government and the need to set priorities," she says.

Funding for new laboratories, buildings, and other major facilities has also been assigned a low priority, says Triono Soendoro, an administrator with BAPPENAS, the national planning agency. That poses a problem for Marzuki, who is already trying to overcome the double whammy of a 30% across-the-board cut in agency budgets imposed this spring and a rupiah that has lost 80% of its value since last summer. Instead of working in his lab, Marzuki sits in his office, writing up research already completed and trying to interest overseas medical philanthropies in his proposal for a high-rise laboratory and office building—a plan that has been shelved indefinitely by his own government.

Marzuki recognizes that, with rising unemployment and soaring food and fuel prices, science policy must take a back seat to more basic human needs. But he worries that even a short-term suspension of RUT and other programs aimed at improving Indonesia's scientific infrastructure could come back to haunt the country. "It may be hard to restore the funding," he frets.

The government is, however, continuing international scientific collaborations, and it is still providing support for sending students abroad and for other training programs deemed essential to the country's long-term economic health. Oceanographer Arnold Gordon of Columbia University is preparing to welcome one of those students next month. And he's packing up his equipment for a September cruise aboard the *Baruna Jaya IV*, Indonesia's newest research vessel, to track regional ocean circulation patterns that affect global climate and weather. The cruise is one of three scheduled for the fall by U.S. scientists that builds on Indonesia's recent offer to open up its waters to scientists around the world (*Science*, 5 December 1997, p. 1703). The surge of cruises will provide a major source of revenue for BPPT's oceanographic program.

While Gordon is planning additional research projects, he's concerned that his longtime ties to the country could start to fray if the political and economic situation worsens. "Unfortunately, Indonesia is being asked to do more at a time when the government is more hard pressed than ever to support such research," he says.

Even with half of BPPT's budget committed to international collaborations, Gordon and others worry that a lack of funds may force the agency to either neglect necessary repairs and routine maintenance on its research vessels or price itself out of the market. "The day rate [for oceanographic cruises] has gone up by two-thirds in the past 6 months," says program manager Eric Itsweire of the U.S. National Science Foundation, which funds Gordon's Arlindo project. "But they are looking at a key region of the world's oceans and at the connection between El Niño and the Asian monsoon, and so far we think the scientific payoff justifies the cost and the difficulty of working there. We plan to stay flexible and see what happens."

Such a wait-and-see attitude has become de rigueur for Indonesian scientists and foreign scientists working in the country. Gordon plans to ship his equipment via Singapore, for example, as a hedge against any last-minute change in plans. But keeping one's options open has its limitations, too. "The worse thing is that you can't make any plans," says Marzuki. "So we take things one day at a time, preparing for the worst and hoping for the best."

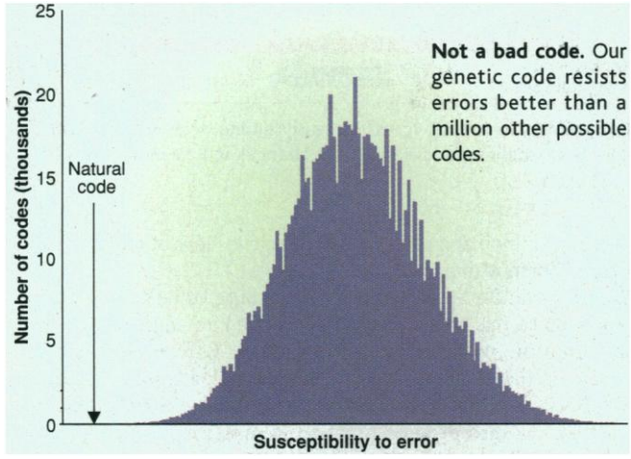
—JEFFREY MERVIS

EVOLUTION

Tracking the History of the Genetic Code

Computer analyses and experiments with RNA molecules offer new insight into the forces that may have shaped the genetic code over time

VANCOUVER—For the 3 decades since biologists cracked the genetic code—the key to translating DNA into proteins—they have debated its origins. Some claimed it must be a random accident forever frozen in time, while others argued that the code, like all other features of organisms, was shaped by natural selection. Most of those debates have been philosophical, with little data to back up either side. But at the annual meeting of the Society for the Study of Evolution held here last month, two speakers presented evidence suggesting that forces other than chance shaped the code's origin and history.



