past 3 to 4 years, says Edwards.

But the pessimists are unmoved. "Much of the technology is aimed to increase production rates," says Campbell. "It doesn't do much for the reserves themselves." And what new technology does do for reserves, it has been doing since the oil industry began in the 19th century, he says. New technologies for better drilling equipment and seismic probing have been developed continually rather than in a sudden leap and so have been boosting the Hubbert curves all along. The shape of the curve therefore already incorporates steady technology development, he and other pessimists note.

As a result, they argue that today's technological fixes will make only slight changes to the curve. "All these things the economists talk about are just jiggling in a minor way with the curve," says Albert Bartlett, a physicist at the University of Colorado, Boulder, who calculates a 2004 world peak. "You can get some bumps on the [U.S.] curve by breaking your back, but the trend is down." For example, when oil hit $40 a barrel in the early 1980s, the U.S. production curve leveled out in response to a drilling frenzy—but it soon went right back down again. And besides, the pessimists note, when high prices drive increased production, the oil pumped is not cheap oil. Economist Cutler Cleveland of Boston University has found that the price-driven drilling frenzy of the late 1970s and early '80s produced the most expensive oil in the history of the industry. So, such production is a hallmark of the end of the golden age and the beginning of the transition stage of expensive oil.

The next few years should put each side's theory to the test. If technology can greatly boost reserves, then the U.S. production curve should at least stabilize, while if the pessimists are right, it will soon resume its steep downward slide. Production from the North Sea should tell how middle-aged oil provinces will fare; pessimists expect it will peak in the next few years. But it is the world production curve that will finally reveal whether the world is due for an imminent shortfall or decades more of unbounded oil.

–RICHARD A. KERR

MOLECULAR EVOLUTION

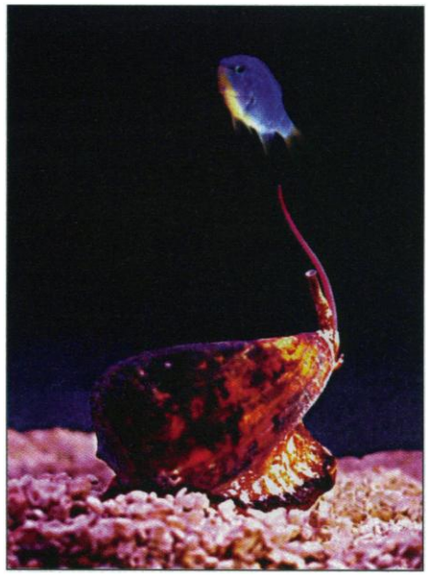
How the Genome Readies Itself for Evolution

Built into the genome's DNA sequences are regions that can promote rapid and extensive genetic change

The renowned author and cancer scientist Lewis Thomas once wrote: "The capacity to blunder slightly is the real marvel of DNA. Without this special attribute, we would still be anaerobic bacteria and there would be no music." Like many others—Nobel laureate Barbara McClintock was a notable exception—Thomas thought that genetic change, and hence the evolution of new species, results from small, random mutations in individual genes. But a growing wealth of data, much of it presented at a recent meeting,* indicate that mainstream biologists need to consider genomes, and the kinds of evolutionary changes they undergo, in a much different light.

The work shows that the mutations leading to evolutionary change are neither as small nor as rare as many biologists have long assumed. Sometimes they involve the movements of relatively large pieces of DNA, like transposable elements, the stretches of mobile DNA originally discovered in maize by McClintock. They can even take the form of wholesale shuffling or duplication of the genetic material (see p. 1119). All these changes can affect the expression of genes or free up duplicated genes to evolve new functions.

What's more, these changes may not be totally random. Researchers have found, for example, that some stretches of DNA are more likely to be duplicated or moved to another place than others, depending on the nature of their sequences. They are also learning that the enzymes that copy and maintain the DNA introduce changes in some parts of the genome and not others, creating hotspots of mutation that increase the efficiency of evolution. As James Shapiro, a bacterial geneticist at the University of Chicago, puts it, "Cells engineer their own genomes."



ZOYA MASLAK

Venom generator. Predatory cone snails have diverse venoms because of hypermutatable sections of DNA.

Findings such as these are leading to what Lynn Caporale, a biotechnology consultant based in New York City, describes as a "paradigm shift." In the past, researchers assumed that genomes evolve to minimize mutation rates and prevent random genetic change. But the new findings are persuading them that the most successful genomes may be those that have evolved to be able to change quickly and substantially if necessary. Or as McClintock said in her 1983 Nobel lecture, the genome is "a highly sensitive organ of the cell, that in times of stress could initiate its own restructuring and renovation."

