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This Week

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Amoebic seesaw

"It's a stretch to imagine how an organism can change its genome depending on its environment," says biologist John Samuelson in "Mystery Amoeba" (SN: 9/30/89, p.216). Maybe so, but substitute "population" for "organism" and perhaps the mystery of the amoeba is cleared up.

Consider two subspecies so closely related that only a single mutation separates them. By chance, benign amoebas occasionally produce virulent offspring, and vice versa, so that there is a kind of equilibrium between them. Normally, though, the benign form is the better competitor and so dominates the population.

Gradually remove the bacterial food source, and the balance shifts in favor of the virulent strain. Restore it, and the benign strain returns to power—yet at all times there remains a faint trace of the minority strain to be detected.

Gregory Kusnick
Sonora, Calif.

Stroke strategies 'partial at best'

"New therapies brighten stroke horizon" (SN: 11/4/89, p.292) nicely captured the growing hope that some effective therapeutic interventions for stroke may be developed over the next several years. I would, however, correct a couple of inaccuracies.

First, glutamate-receptor blockers have not yet been tested for effectiveness against brain damage in humans. Second, it is unfortunately unlikely that any currently known approach, including glutamate-receptor blockers, would "totally prevent neurological symptoms" in stroke patients. The range of therapeutic strategies discussed in the article could at best be expected to produce a partial reduction in the brain damage caused by a stroke.

Still, even a partial victory against this ancient scourge might be cause for modest celebration.

Dennis W. Choi
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Elephants and equilibrium

Richard Miller (Letters, SN: 9/30/89, p.211) has misinterpreted the intentions of the CITES treaty on the ivory trade. Although he is correct that some southern African countries have reduced elephant poaching by using animal husbandry techniques, his insinuation that these countries should be rewarded by continuing the ivory trade is unconscionable.

These countries are making progress not because they legally cull elephants and sell the ivory, but because their "successes" are based largely on improved regional, political and economic conditions, which are highly unstable. A total ban on the ivory trade would create a permanent state of equilibrium that would be independent of regional political shifts.

If, as Mr. Miller claims, the ban on ivory trade appears to have a negative economic effect on "cull-and-market" conservation, then this is a good indication that the culling-

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globin. Lennette J. Benjamin, codirector of the Comprehensive Sickle Cell Center at Montefiore Hospital Medical Center in New York City, led a 1986 study showing that an experimental drug called cetiedil reduced patients' painful episodes of blood vessel blockage. Benjamin told participants at the September symposium that she seeks to improve cetiedil's effectiveness by administering it more frequently to patients. In lab tests, commercially available calcium-channel blockers such as verapamil and diltiazem also show promise of inhibiting sickling, Benjamin says.

Biochemists James M. Manning and Anthony Cerami of Rockefeller University in New York City discovered almost 20 years ago that cyanate salts could inhibit sickling *in vitro* by bonding to a site on the hemoglobin molecule, preventing the hemoglobin from taking on the rod configuration when deoxygenated. But other researchers who used sodium cyanate in sickle cell patients found it reacted with other proteins, producing toxic neurological effects. Manning then searched for other drugs that might bind more specifically to the hemoglobin molecule to prevent sickling. The most promising, he says, is methyl acetyl phosphate, an experimental drug that inhibits polymerization of hemoglobin *in vitro*. Manning is now planning preliminary tests of methyl acetyl phosphate in sickle cell patients.

But even the best of these therapies would leave patients dependent on medication to prevent the sickling; they cannot offer a cure. While bone marrow transplantation *has* cured a few sickle cell patients, this procedure carries a higher mortality risk than the disease itself. In 1984, researchers at St. Jude Children's Research Hospital in Memphis, Tenn., and others reported in the NEW ENGLAND JOURNAL OF MEDICINE that they had cured an 8-year-old girl of both sickle cell anemia and leukemia with a bone marrow transplant. And Belgian researchers reported in the June 25, 1988 LANCET that they used marrow transplants to cure sickle cell anemia in five children from Zaire. But physicians consider the procedure too risky and expensive for widespread use in treating sickle cell disease, Charache says, and some researchers have criticized the Belgian team for using it.

