Bright Ideas

"It might be possible to prevent malaria by

Beta Blocker Could Also Stop Malaria

Plasmodium *falciparum* is one nasty parasite. The species that causes the most virulent form of malaria, *P. falciparum* kills more than 1 million children each year and is responsible for 25 percent of the infant mortality in Africa, according to the World Health Organization. Growing resistance of *P. falciparum* to cheap and effective anti-malarial drugs is contributing to a resurgence of the disease, especially in sub-Saharan Africa.

Investigators at Vanderbilt University Medical Center and Northwestern University have added another piece to the puzzle of how the malaria parasite enters red blood cells. The team reported last September in *Science* that the red blood cell's own signaling machinery participates in malaria entry, suggesting a new therapeutic approach to fight the deadly parasite.

The new studies demonstrate that drugs developed to block the beta-adrenergic receptor, a receptor important to cardiovascular function and blood pressure control, may be useful agents in the fight against malaria. Propranolol, a so-called "beta blocker," prevented malaria infection of red blood cells in the laboratory and in mice.

"Our studies open a whole new therapeutic dimension for the future," says Heidi E. Hamm, Earl W. Sutherland Jr. Professor and Chair of Pharmacology at Vanderbilt. "The idea that it might be possible to prevent malaria infection by blocking parasite entry into the red blood cell using well characterized, safe and relatively inexpensive drugs like beta blockers is intriguing.

"Of course, it's very far from showing something in vitro or even in mice to actually being able to do this in humans," she says, "but the fact that propranolol is already on the market will speed clinical trials of it as a way to prevent malaria infection in at-risk individuals."

Malaria is a blood-borne illness transmitted by mosquitoes. The malaria parasite infects both liver cells and red blood cells, but it is the blood-cell

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stage of the infection that is responsible for all the symptoms and pathologies of the disease.

Kasturi Haldar, professor of pathology and microbiology-immunology at Northwestern University, has been investigating how malaria infects red blood cells. Her group discovered that the parasite uses "lipid rafts" from the red blood cell membrane to build its own unique membrane-enclosed compartment inside the cell and that a signaling protein, called G-alpha-s, was present in the hijacked membranes. Because Hamm, a recognized expert on G proteins including G-alpha-s, was Haldar's laboratory neighbor at the time, the two began to collaborate.

G proteins act as molecular switches to pass signals along from activated receptors at the cell surface to other proteins inside the cell. Hamm had pioneered an approach to block the interaction of G proteins with receptors, using small

blocking parasite entry into the red blood cell.” —HEIDI E. HAMM


Heidi E. Hamm

peptides—bits of proteins.

The research project will produce a book of essays designed to set the future course for scholars on the subject, a list of relevant books and films, and a Web site to serve as a central source of information.

The peptides designed to block G-alpha-s inhibited *P. falciparum* infection of red blood cells in the laboratory by nearly 90 percent, suggesting that G-alpha-s signaling is playing an important role in the infective process, Hamm said. Because the complete genome of *P. falciparum* has been sequenced, the investigators knew that the parasite does not have any G proteins of its own, confirming that it is using the red blood cell's signaling machinery.

It was known that red blood cells contain at least two types of receptors that activate G-alpha-s: the beta-adrenergic receptor and the adenosine receptor. The investigators wondered if drugs that block these receptors—and therefore also prevent activation of G-alpha-s—would act like the peptides and prevent parasite infection. Propranolol, a beta-adrenergic receptor blocker, had exactly that effect, in both cells and mice.

The results offer an attractive option for fighting malaria before it infects red blood cells, Hamm says, and because the treatment would target red blood cells' own machinery, it should prevent the ability of malaria to evolve resistance to the therapy.

“A lot more basic science research must be done to understand fully how the *P. falciparum* is hijacking red blood cell-signaling machinery,” Hamm says. “It's really a problem of cell fusion and how pathologic organisms change membrane trafficking mechanisms in order to get into cells. Malaria is actually a very useful tool for studying how G proteins are involved in the regulation of membrane trafficking.”