Nature's genetic engineers

One of the oddest examples of how the genome can restructure itself comes from David Prescott, a molecular geneticist at the University of Colorado, Boulder. For the past 25 years, he has studied the genetic makeup of a group of single-celled organisms called hypotrichous ciliates, whose genomes are truly bizarre.

In addition to its large working nucleus, called the macronucleus, which contains multiple copies of all the genes, every ciliate has one or more micronuclei, each of which carries two copies of all the genes. The micronuclear genes, which are normally inactive, are split into multiple sections, with lots of interrupting DNA, called internal eliminated sequences, between the coding regions. In three of the 10 genes analyzed thus far, the coding regions are also in the wrong order.

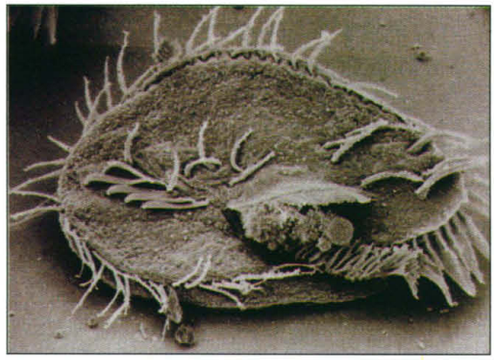
These micronuclear genes have to undergo a dramatic change during sexual reproduction when the micronuclei from the two partners fuse and give rise to both a new micronucleus and a new macronucleus. As the macronucleus takes shape, not only is the DNA between gene coding regions removed, but the coding regions have to be put into the correct order—"all in a matter of hours," Prescott notes.

Although having the gene-coding regions shuffled and split up in the micro-

* "Molecular Strategies in Biological Evolution," 27 to 29 June, organized by the New York Academy of Sciences, in New York City.

nucleus may seem a waste of time, Prescott thinks this arrangement helps generate new genes that can help the ciliates adapt to changes in their environment. In examining the DNA sequences of six species, he and his colleagues found that the sizes of the internal eliminated sequences vary from one to another. Sometimes they shift their positions by a few nucleotides, creating a slightly different coding region. This adds a new dimension to the changes that can occur, as now not just the original coding region but also this slightly altered one become available for shuffling and rearrangement into a new gene.

Most organisms do not go to the extremes that the ciliates do, but they have the potential to perform similar DNA rearrangements, if only on a lesser scale, because they have the necessary enzymes for cutting and rearranging DNA, as well as splicing it back together. Thus, Prescott concludes, the ciliates are "teaching us about what trickery DNA can perform to support evolution."



K. G. MURTI / ST. JUDE'S CHILDREN'S HOSPITAL, MEMPHIS

Nonrandom mutations

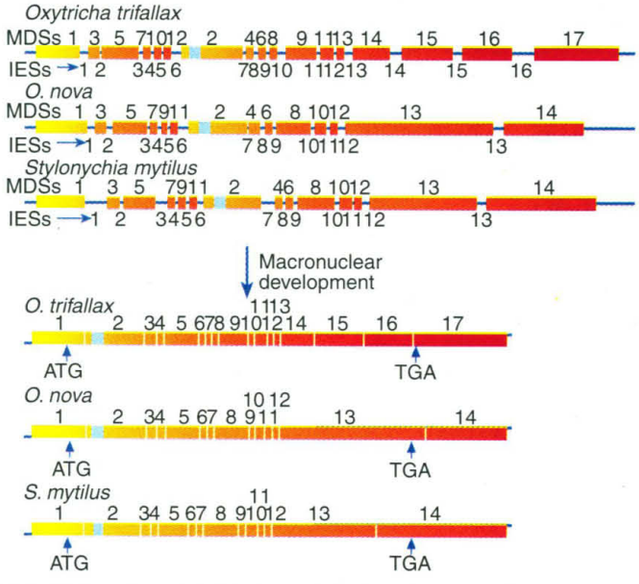
The changes in the ciliate genes appear to occur randomly, but researchers studying other species are finding, says Caporale, that the "rate of mutation is not monotonous throughout the whole genome." One striking example comes from Baldomero Olivera, a molecular biologist at the University of Utah, Salt Lake City, who has been assessing the incredible variation that exists in the toxins of predatory *Conus* snails.