The most promising – and the most distant – prospect for a cure would involve replacing or altering the defective hemoglobin gene with a normally functioning one. Bone marrow cells appear the best candidates for gene therapy because they can be removed, treated and reinserted without perishing. Arthur W. Nienhuis, chief of clinical hematology at the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, Md., and others are working with laboratory animals to find ways to alter stem cells – extremely rare bone marrow cells that seem to provide the marrow with a blueprint to produce hemoglobin.

"We hope ultimately to cure sickle cell disease and other bone marrow diseases by inserting [a normally functioning] gene into the stem cells . . . thereby replacing the function of the defective gene product," Nienhuis says. He is studying whether a genetically altered viral particle can be fashioned to carry a normal gene into stem cells of patients with sickle cell disease to make them produce normal adult hemoglobin.

Already, scientists have succeeded in inserting a gene for human adult hemoglobin into mice, which then produced large quantities of the substance (SN: 9/2/89, p.149). And Stamatoyannopoulos, working with University of Washington colleague Tariq Enver and others, has managed to insert a human fetal hemoglobin gene into fertilized mouse eggs. After birth, the genetically altered mice expressed the human gene, the researchers report in the September PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.86, No.18).

Tim M. Townes, a molecular biologist at the University of Alabama at Birmingham, says he and his collaborators at the University of Pennsylvania in Philadelphia are close to creating mice that produce human sickle hemoglobin. Such mice could provide a valuable animal model for studying the disease, he says.

One researcher expressing both optimism and caution about the new developments in sickle cell research is Marilyn H. Gaston of the Health Resources Services Administration in Washington, D.C. In 1986, while serving as deputy chief of NHLBI's Sickle Cell Branch, Gaston led a study demonstrating that penicillin could prolong the lives of sickle-cell-afflicted children, who are especially susceptible to bacterial infections until age 5. That finding has led many states to require or recommend that hospitals screen all newborns for sickle cell disease so that afflicted infants can receive preventive treatment with penicillin.

Gaston says she considers hydroxyurea the most immediately promising treatment and gene therapy the most hopeful long-term strategy. But she warns that sickle cell anemia has a tendency to baffle researchers.

"I'm kind of jaded," she confesses. "I've gotten so close to this illness, then it moves away. It's elusive. Now we're trying to bridge the gap between theory and therapy." □

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and-marketing program is flawed. When the fate of a program involving legally harvested elephants relies too heavily on the presence of an ivory market, Mr. Miller might ponder whether his solution is actually part of the problem.

Phillip K. Bigelow
Bellingham, Wash.

Musings on membrane DNA

I read with fascination the article on cell-surface-bound DNA ("DNA's Extended Domain," SN: 10/7/89, p.234). What puzzles me is why many eukaryotic biologists have ignored or doubted this concept for so long, since prokaryotes (i.e., bacteria) have been doing the same thing for eons.

Both gram-positive and gram-negative bacteria have specific DNA-binding proteins or "receptors" that bind to and promote the uptake of naked DNA molecules. In fact, the first genetic exchange mechanism to be discovered in bacteria, namely transformation, is based on this phenomenon.

Although I am unaware of any immunity provided to a bacterium with DNA bound to it (perhaps this should be an area of future investigation), this process definitely represents a conservation as well as a recycling mechanism for discarded DNA molecules.

Francis X. Steiner
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Your excellent article on membrane-bound DNA has led me to exercise my scientific imagination.

The purpose of DNA receptors may initially have been to act as a primitive means of sharing genetic information between cells. Their function as a salvage pathway for conserving DNA precursors could be more coincidental.

A more recent function could be to serve as a mechanism to stimulate interferon production; viral or cellular DNA that is bound and internalized could trigger production of protective interferon molecules. (Can nonimmunogenic strands of DNA be used to stimulate interferon production *in vivo* and provide therapeutic benefit?) Further, membrane DNA receptors could serve as convenient entry sites for viral genomes, validating this mode of pathogenic attack.

As to how membrane-bound DNA survives, perhaps it doesn't. It's true that it faces a hostile environment. Quite possibly the DNA visualized by staining has been damaged by reaction with oxidizing radicals and is irreversibly bound to its receptor until other enzymes or processes can clear the blocked site.

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