

Bloodsuckers. A new compound kills malaria parasites (yellow) within red blood cells.

resistant strains of *Plasmodium falciparum*," says David Fidock, a molecular parasitologist at the Albert Einstein College of Medicine in New York City.

The compound, dubbed G25, aims at the third stage of the malaria life cycle in humans. The parasites first enter the bloodstream, dribbled in with the saliva of mosquitoes, as sporozoites, and then they quickly burrow into liver cells. There they multiply by the tens of thousands and emerge a week later as merozoites, which infiltrate red blood cells. These merozoites are the target of G25. Once inside the red blood cell, also known as an erythrocyte, a single merozoite produces some 20 progeny. These erupt from the cell, reinstate the bloodstream, and colonize yet more erythrocytes. This stage of the parasite's growth cycle is responsible for virtually all clinical symptoms of malaria, because the parasites can eventually colonize and destroy up to 70% of all red blood cells, causing severe anemia, fever, convulsions, coma, and death.

To Vial and his colleagues, the parasites were vulnerable because of their need to package each of their erythrocyte-born progeny in protective lipid membranes. Uninfected erythrocytes, in contrast, engage in no lipid synthesis of their own. By targeting this synthesis, Vial says, "in theory we would be attacking metabolism that is not present in the host cell and so would not affect the host cell. But if you prevent the parasite itself from synthesizing lipids, it will not survive."

Over the course of 20 years of research, Vial and his colleagues dissected the pathway by which the parasite takes choline from blood plasma and converts it into the major component of its protective membranes. They then demonstrated that blocking synthesis of phospholipids stops parasite replication. Finally, they designed the newly reported compound, G25, to block the receptor for choline transport, which can be

found both on the surface of the infected erythrocytes and on the membrane of the parasite sequestered within.

The results were dramatic. In rodents and primates infected with *P. falciparum*, the most lethal form of malaria, G25 effected quick and total cures at low doses. "A few days after the first injection, all the parasites in the monkey were dead," says team member Clemens Kocken of the Biomedical Primate Research Center in Rijswijk, the Netherlands.

G25 is both easy to make and inexpensive—essential qualities for a drug that will be used in sub-Saharan Africa, where 90% of all malaria cases arise, and Southeast Asia, both of which are plagued by multidrug-resistant malaria. One drawback is that the drug must be injected. And, as Michael Gottlieb, chief of parasitology at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, points out, the researchers "obviously need a lot more toxicity data before it becomes obvious that this compound will be therapeutically effective." Vial says his team hopes to have a more convenient oral candidate for preclinical studies within 2 years.

—GARY TAUBES

PALEONTOLOGY

Earliest Animal Tracks Or Just Mud Cracks?

When they were first discovered, the wiggly grooves on slabs of ancient sandstone from central India were dramatic enough: They appeared to some to be 1.1-billion-year-old worm tracks. That date would push the earliest known record of complex animals back a startling half-billion years (*Science*, 2 October 1998, p. 19). But, it



Wormy or just groovy? These putative worm tracks are now dated at 1.6 billion years.

ScienceScope

Rockefeller Rocked Rockefeller University is reeling from the resignation this week of its president, molecular geneticist Arnold Levine (below). The New York City university's trustees released a terse note on 10 February saying that Levine had offered to resign, "effective immediately," because of "health considerations." Rockefeller's interim president during the search for a new chief will be molecular biologist Thomas Sakmar, currently chair of the academic senate.

Levine, a prominent molecular biologist best known for his role in discovering the *p53* gene implicated in many cancers, was not available to comment. But in the statement he said that "I have become aware of matters affecting my own personal health that I need to address immediately." According to sources close to the university, Levine tendered his resignation after the board learned that he and a single female student had behaved "inappropriately" in the faculty club bar on 10 January.

Levine has been "an admired and inspirational leader," said chief trustee Richard Fisher, noting that he recruited 14 new lab chiefs and launched a \$350 million fund-raising campaign.