SOURCE: FREELAND AND HURST

Experiments with RNA have shown that chemical attractions between the genetic material and the components of proteins may have helped shape the original code, reported one speaker. Another researcher, using powerful computer analyses, suggested that the modern code is the product of evolution because it is so error-proof: Only one in a million other possible codes is better at producing a workable protein even when the DNA carries mistakes.

Doubters such as evolutionary biologist Niles Lehman of the State University of New York, Albany, still remain unconvinced that the code is anything but an accident. But he and others say that new studies such as these, as well as other work probing the history of individual genetic "words" (see sidebar, p. 330), are beginning to make a dent in their skepticism. "We're at a turning point" for probing the origins and history of the code, says Lehman.

Living things use DNA to store the instructions for making the proteins that build cells and direct them to develop into a complete organism. The four different subunits, or bases, that make up the DNA chain are grouped into three-letter "words" called codons, and each codon specifies a protein's amino acid building block. Specialized cellular machinery copies the DNA code into RNA—which has a similar code—and then reads the RNA to piece together the amino acids to make proteins. A codon "means" the same thing in a koala as it does in a rose or a bacterium. Yet there's no clear pattern in the pairing of codons and amino acids, which has persuaded many scientists that the code arose by accident.

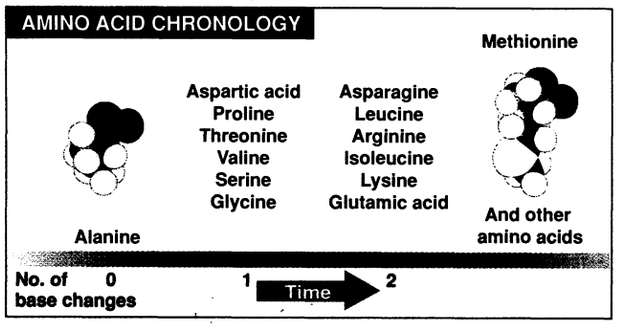
But test tube experiments now suggest that before cellular machinery had evolved to read the code and build proteins, the code could have been shaped by affinities between specific base sequences and amino acids. Many scientists have speculated about such a scenario, but new data from experiments in which short strands of RNA are

The First Codon and Its Descendants

NEW YORK—An expert in signal processing, Edward Trifonov excels in gleaning information from complex patterns. While others probe the overall origin of the genetic code, which specifies how the sequence of nucleotide base "letters" spell out the amino acids that make up proteins (see main text, p. 329), this biophysicist at the Weizmann Institute for Science in Rehovot, Israel, has applied his skills to determining which of the code's words came first.

"There are traces in [modern] sequence of the distant past," Trifonov said here last month at a New York Academy of Sciences meeting on Molecular Strategies in Biological Evolution. By looking for common features in the messenger RNA (mRNA) molecules that carry genetic messages from genes to the cell's protein factories, he concluded that the first word—a triplet of bases, or codon, that codes for a single amino acid—was GCU; that word stands for the bases guanine, cytosine, and uracil and codes for the amino acid alanine. He then went on to calculate how GCU might have evolved into the current set of 61 codons that specify the 20 amino acids. Trifonov has "come up with a unifying view of the origin of the genetic code," says Giorgio Bernardi, a molecular biologist at the Jacques Monod Institute in Paris, who considers Trifonov's results quite plausible.

Trifonov looked at mRNA for clues to the early code, because many researchers think that RNA predated the DNA of modern genomes. He noticed a hidden pattern of GCU repeats in mRNA sequences in many organisms: The GCU repeats are spaced in such a way as to align with matching bases in the ribosome, the structure that translates mRNA into protein. Matching bases attract, so the GCU repeats seem to help bind the mRNA to the ribosome. Because GCU is so common and plays so basic a role in translation, "it could also represent ancient RNA code," Trifonov thought.



Word gains. Genomic "words" for early amino acids evolved from single base changes; additional base changes led to more complex amino acids.

Then he and his colleague Thomas Bettecken, now at Magdeburg University in Germany, realized that RNA made up of this triplet might have gained an edge over other potential codons early in evolution, by interacting more easily with other nearby molecules. The DNA equivalent of the codon is GCT (T for thymine), a triplet that can cause a glitch in the cell's DNA-copying machinery and result in excess copies in daughter cells—a property that can disrupt gene function in diseases, including myotonic dystrophy and Huntington's disease. Assuming that GCU had the same property when RNA was the genetic material, this triplet would be more likely than others to produce longer RNA molecules that could fold in multiple ways to recognize and interact with amino acids and other molecules. "This exceptional property of expandability would give an advantage to that [triplet]," says Trifonov.