With 500 species, these organisms are the most successful marine invertebrates. All use venom-laden harpoons to immobilize worms, fish, and other mollusks for food, and depending on the species, the venom contains 50 to 200 peptides. "Each *Conus* has its own distinct set" of toxin peptides, says Olivera. The genetic variation responsible for this toxin diversity, which may enable *Conus* species to identify one another, seems to be concentrated at particular hotspots in the snail DNA.

When Olivera and his colleagues began looking at the coding sequences for the large precursor proteins that break down to form the toxin peptides, they found that the first coding section, or exon, was almost identical in the pairs of *Conus* species examined. In contrast, Olivera reported at the meeting, the third exon, which is the one that codes for the peptide that becomes part of the venomous cocktail, "has just gone crazy in terms of changes." Because normally the functional parts of precursor proteins tend to change less over the course of evolution than the other parts, this finding suggests, he says, that the malleable exon somehow has a built-in tendency to mutate. The snails "are a good example of how expert nature is in using genome flexibility ... to generate genetic variation," says Thomas Kunkel, a biochemist at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina.

Kunkel stresses that there could be several different explanations for such mutational hot spots. For one thing, he notes, the efficacy with which the errors that creep into the genome are repaired can vary greatly. In test tube studies of DNA repair enzymes, Kunkel finds that the error rate for the repair of mistakes made during DNA replication can vary from 99% to 3%, depending on the nature of the sequence that needs repair. That may be because the sequence influences the ease with which the repair enzymes do their job.

What's more, some sequences are much more prone to error when the DNA is copied than others. In particular, DNA consisting of the same base repeated several times or simple two- and three-base repeats can be quite hard to replicate accurately. The problem is that the newly synthesized strand tends to slip relative to the strand being copied so that it may end up longer or shorter than the original, depending on whether it slips forward or backward.



DNA scrambler. In hypertrichous ciliates *(top)*, micronuclear genes have to be unscrambled to create functional genes for the larger macronucleus. The diagram shows how the coding regions (MDS) and interrupting sequences (IESs) of the same gene from three ciliate species shift, rearrange, and change size, but still manage to make coherent genes.

ADAPTED FROM PRESCOTT *ET AL.*

Genomic flexibility

Such simple repeats are best known for the problems they cause. Researchers have traced the mutations causing Huntington's disease and several other hereditary disorders to large increases in the number of repeating triplets associated with the relevant genes. But the repeats also provide the genome with a means for fine-tuning gene expression, say Edward Trifonov, a biophysicist at the Weizmann Institute for Science in Rehovot, Israel, and David King, an evolutionary biologist at Southern Illinois University in Carbondale, and their colleagues. Because the number of repeats associated with genes can vary randomly among individuals, some people may have an advantage over others under certain environmental conditions if the number of repeats influences gene function. One example King cites are the genes controlling how much fat is produced in a mother's milk. Those genes sometimes contain repeats, which could help set their level of activity without changing the coding regions of the genes themselves, he suggests.

Repeats may also affect gene activity indirectly. In the fruit fly, for example, researchers have found that certain genes are less likely to be expressed when they are close to a series of repeats than when they are located elsewhere on the chromosome. Also, at least 60 genes encoding transcription factors, which control the expression of other genes, contain adjustable repeats. In 1994, researchers showed that a change in the number of the repeats can affect the rate at which a transcription factor is produced (*Science*, 11 February 1994, p. 808). This change could in turn affect the activity of other genes controlled by the factor, King points out.

The repeated sequences known as transposons or transposable elements, which can move from one stretch of DNA to another, provide another source of genomic flexibili-

ty. McClintock first proposed the existence of transposons in 1948 based on studies of such things as color variation in corn kernels. She noted, for example, that the colors can change from one generation to the next—far too fast for ordinary evolutionary change. This led her to propose that what she called "controlling elements" could jump about the genome each time it is replicated. If one of those elements landed in a gene, say for a corn pigment, it would interrupt the gene sequence, resulting in loss of function. Then, if it popped back out, the gene's function, and the corn kernel color, would be restored.

A great deal of work has since confirmed that idea. But transposable elements have long been considered to be rogue DNAs that seemed to land anywhere in the genome, making their effects little different from random gene mutations that are more likely than not to be detrimental to the organism's survival. "Some people see them as parasites," says Caporale.

As McClintock realized, however, these movements can not only have profound effects on the expression of genes but also provide grist for the mill of evolution. A recent study of morning glories by Shigeru Iida, a molecular biologist at the National Institute for Basic Biology in Okazaki, Japan, and his colleagues provides an example. They traced the loss of blue or purple pigmentation in the flowers of some mutants to the insertion of transposable elements into genes needed to make the colored pigments.

