast may reproduce vegetatively by cloning, or forming buds, which ultimately break off to become independent cells. What puzzled the investigators, however, was that in certain strains there was almost invariably a switch of mating type—from *a* to *alpha* or vice versa—as one generation cloned and passed its genetic heritage to the next.

That didn't seem likely. The parent yeast cell has only one set of genes, which means it presumably has only one kind of mating gene. How then could an *a* clone an *alpha*, or an *alpha* an *a*?

From careful genetic analysis of the mating type of conversion, the Oregon investigators developed the cassette-model hypothesis to explain this generation-to-generation sex change. The hypothesis says that each of these yeast cells harbors a total of three genes for mating type, all located on the same chromosome. In the cassette model, one gene (either *a* or *alpha*) occupies the "playback" site. It determines the expression of mating type for the cell. On either side of the playback site and at some distance from

it are two other, "library," loci, one containing an *alpha* gene, the other an *a*.

On the command of an operator or "start-button," gene, one or the other mating gene is dubbed, or copied. The copy—the original remains in the library—replaces the one al-already in playback position.

The cassette analogy accounts for some hitherto inexplicable behavior, such as the phenomenon of DNA healing. Assume, for instance, that a yeast cell exists with a faulty or sterile *alpha* gene in the playback position, preventing the cell from mating with its opposite number. Yet in a pair of sequential buddings—first to normal *a*, then to normal *alpha*—the yeast recaptures the ability to mate. According to the Herskowitz/Hicks/Strathern hypothesis, the original damaged *alpha* cassette is excised and replaced by a dubbed copy of a different, fully functioning one. (See "Master Molecule, Heal Thyself," in this *Mosaic*.)

In a subsequent series of laborious trials, Hicks and Strathern—both now at Cold Spring Harbor Laboratory—together with Amar Klar succeeded in isolating and cloning large number of genes of the mating type. This achievement enabled the scientists to perform a variety of experiments with which to test crucial predictions devolving from the cassette-model hypothesis. As such, they were able to demonstrate (1) a difference between the DNA of the *a*-type matching gene and that of the *alpha* gene, (2) that one exists to the left and one to the right of the playback locus; and (3) that at switch time, storage cassettes don't merely shift sites and displace the gene at the playback site—they produce copies of themselves for insertion, while preserving the original.

Orchestrating antibodies

Perhaps the most spectacular instance of jumping genes discovered to date concerns the rearrangement strategies governing the production of antibodies in higher order eucaryotes—specifically mouse cells. What's especially exciting here is that the new observations offer important clues for the solution of a fundamental problem of immunology: how to account for the ability of a single organism to make as many as a million or more different species of antibody, each tailor-made to neutralize a very specific kind of antigen.

The antibody is an extraordinarily complex protein, consisting of four separate chains of amino acids—two identical light chains and two identical heavy ones; the composite is divided into two regions, one called a variable, or V region and one called constant, or C. In simple two-dimensional terms, the antibody can be imagined as having the shape of the letter Y, each arm formed by a light chain paired to a section of heavy chain, and the stem being the product of the remaining fragments of the two heavy chains. The V regions of the light and heavy chains, in the arms of the Y, together form the part of the antibody that recognizes a specific antigen and binds to it, lock-and-key fashion. The other, C, regions—the heavy-chain pair in the stem of the Y—serve a disposal function. They determine the way the molecular debris of antibody and conquered antigen is to be removed. Constant-region segments also determine the class, or type, an antibody is to assume.

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What manner of genetic orchestration gives rise to these extraordinary molecules? In 1965 William Dreyer of the California Institute of Technology introduced the heretical notion that perhaps two separate or split-gene segments—one for the constant region, another for the variable region—were engaged in directing the synthesis of a single antibody chain. Dreyer's two-gene/one-chain theory ran into fierce opposition. As Lee Hood, then a graduate student under Dreyer, recalls: "Dreyer's proposal [in a now-classic paper that appeared in the 1965 *Proceedings of the National Academy of Sciences*] came in for severe shelling. It ran counter to accepted dogma—one gene/one protein. It was a paradigm before its time, hence totally unacceptable to most molecular biologists. There were many vindictive phone calls to the department chairman asking him to explain how he could allow such trash to be published."