Hamm's and Haldar's coauthors of the *Science* study were Travis Harrison, Benjamin U. Samuel, Thomas Akompong, and Jon W. Lomasney of Northwestern University and Narla Mohandas of the New York Blood Center. The research was supported by the National Institutes of Health.

Rising Gas Prices, Falling Birth Rates

As world reserves of oil and natural gas dwindle over the coming decades—a prospect predicted by many energy experts—the rate at which people in most societies around the world have babies is likely to drop precipitously as well.

That is the prediction of anthropologist Virginia Abernethy, professor emerita of psychiatry at Vanderbilt University, who spoke Feb. 13 in the symposium “From the Ground Up: the Importance of Soil in Sustaining Civilization” at the annual meeting of the American Association for the Advancement of Science, held in Seattle.

“The availability of energy has been a major factor in population growth,” says Abernethy. “In the modern context, energy use per capita affects economic activity. So a prolonged decline in energy use per capita will tend to depress the economy which, in turn, will cause a decline in the fertility rate.”

Abernethy's argument has two parts: the link between the availability of petroleum and the economy, and the link between changes in economic conditions and fertility rates.

Not only does petroleum provide the fuel that powers modern vehicles and the natural gas that people use for home heating and cooking, but petroleum products are the source for hundreds of industrial and agricultural products, including fertilizer, pesticides and plastics. Petroleum cannot be easily replaced by other fuels and feed stocks.

Despite the fact that historically low prices have encouraged Americans and the inhabitants of other industrialized countries to consume oil and gas at profligate rates, “numerous geologists, physicists and computer scientists have calculated that petroleum and liquid natural gas production will begin to plateau and then decline within five to 10 years,” she says.

Such a downturn will have major economic effects, Abernethy expects. In the United States since World War II, rising oil prices have preceded most U.S. recessions, and unemployment rates have risen following significant increases in the real price of oil.

"Higher-priced energy may force policymakers to think of economic recession or slow growth as the usual state, and force farmers to rethink agricultural inputs," says Abernethy. "The shift away from high inputs to soil-conserving technology is theoretically ideal from the perspective of moving to a sustainable agricultural system. The downside, however, is that crops will be smaller and food costs higher—probably much higher—than with industrial agriculture."

The second link, from economic change to the fertility rate, is based on a theory called the "economic opportunity hypothesis" that Abernethy first proposed more than 30 years ago. According to her hypothesis, people increase the size of their families when they are convinced that economic opportunities are expanding, and decrease family size objectives when they believe resources are shrinking and the difficulty of raising children is increasing.

What is important is not how rich or poor a society is, but the perception its people hold about how things are changing. When the future appears threatening, people tend to exercise reproductive caution and adopt such measures as marrying later and putting more space between births within marriage. According to Abernethy, this correlation holds true over the entire socioeconomic range, and its predictions differ substantially from the conventional view that increasing educational levels in a society by itself can reduce fertility rates.

Abernethy uses recent U.S. history to support her proposed energy-fertility link.

The 15-year burst in fertility rates that followed World War II, known as the "baby boom," was accompanied by the widespread substitution of energy-intensive technology for labor that substantially improved productivity. Higher productivity and labor shortage in an expanding economy produced an increasingly large and affluent middle class that "responded with early marriage and closely spaced births." The baby boom ended within a year following rising energy prices and the 1961 recession.

Fertility rates fell to the lowest level ever recorded in the United States following the oil-induced recession of 1980–81. Both white and black fertility rates plunged below replacement level. In the late 1980s, lower oil prices and other factors encouraged rapid job growth. Nevertheless, the bottom half of wage earners enjoyed little increase in real income. So fertility rates rose only slightly, and the recession at the beginning of 1990 reversed the modest upward trend.