Transposon art. Mobile genetic elements caused these prized color patterns in morning glories.

PORTER LOWRY

JIM MILLER

As in corn, the transposons don't always stay put. Some of the mutant plants, whose flowers were originally all white, later produced speckled or streaked blossoms, a signal that, in the colored cells, the function of the altered gene had been restored because the transposon had moved. In the wild, the resulting streaked and speckled patterns could play a role in evolution, as one design may be more attractive to pollinators than another, causing plants with those patterns to become predominant, Iida notes.

Transposons likely played a pivotal role in the evolution of higher vertebrates as well. New data suggest that two enzymes key to generating the immune system's inexhaustible variety of antibodies are relics of an ancient transposon. A great deal of this variability is due to the way antibody genes are assembled: by joining three separate sequences (denoted V, J, and D), each of which comes in many variants, into a single antibody gene. Two reports, one in this week's *Nature* from David Schatz of Yale University and his colleagues and the other in *Cell* from Martin Gellert's team at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland, now show that the enzymes that do this assembly, Rag1 and Rag2, work just like enzymes called transposases that mobilize transposons.

The transposases recognize the ends of the transposon and cut it out of a chromosome. That freed-up piece of DNA, with the transposase still attached, can loop around itself and move to a new place in the genome. That's just what Rag1 and -2, which act together in a complex, do, Schatz says: "In a test tube, [Rag1 and -2] are indistinguishable from a transposase."

This discovery helps explain why the adaptive immune system seems to have appeared so abruptly during evolution. Unlike most vertebrate features, the immune system has no counterpart in invertebrates, says Ronald Plasterk, a molecular biologist at the Netherlands Cancer Institute in Amsterdam. The sudden introduction of a transposon into the part of the genome containing the remote predecessors of the antibody genes could have set the stage for the many gene duplications that allowed the large antibody gene complex to evolve. "[The immune system] is a wonderful example of how a mobile piece of DNA can have an astounding impact on evolution," Schatz says.

Besides altering genomes by disrupting specific genes, mobile elements may also reshape the whole architecture of the genome, providing yet another kind of genomic flexibility. Iida has found parts of foreign genes buried in the morning glory's transposons, suggesting that transposons may capture genes and move them wholesale to new parts of the genome. If this is true, then they make possible DNA shuffling that can place genes in new regulatory contexts and, possibly, new roles.

And in May, Evan Eichler of Case Western Reserve University in Cleveland, Ohio, and his colleagues showed how a repeat sequence was likely responsible for the duplication of several genes' worth of DNA in humans and other primates (*Science*, 12 June, p. 1692). The researchers found copies of one piece of chromosome 16 in several other parts of the human genome, and Eichler suggests that repeated sequences at the ends of the inserted pieces of DNA were signals to enzymes that cut out that DNA as it replicated and allowed it to insert elsewhere. Sequence similarities between transposons and the repeats hint that the repeat sequence might be a remnant of an ancient mobile element. "It's no longer a matter of conjecture that transposable elements contribute to evolution," concludes Nina Fedoroff, a molecular biologist at Pennsylvania State University in University Park. "It's a fact."

These evolutionary contributions may increase when a species faces new selective pressures, says Caporale. As she puts it, "Chance favors the prepared genome." Researchers first noticed this happening in 1988 when John Cairns, then at Harvard University, showed that mutation rates in the bacterium *Escherichia coli* increased when the microbes needed to evolve new capabilities in order to survive changes in their environment. At the time, it seemed that only those genes directly involved with the adaptation changed, and this idea of adaptive or directed evolution caused quite a stir.

But then last year, molecular geneticist Susan Rosenberg at Baylor College of Medicine in Houston and her colleagues showed that mutation rates increase throughout the genome, although only in a subset of the population. Another group also found that more than just the relevant genes changed. The bacteria are "smart" about how they evolve, explains Rosenberg. In response to adverse conditions, they "turn on mechanisms of mutation that are nothing like the usual [mutation] mechanisms," she adds. They activate different repair enzymes and promote DNA shuffling, for example.

Not long ago, these ideas would have been considered heretical, but "I see more and more people looking at [evolution] this way," says Werner Arber, a Nobel laureate and microbiologist at the University of Basel in Switzerland. Whether by radically rearranging themselves, making use of mobile elements to generate variation, or causing certain stretches of DNA to mutate at high rates, genomes are showing that they can help themselves cope with a changing environment. Says Shapiro, "The capability of cells has gone far beyond what we had imagined." —ELIZABETH PENNISI