Once they had identified the potential first codon, the team made a series of one-nucleotide changes in the triplet (GCU to UCU, for example, or to GAU) to come up with six more codons. Because these could have evolved from GCU in a single step, they may have specified the next generation of amino acids. "The earliest changes were one-letter changes in GCU," Trifonov explains. "[Two-]letter changes were all later."

Then last year Trifonov and Bettecken compared their results to two other lists of potentially ancient amino acids, from origin-of-life experiments that came up with amino acids from the primordial soup, and chemical studies that identified amino acids with relatively simple structures. "If you put [these results] together, they overlap," Trifonov reported.

Trifonov himself emphasizes that this history is just a theory, and other researchers say no one may ever know for sure if he's right. Still, "these are nice arguments," says James Shapiro, a bacterial geneticist at the University of Chicago. "They all fit together and are very satisfying."

—ELIZABETH PENNISI

chosen based on their affinity for an amino acid are allowing them to test the idea. Several years ago, Michael Yarus of the University of Colorado, Boulder, noticed that in his experiments, the RNA strands that were best at binding a given amino acid tended to contain codons for that amino acid. But because the three-base codons often show up at random, the data were inconclusive.

Now evolutionary biologist Laura Landweber and graduate student Rob Knight of Princeton University have done a more careful analysis, looking specifically at where the amino acid arginine binds to random RNA strands generated in several researchers' experiments. If there is no real affinity, they reasoned, codons for arginine will appear as often in the regions where the amino acid does not bind as in regions that arginine homes in on. They found, instead, that while arginine codons made up 30% of the nonbinding RNA sites—the expected percentage, given that arginine has many possible codons—they made up 72% of the sequences in the binding regions. That suggests, says Landweber, that it's no accident that these codons specify arginine.

SOURCE: ADAPTED FROM E. TRIFONOV

The arginine evidence is intriguing, says evolutionary biologist Leslie Orgel of the Salk Institute in La Jolla, California. "But it's premature to draw any very strong conclusions" from data on the affinities of a single amino acid, he says. Researchers are delighted, however, that experimenters are now tackling the question. "Previously we had to rely solely on theory," says Lehman, but "if [Landweber's analysis] holds up, it will provide a convincing body of evidence" that basic chemical forces helped to shape the code.

Once the code was born, a different kind of pressure, the need to minimize errors, might have refined it. While some researchers have argued that any changes to the code over its 3.5-billion-year history would have been like switching the keys on a typewriter, leading to hopelessly garbled proteins, others argued that the existing code is so good at its job that it must have been shaped by natural selection. For example, in 1991, evolutionary biologists Laurence Hurst of the University of Bath in England and David Haig of Harvard University showed that of all the possible codes made from the four bases and the 20 amino acids, the natural code is among the best at minimizing the effect of mutations. They found that single-base changes in a codon are likely to substitute a chemically similar amino acid and therefore make only minimal changes to the final protein.

Now Hurst's graduate student Stephen Freeland at Cambridge University in England has taken the analysis a step farther by taking into account the kinds of mistakes that are most likely to occur. First, the bases

fall into two size classes, and mutations that swap bases of similar size are more common than mutations that switch base sizes. Second, during protein synthesis the first and third members of a codon are much more likely to be misread than the second one. When those mistake frequencies are factored in, the natural code looks even better: Only one of a million randomly generated codes was more error-proof.

That suggests, Freeland says, that the code has been optimized over the eons and isn't simply the product of chance. Lehman agrees that the one-in-a-million result looks impressive, but cautions that the statistics could be misleading. A high degree of similarity within one clan of amino acids could account for the code's apparent resistance to error, and the rest of the code could be random, he says.

With both the genesis and history of the code looking less and less accidental, Landweber and Freeland plan to collaborate next year, hoping to "build a grand scheme of the code's raison d'être," Landweber says—whether it be accident or design.

–GRETCHEN VOGEL

MEETING PLANT PHYSIOLOGY

Plant Biology in the Genome Era

MADISON, WISCONSIN—More than 2000 plant scientists dug in here from 24 June to 1 July for two back-to-back meetings: the 9th International Conference on *Arabidopsis* Research and the annual meeting of the American Society of Plant Physiologists. While some researchers put the wealth of data from genome projects to creative uses such as making vitamin-fortified plants, others use it to enhance work on such questions as how flowers form.