Grant Nixed The U.S. Red Cross last week unexpectedly turned down the first stem cell research grant awarded under the Bush Administration's new policy (*Science*, 17 August 2001, p. 1242). On 7 February the National Institutes of Health (NIH) told Red Cross researcher Robert Hawley that he had won a \$50,000 grant to extend to humans his mouse studies of blood cell production. But Red Cross chief scientist Jerry Squires returned the cash, saying that the group's research priorities have changed since he took over last summer.

Some observers believe the Red Cross, already reeling from a fund-raising controversy that prompted former head Bernadine Healy to resign in October 2001, rejected the grant to avoid criticism from anti-stem cell research groups. "My fear is their fund-raising agenda is affecting their research agenda," says Tony Mazzaschi of the Association of American Medical Colleges.

Meanwhile, NIH announced last week that it has added six South Korean stem cell lines to its registry of approved lines, bringing the total to 73.



BIOMEDICAL ETHICS

Study of Brain Dead Sparks Debate

Renata Pasqualini and her husband Wadiah Arap, biologists at the M. D. Anderson Cancer Center in Houston, Texas, had for several years been working on a new approach to designing targeted cancer drugs, but they were not sure how to test it on people. At the same time, they were deeply moved by the families of cancer patients they encountered. Watching loved ones decline, their brains silent, their bodies tethered to life support, the families sometimes offered to donate their relative's organs, but advanced cancer made that impossible. From this juxtaposition arose a novel experiment: Pasqualini, Arap, and their colleagues have infused millions of peptides into brain-dead and near-death patients to determine which ones end up in specific tissues.

Despite the initial "yuck factor," as Anne Flamm, a clinical ethicist at M. D. Anderson who helped design the protocol, describes it, she and others believe that with stringent informed consent procedures, such studies are ethically sound. And the first of the experiments, on a 48-year-old brain-dead man, reported in the February issue of *Nature Medicine*, has yielded a wealth of data.

"Being able to get information from a human being, in vivo—not just taking cells out—has wide-ranging implications," says Donald McDonald, a vascular biologist at the University of California, San Francisco (UCSF). "Everyone recognizes that this was a risk that [the researchers] took because of the [study's] obvious sensitivity."

Pasqualini, Arap, and their colleagues believe that tracking which peptides—short strings of amino acids—are drawn to blood vessels in certain tissues could pave the way toward drugs that might target those peptides, and hence the blood vessels feeding particular tumors. In the late 1990s, they helped establish that in mice, different peptides bind to blood vessels in different parts of the body, and that vessels feeding tumors differ from healthy ones. From tissue biopsies taken after infusing the peptides, the

team determined which classes of peptides were present in each. But they worried that the same types of peptides would not migrate to the same blood vessels in humans.

Finding out posed ethical challenges: The multiple biopsies needed—of skin, muscle, bone marrow, prostate, fat, and liver—would be too invasive to gather from conscious individuals. So in late 1999, Arap and Pasqualini approached M. D. Anderson ethicists about the idea of experimenting on brain-dead and near-death patients.

Flamm and fellow ethicist Rebecca Pentz scanned medical literature for precedents but unearthed few. In 1981, researchers received permission to test an artificial breathing device on brain-dead children; 6 years later a brain-dead man was infused with monoclonal antibodies.

The pair recommended strict rules. First, the impetus to participate must come from families: Only after a family inquires about organ donation or research can it be told of the study. The procedure must last no more than an hour, and families of near-death patients must be warned that death could occur during the experiment. In early 2000, the hospital's Institutional Review Board (IRB) gave the green light for the team to infuse roughly 200 million different peptides into their subjects.

Still, the studies have prompted ethical questions few have considered before.

