Biomedicine

New attack on *E. coli*, other bacteria

Scientists racing to develop antibiotics that would wipe out new microbes and drug-resistant versions of old ones have developed a novel weapon that robs some bacteria of their ability to produce an outer coating. Without this coating—known as lipid A—the bacteria almost always die. Moreover, tests have shown that any surviving bacteria become hypersensitive to standard antibiotics, such as erythromycin, report Christian R.H. Raetz and his colleagues in the Nov. 8 SCIENCE.

To accomplish this feat, the researchers employed a class of zinc-binding substances that they had discovered earlier. Two of the new drugs—designated L-573,655 and L-161,240—block an enzyme that needs zinc to synthesize lipid A.

"Our compounds were capable of curing mice infected with live *Escherichia coli*," says Raetz, a biochemist at Duke University Medical Center in Durham, N.C. "And we're not nearly at the theoretical limits of potency. Hopefully, we'll develop more potent antibiotics as we continue to refine them."

Novel strategies such as this are urgently needed if researchers are to kill drug-resistant bacteria, says Martti Vaara of the University of Helsinki, Finland, in an accompanying commentary. "Most new agents exert their action on classic targets and are just improved versions of existing drugs."

Disabling the enzyme that produces lipid A may serve another useful purpose, the researchers say. It may prevent septic shock, which occurs in people suffering from overwhelming infections of bacteria coated with lipid A, a potent toxin. About half of the bacteria that infect humans and animals have such a coating.

Vaara notes that long-term clinical trials are needed to determine whether the new compounds are safe and effective.

Tamoxifen therapy should last 5 years

The much-criticized drug tamoxifen—a synthetic hormone widely prescribed to prevent recurrences of breast cancer—should be taken for 5 years after early-stage cancers are removed and should then be stopped, two new studies show.

Tamoxifen has been engulfed in controversy ever since several major studies detected a steep increase in the incidence of uterine cancer among women taking the drug (SN: 4/16/94, p. 247). In March, the World Health Organization formally labeled tamoxifen a carcinogen (SN: 3/2/96, p. 132).

Now, a Swedish study of 3,887 women indicates that those who took tamoxifen for 5 years had fewer recurrences of breast cancer—and fewer related deaths—than women who took the drug for just 2 years, says Lars E. Rutqvist of Karolinska Hospital in Stockholm.

A U.S. study of 2,818 women, known as the National Surgical Adjuvant Breast and Bowel Project, found that the benefits of 5 years' worth of tamoxifen therapy persisted for 5 years after women stopped taking the drug, reports Bernard Fisher of the University of Pittsburgh School of Medicine. Both studies appear in the Nov. 6 JOURNAL OF THE NATIONAL CANCER INSTITUTE.

A second phase of the U.S. study, designed to assess the benefits of taking tamoxifen for a decade, was stopped last December, 6 years early.

Fisher says the results failed to show any additional advantage of a longer course of treatment—or any likelihood that a longer course would be worth the accompanying risk of uterine cancer. Of the U.S. women treated with tamoxifen, 21 developed uterine cancer in the first 5 years, while 17 developed the cancer in the 5 years after treatment. Only four of the women who did not receive tamoxifen developed uterine cancer.

In an accompanying editorial, Sandra Swain of the Greater Washington (D.C.) Area Comprehensive Breast Center, called a 5-year limitation on tamoxifen therapy "prudent," since the risks and benefits of a longer course of treatment remain uncertain.

Evolution

Deflating the biological Big Bang

Charles Darwin and generations of biologists since him have struggled to explain the sudden appearance of animal fossils just after the start of Earth's Cambrian period, 543 million years ago. If evolution were a slow process, as Darwin believed, how could so many groups of animals emerge so abruptly in a biological version of the Big Bang?

A trio of molecular biologists has finally come to Darwin's rescue. Using genes as a clock to time the speed of evolution, they find that various animal phyla emerged about a billion years ago, leaving time for a protracted period of evolution. Gregory A. Wray, Jeffrey S. Levinton, and Leo H. Shapiro of the State University of New York at Stony Brook report their results in the Oct. 25 SCIENCE.

To construct their molecular clock, the Stony Brook scientists analyzed the DNA sequences of seven genes in living animals. Gene sequences change naturally with time. By assuming that the genes mutated at a relatively constant rate, the researchers could use the genetic differences among animals to test how long ago their ancestors split apart.

According to this analysis, the branching of several invertebrate phyla took place about 1.2 billion years ago. Invertebrates diverged from chordates—the phylum to which vertebrates belong—about a billion years ago.

These conclusions have upset some paleontologists because the fossil record shows no sign of such early animals. The oldest fossilized creatures hail from the Vendian period at the end of Precambrian time, roughly 565 million years ago.

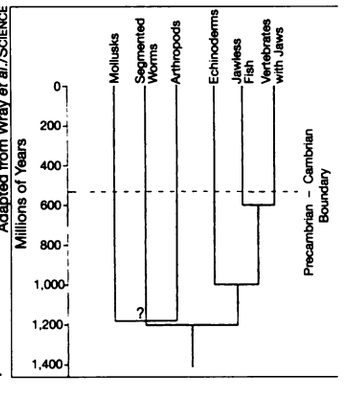
"Paleontologists like to have hard evidence in the form of fossils," says Wray. "But there is the distinct possibility that we're not going to find fossils [from these earliest animals] because they might have been tiny and squishy and not able to leave a fossil record."

If so, the creatures would have evolved for hundreds of millions of years before they eventually grew large enough to produce recognizable fossils at the end of the Precambrian.

Douglas H. Erwin, a paleontologist at the Smithsonian Institution's National Museum of Natural History in Washington, D.C., says the new study improves on past molecular clock efforts. But he takes issue with the technique because Wray and his colleagues calibrated the clock for only the last 500 million years. To pinpoint the emergence of animals, they had to extrapolate rates of genetic change much further back than their calibration point. If genes mutated more quickly early in animal history—as some scientists suspect—then this technique would overestimate the age of animal phyla.

Wray and his colleagues contend that they tested the reliability of the molecular clocks by examining rates of genetic change for different animal groups and for much simpler organisms, such as yeast and fungi. In all cases, the tests indicated steady rates of mutation.

Bruce Runnegar of the University of California, Los Angeles hails the new study because it supports estimates he obtained in 1982 by using blood protein as a molecular clock. "The molecular sequence information is showing us very strongly that the radiation of the animal groups can't have happened at the Cambrian-Precambrian boundary. I don't think we know how early it happened, but it's some long time before the Cambrian," says Runnegar.



Distinct animal phyla may have emerged more than a billion years ago.