Dreyer's triumph, by way of direct proof, finally came in 1976 when Susumu Tonegawa and his colleagues at the Basel Institute for Immunology in Switzerland demonstrated that the DNA segments coding for the variable, V, and constant, C, regions of the light chain were indeed separate and apart in the embryonic mouse lymphocyte. At this stage, the lymphocyte was not yet capable of making antibodies. But by the time these cells had matured—differentiated—to become full-fledged factories, the V and C sections had somehow "jumped" closer together.

In subsequent studies, a more subtle reality was revealed. The Basel investigators mapped not just two but three distinct split-gene fragments, tethered to each other by long, intervening sequences of "silent" material. These include: (1) a string of nucleotides coding for the V region, (2) a small block of nucleotides designated the J, for joining, region and (3) the sequence coding for the light chain's C region.

In the mature cell, however, the V-region and J-region genes link up; the J fragment jumps to become contiguous with V, carrying the C region along, still at the end of its intervening tether. This brand of DNA recombination is known as V-J joining; it determines the antigenic specificity of the immunoglobulin. (Actually, the mouse produces two types of light chains, designated lambda and kappa, with the genes for each located on different chromosomes. Tonegawa and his Basel group based their findings on the lambda-gene chains. Studies of the kappa chain by Philip Leder and his colleagues at the National Institute of Child Health and Human Development turned up the same fusing of once-distant V and J segments.)

Bringing in the C

Caltech's Lee Hood meanwhile was directing efforts to map the genes or gene segments carrying the blueprint for the manufacture of the heavy chain—again in lymphocytes of the lab mouse. Hood and his co-workers found a situation analogous to that observed in light-chain synthesis, except that an extra gene element, D for diversity, participates in the assembly of a complete heavy-chain V gene. Accordingly, the V, D, and J segments are joined together as the antibody-making lymphocyte matures.

But there is another vital step, a second, distinct rearrangement beyond that of V/D/J joining, involved in the heavy-chain genetic strategy. This second piece of genetic recombination is known as C_H (for heavy) switching.

As Hood explains it, antibody molecules fall into five different immunoglobulin classes, determined by one of the eight distinct genes that code for the constant, debris-handling region of the heavy chain. The process of differentiation is complex and a variety of conflicting views exist on these transitional stages. It is generally agreed, however, says Hood, that the immature im-

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munoglobulins, the product of V/D/J joining, apparently have the capacity to differentiate along a variety of discrete pathways. They thus can produce progeny that may switch between the immunoglobulin classes. The final stage, says Hood, "is the adult plasma cell which [alone] is committed to synthesize and secrete large quantities of a single molecular species of antibody."

The Caltech group was able to show that the conversion of a lymphocyte cell from one immunoglobulin class to another involved the relocation of a heavy-chain C gene; in switching from one class to another, the C gene representing the second class replaces the one representing the first by a type of DNA rearrangement called class switching.

Hood says further that once V/D/J joining has occurred, the antigen-recognizing V domain remains fixed thereafter, even though the antibody may still undergo a class change. In this way, each antigen-recognition domain can be affixed to any or every class of immunoglobulin. So, no matter what the antigen or site of invasion, the right kind of antibody can get to it with the appropriate means of disposal.

The exact role of the J segment still remains unclear. In some ways it seems to serve as a biological marriage broker, dragging a constant-gene region to its ultimate assignation with the variable gene. Nucleotide sequence studies by Hood and others have led to the detection of inverted repeats at the tail end of the V gene and the beginning of the J segment, suggesting that this may serve as a signaling mechanism for bringing the two gene segments together.