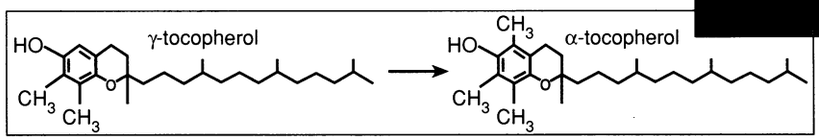
Engineering Plants, From A to Zn

In the past 2 decades, genetic engineers have brought us plants that resist disease and herbicides, plants that produce drugs, and even plants that make plastic. Now they have hit on what observers say is a very obvious and good idea: altering plant genomes to crank out increased amounts of vitamins and minerals.

A handful of academic and industry labs around the world are working on such "nutritional genomics," as biochemist Dean DellaPenna of the University of Nevada, Reno, calls it. DellaPenna himself is coaxing plants to churn out more vitamin E in a form that the human body can easily use, while other projects still in the works focus on vitamin A and iron. The market for such fortified plants might be health-conscious consumers who dislike taking vitamin pills, or those in the developing world who lack access to the necessary micronutrients, DellaPenna said at the meeting.

In the case of vitamin E, DellaPenna noted that an average U.S. diet provides the tiny amount needed to keep blood cells and neurons functioning. But many consumers are loading up on vitamin E supplements in response to recent reports that large doses of vitamin E and other antioxidants might protect against cancer and heart disease. "You'd need to eat one to one-and-a-half kilograms of spinach daily, or 3000 calories of soybean oil, to get the therapeutic dose," said DellaPenna.

So he and David Shintani of his lab tweaked the experimental plant *Arabidopsis*, a member of the mustard family, to increase its production of the most useful form of vitamin E, a ring and chain of carbon known as α-tocopherol. They found that *Arabidopsis* seeds normally produce γ-tocopherol, one enzymatic step short of α-tocopherol. To find the gene responsible for that key enzyme, they hunted through the sequenced genome of the photosynthetic bacterium *Synechocystis* for a known gene that operates earlier in the pathway. Then they tested nearby genes until they found the one that codes for the enzyme, γ-tocopherol methyltransferase. Finally they scrolled through the growing database of *Arabidopsis* genes and found its version of the gene, apparently lurking unexpressed in the plant seeds.



No more pills? Researchers tweaked the *Arabidopsis (right)* genome to produce α-tocopherol, or vitamin E.

The two next hooked the gene to a regulatory sequence that specifies expression in the plant seed and engineered the whole package back into developing *Arabidopsis* plants. The result was a 10-fold increase in the amount of α-tocopherol in the seeds. "The bulk of the γ-tocopherol is converted to α-tocopherol," DellaPenna reported. The offspring of the first-generation plants also produced more vitamin E in their seeds.

The effort is "an intelligent use of genomic information" with practical promise, says plant scientist Chris Somerville of the Carnegie Institution of Washington's plant laboratory at Stanford University. The next step is to similarly engineer a food plant such as soy, which already makes a small amount of α-tocopherol in its seed. "I'm sure it'll be in crop species very quickly," says Somerville.

Plants expressing increased amounts of other micronutrients may not be far behind. For example, Ingo Potrykus at the Swiss Federal Institute of Technology in Zurich and his colleagues have been working to engineer rice to produce vitamin A. They're using genes from bacteria and daffodils, which make the carrot-colored carotenoids that provide vitamin A. If they are successful, vitamin A–rich rice could help alleviate deficiencies of the vitamin in regions where rice is the dietary staple.

Iron—the most common nutritional deficiency worldwide—is another target, plant biologist Mary Lou Guerinot of Dartmouth College in Hanover, New Hampshire, told the meeting. She hasn't engineered iron-fortified plants yet, but so far they have identified an *Arabidopsis* gene that codes for a protein that allows the plant to take up iron from the soil. They have also just found a similar group of transporters for zinc, another necessary micronutrient. Manipulating these transporter proteins could allow them to boost the amount of minerals a plant takes in, she says. If such work eventually produces fortified crops, there may be an alphabet of new reasons to eat your vegetables.

DEVERE PATTON

Shaping a Flower's Heart

The bud of a flower is a picture of petaled symmetry, a look that it usually maintains even as the bloom opens and then fades. But a new look at an early, crucial stage in flower development reveals an asymmetry deep in the heart of the flower, plant anatomist Judith A. Verbeke of the University of Arizona, Tucson, reported at the