"The improving standard of living to which many societies have become accustomed will be difficult to maintain in the face of rapidly rising prices for energy. In these circumstances, fertility rates are unlikely to rise. Indeed, a future marked by declining energy use per capita may be the ultimate driver of worldwide declines in fertility," Abernethy writes.

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Virginia Abernethy

Exploding Stars Confirm Universe's Expansion

3 Hubble Space Telescope measurements of 11 exploding stars throughout the visible universe confirm earlier, ground-based studies that produced the first evidence that the universe is not only expanding, but expanding at an increasing rate.

The new study, which appeared last year in the *Astrophysical Journal,* also provides tantalizing new insights into the nature of the mysterious repulsive force, dubbed "dark energy," that appears to be propelling this runaway expansion.

"As far as the ultimate fate of the universe goes, the most straightforward conclusion is that over the next few billion years it is going to become an increasingly thin, cold and boring place," says Robert Knop, an assistant professor of physics and astronomy at Vanderbilt who led the analysis of supernova data for the Supernova Cosmology Project (SCP), an

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international collaboration of 48 scientists directed from Lawrence Berkeley National Laboratory in California.

Using the Hubble Space Telescope, Knop and his colleagues measured the light curves and spectra of a special kind of exploding star, called a Type 1A supernova, that occurs in binary star systems made up of a normal star and a collapsed star called a white dwarf. Basically, the white dwarf pulls material from its companion until it reaches a critical size, at which point it is consumed in a giant thermonuclear explosion. Astronomers consider Type 1A supernovae to be so similar that their brightness provides a dependable gauge of their distance, and they are so bright that they are visible billions of light years away.

Knowing this, astronomers can get a good estimate of the distance of a Type 1A supernova by comparing its brightness curve with those of comparable stellar outbursts that have taken place nearby. The dimmer the image, the greater the distance. Because it takes light time to travel these great, intergalactic distances, as astronomers look further out into the universe, they are also looking back in time. So the estimates of supernovae distances also provide estimates of the age of their images.

By measuring the extent to which the light spectrum of each of these images has been shifted to longer, redder wavelengths—a phenomenon called "redshift"—astronomers can determine how much the universe has expanded since the time when the star exploded. As the universe expands, the wavelength of light is stretched along with the fabric of the space through which it is traveling. (For relatively nearby "local galaxies," this redshift looks just like the Doppler shift produced by the velocity at which these galaxies are moving away from our galaxy.)

By comparing the redshifts and look-back times of the supernovae, astronomers can measure the rate at which the universe is expanding. The fact that the exploding stars are dimmer and older than expected based on their redshift indicates that the universe is expanding at an increasing rate.

The new study reinforces the initial discovery made five years ago that the expansion rate of the universe appears to be speeding up rather than slowing down, as most scientists had expected. The discovery was made independently by the Supernova Cosmology Project and a competing group, the High-Z Supernova Search Team.

One criticism of the initial studies was the possibility that dust from the distant galaxies may have dimmed the images of the supernovae enough to skew their results. The initial studies used data from supernovae obtained primarily with ground-based telescopes. Because the supernovae images obtained by the Hubble Space Telescope are unaffected by the Earth's atmosphere, they are sharper and stronger than those taken from the ground, and their colors are more accurate. The improved color measurements provided the scientists with a more stringent test of the host-galaxy extinction problem. In addition to absorbing and scattering the supernovae's light, galactic dust should also make a supernova's light redder, much as the sun looks redder at sunset because of dust in the atmosphere. Because the Hubble data show no anomalous reddening with distance, Knop says, the supernovae "pass the test with flying colors."

"Limiting such uncertainties is crucial for using supernovae—or any other astronomical observations—to explore the nature of the universe," says Ariel Goobar, a member of SCP and a professor of particle astrophysics at Stockholm University in Sweden. The extinction test, says Goobar, "eliminates any concern that ordinary host-galaxy dust could be a source of bias for these cosmological results at high-redshifts."

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Robert Knop

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