The new understanding of antibody/gene layout and rearrangement goes a long way toward helping scientists unravel a basic biological riddle concerning the body's ability to marshal a specific tailor-made response to so diverse an arsenal of antigens. Hood explains this antibody diversity on the basis of the number of possible V-gene combinations available to the three antibody-gene families: lambda, kappa, and heavy-chain. In the light, kappa, family for instance, perhaps 200 different variable genes are strung out along the same DNA strand, ready to hitch up to one of four different J-gene segments further downstream. Thus the combinational joining of all V and J kappa-chain gene segments would generate 800 genes. The heavy-chain family meanwhile includes as many as 200 variable genes, ten D genes, and four J genes, which can mix and match with each other. The existence of the D gene in the heavy-chain family exponentially increases the potential for V-gene diversification, with the V/D/J combination generating as many as 8,000 different genes. The fact that any kappa chain can be joined to any heavy chain brings the number of combinations—the total of possible unique antibody types—to 6.4 million (800 X 8,000). Additional combinations involving the lambda chain explain the vast diversity of antibodies the immune system makes possible.

Cell differentiation

Of all the new research advances scored—and profound biological insights acquired—in the relatively short time since those now-dead dogma days of the stable gene, there now emerges one prospect above all that most excites scientists involved in the discovery and exploration of nature's stunning genetic repertoire. The investigators believe that movable genetic elements may well hold the answer to one of the most fundamental unsolved mysteries in the biology of higher organisms: How do cells differentiate? What is the process by which a fertilized egg develops into so many different kinds of cells? The gene complements of cells in a developing embryo are identical to each other. Thus the variant tissues must reflect the genetic program—a difference in the specific genes that are turned on and off in each type of cell. Movable genetic elements—jumping genes—now seem to provide logical regulatory mechanisms.

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At the simplest level, entities akin to DNA insertion sequences could readily serve as a vehicle for gene regulation, though they have yet to be detected in eucaryotic cells. San Diego's Melvin Simon, meanwhile, speculates on how flip-flop elements might be involved in differentiation: "If phase transitions exist during the early stages of embryogenesis," he says, "they might be 'fixed' at some point during development. If, for example, the enzyme that catalyzed the rearrangement were no longer formed, cells would be trapped in one phase or the other. Futhermore, it is [likely] that there are as yet undiscovered inducing events that...coordinate the timing and direction of gene arrangements." And James Hicks of Cold Spring Harbor sees possible parallels between cassette-model switching in yeast and the patterns of animal cell differentiation in which a precursor stem cell can give rise to a variety of different cell types—for instance, red blood cells, lymphocytes, and leukocytes from stem blood cells.

An address code

At Caltech, Lee Hood and his associates have developed perhaps the most elaborate theory of differentiation. Designated the "area-code hypothesis," it emerged from analysis of the events occurring in the development of antibody-producing and other immune-system cells. The theory rests on the premise that, as a cell undergoes successive stages of differentiation, changing patterns of area-code molecules are displayed on the cell surface.

"These molecules, singly and in groups, constitute the cell surface display system," says Hood, "that gives a cell or group of cells an individual address." He uses the analogy of the digits in a phone number or a postal zip code, which similarly identify individual locations. "These enable like cells to find each other," he explains. "They also provide cell-surface receptors essential for sensing...differentiation signals, such as those provided by hormones."

The underlying mechanism for many of these address changes, or changes in surface display, according to the hypothesis, may be DNA reshuffling. Any technique in the repertoire might be involved—a complex recombination such as V-J joining, or IS element insertion or excision, or a genetic flip-flop, or some other genetic razzle-dazzle yet to be discovered. Presumably these DNA rearrangements occur at the branch points of differentiation—at specific forks in the development road—as chromosomal modifications which then get passed on to cell progeny.

No one can say with any certainty that jumping genes lie at the heart of differentiation. Or, for that matter, that movable genetic elements provide the missing narrative drive for the still-incomplete story of evolution. Or that DNA reshuffling offers the full and final resolution of the mystery of antibody diversity. These all remain postulates, theoretical trial balloons, exercises in the tentative that are the bread and butter of scientific inquiry.

Small wonder that molecular biologists have taken such a fancy to this business of genetic capriciousness. After all, not very long ago these self-same scientists were themselves wandering about—in a landscape of frozen horizons. Now, amidst the clutter of toppled dogma they can once again see new horizons beckoning. •

The National Science Foundation contributes to the support of the research discussed in this article principally through its Genetics Program.