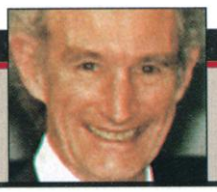


1212
Royal Society faces inquiry

LEAD STORY 1214
Becoming human

Such a reassessment may be about to happen. A National Academy of Sciences panel will soon begin an examination of the "responsibilities of authorship in the biological sciences." Chaired by biologist Thomas Cech, president of the Howard Hughes Medical Institute, the group will hold its first public meeting on 25 February, with a goal of trying to figure out whether there should be "a single set of accepted standards" for data sharing. **–ELIOT MARSHALL**

INFECTIOUS DISEASES

Researchers Crack Malaria Genome

LAS VEGAS, NEVADA—Genome scientists call it the toughest microbe they ever took on. But at a meeting* last Monday, an international group presented the long-awaited first glimpse of the full genome of *Plasmodium falciparum*, the most important malaria parasite. A project to sequence the genome, begun 6 years ago, is now almost finished, and the results could be published this summer.

The announcement marks the beginning of what appears to be shaping up as a milestone year for malaria research. The same groups have now put their teeth into a handful of other *Plasmodium* species, and most could be done before the year is over. To top it off, another international consortium plans to publish the genome sequence of the most important malaria mosquito, *Anopheles gambiae*, also this year. And a new class of inexpensive drugs is showing promise in animal trials (see next story and p. 1311).

Malaria researchers say the flood of new data is a welcome boost for their field. Most of the *Plasmodium* sequence has already been put in public databases and has stirred excitement among scientists, says Dyann Wirth, director of the Harvard Malaria Initiative: "It has really energized the field and brought it together."

The *P. falciparum* genome was cracked in a joint effort by the Sanger Centre in the U.K., The Institute for Genomic Research (TIGR) in Rockville, Maryland, the U.S. Naval Medical Research Center (NMRC) in Silver Spring, Maryland, and Stanford University. When they started in 1996, the teams thought the organism's 30-million-base-pair genome was too hefty to handle for a now-popular technique called whole-genome shotgun sequencing. Instead, they divided up the organism's 14 chromosomes and attacked each of those using the shotgun method.

The project was a "real nightmare," says TIGR's Malcolm Gardner, because adenine and thymine, two of the four building blocks of DNA, together make up 80% of the organism's genome. (The proportion is about 59% in humans.) That made it hard to clone *Plasmodium*'s genetic material in bacteria and to sequence it, says Gardner.

After developing new techniques and software to overcome those problems, the teams now have the sequence almost complete, with more than 10-fold coverage and just over 500 gaps left, most of them in three particularly difficult chromosomes. While some members are trying to close them, others are "working furiously" to annotate the more than 5600 candidate genes found by gene-finding software, Gardner says.

Using the same techniques, the TIGR team has also sequenced the genome of *Plasmodium yoelii,* which causes malaria in rodents, with fivefold coverage; the group is also working on *Plasmodium vivax*, which causes a less severe form of human disease. The Sanger Centre, meanwhile, has taken on several other *Plasmodium* species. Those additional genomes will be particularly useful for researchers using animal models and should help identify what exactly makes *P. falciparum* such a killer to humans.

Already, the raw data posted so far have been "tremendously helpful" for scientists searching for new drugs, says Stewart Shuman of the Sloan-Kettering Institute in New York City, one of many researchers who have dredged the data and come up with new drug targets. One group of German researchers not only found an enzyme that could make a good target, but also discovered that an existing antibiotic could block it, and clinical trials are being planned (*Science*, 3 September 1999, p. 1573).

But new drugs, although desperately needed, won't win the war against malaria, cautions Stephen Hoffman, a veteran malaria researcher at Celera Genomics in Rockville, Maryland, and former head of the Malaria Department at NMRC, who's involved in both the *Plasmodium* and *Anopheles* sequencing projects. Existing drugs can cure malaria, Hoffman points out—but they are too expensive or difficult to get to the people who need them most, and drug resistance is an increasing problem. A vaccine holds the surest hope of preventing the more than 1 million malaria deaths each year, mostly of African children. That's why Hoffman urged his fellow researchers to find such a vaccine, using a concerted, systematic approach—much like the genome project itself.

–MARTIN ENSERINK AND ELIZABETH PENNISI

CREDIT: CHARLES HANLEY/AP

Tragic toll. Malaria kills 1 million children a year, mostly in Africa.

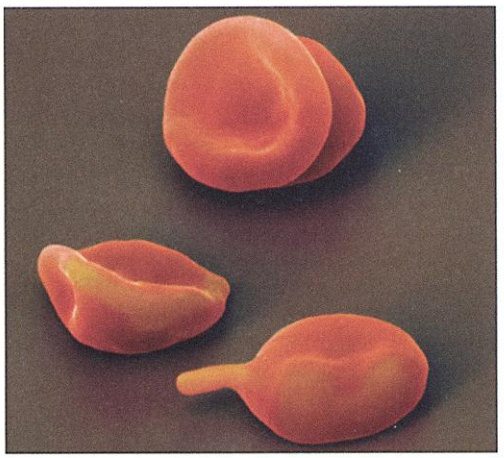
* Second Conference on Microbial Genomes, Las Vegas, Nevada, 10–13 February.

INFECTIOUS DISEASES

Candidate Drug Breaks Down Malaria's Walls

The global picture of malaria is grim: Each year 300 million to 500 million people are infected and more than 1 million die, mostly children under the age of 5. Malaria parasites have become increasingly resistant to the most commonly used and least expensive antimalarial drugs. What's needed, experts say, are new potent and inexpensive drugs, ideally aimed at entirely new therapeutic targets that will make it that much harder for the parasites to acquire multidrug resistance.

On page 1311, a team led by biochemist Henri Vial of the University of Montpellier II and the Centre National de la Recherche Scientifique in France reports on just such a new class of antimalarial drugs, one that has shown remarkable effectiveness in rodents and primates. Unlike most commonly used antimalarials, which target the parasites' hemoglobin metabolism or DNA synthesis, the new compound inhibits the parasites' ability to synthesize protective membranes while sequestered away within red blood cells. The compound "seems to be extremely potent and active against even multidrug-



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, reinvade 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 Gottleib, 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

CREDITS: (TOP TO BOTTOM) OLIVER MECKES/NICOLE OTTAWA/PHOTO RESEARCHERS; STEPHEN CHERNIN/AP; A. SEILACHER *ET AL.*, *SCIENCE* **282**, 80 (1998)

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.