Elizabeth Hohmann, an infectious-disease specialist and chair of the IRB for Massachusetts General Hospital and Brigham and Women's Hospital, both in Boston, says she has never encountered proposals to experiment on brain-dead people on life support. Nor has John Falletta, a pediatric oncologist and lead chair of Duke University's IRB. If the body is respected, he says, "such research could be very important."

A smattering of hospitals seem to agree. Pasqualini's group has since infused peptides into two more individuals as part of the same study. The University of Pittsburgh in Pennsylvania recently approved two studies on brain-dead subjects on life support; one tests a device to treat heart and lung failure. And M. D. Anderson approved another study last May, in which patients declared dead are connected to a mechanical resuscitation device intended for those in cardiac

turns out, the first publication on the find was greatly understated.

Two groups report in the February issue of *Geology* that the rock marked by the putative tracks is a whopping 1.6 billion years old. That predates the earliest generally accepted trace fossil of a complex animal—dated at 575 million years ago—by about a billion years. To some researchers, such a long gap strains credulity. Instead of traces of life, they are now seeing meaningless doodlings in ancient, squishy muds.

The new, solid age for the Indian grooves comes from radiometric dating by two independent groups. They measured the clock-like rate of radioactive decay of uranium to lead in tiny crystals of zircon deposited with volcanic ash just before and just after the grooves formed. Both groups—one led by paleontologist Birger Rasmussen of the University of Western Australia in Crawley, the other by geochemist Jyotirnanjan Ray, now at the University of Hawaii, Manoa—got ages of just over 1.600 billion years, give or take less than 0.008 billion years.

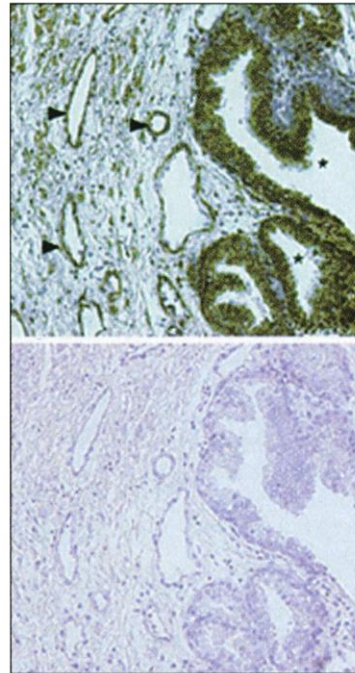
"There's no question" that the groovy rock is very ancient, says geochronologist Samuel Bowring of the Massachusetts Institute of Technology, a co-author of the Ray paper. Dating by various other techniques that pointed to an age of 1.1 billion years or younger (*Science*, 16 April 1999, p. 412) must have been affected by alteration of the rock, Bowring says.

With doubts about the appropriate age resolved, the biological origins of the grooves become "even more exciting or more improbable," says paleontologist Adolph Seilacher of Yale University, who with colleagues proposed that the grooves were formed by evolutionarily advanced worms burrowing just beneath the sea floor. "This age makes it unlikely these are animal trace fossils," Seilacher says. "At the same time, I have to go with the evidence. I have not found or heard of any other explanation. Do we have any non-biological interpretation of these things?"

As it happens, the answer is yes. "No one is better in the field than Seilacher," says paleontologist Mary Droser of the University of California, Riverside, but, on closer inspection, she finds that the grooves "look much more like cracks than trace fossils." The details of groove diameter, the V shape of groove floors, and the irregular pattern of grooves all point to cracked mud rather than burrowing, Droser says. In addition, "you wouldn't expect a billion years without [similar traces]."

The debate over the earliest traces of animal life "is a great dress rehearsal for when we get samples from Mars," says Bowring. "How do you decide when something is biogenic? Paleontologists haven't completely come to grips with that." Perhaps squiggly grooves from India can help prepare us for that encounter.

—RICHARD A. KERR



Picky. Certain peptides latch onto prostate blood vessels (top) but not skin (bottom) in tissue collected from a brain-dead man.