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Evolutionary Biology and Human Health

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The 2007 AIBS annual meeting focused on the importance of evolutionary biology in many aspects of health science, such as understanding the human genome, the normal functions and malfunctions of human genes, and the origin and evolution of infectious diseases.

A Maasai shepherd moving his goats through Olduvai Gorge lives the way humans lived for much of their early history. The Maasai, who have relied on herding for survival for thousands of years, have evolved the ability to make the enzyme lactase throughout their lives. By applying evolutionary biology to medicine, scientists are finding that many degenerative diseases can be better understood when human adaptations are taken into consideration. Photograph: Ilya Raskin.

Biologists and physicians drew attention to the links between evolutionary biology and human health at this year's annual American Institute of Biological Sciences (AIBS) conference in Washington, DC. More than 250 scientists gathered in May to tease apart the relationships between Darwin's origin-of-species thinking and modern-day medicine. What they found were some of the most surprising connections on Earth, links that will lead to new paradigms in health care, the researchers hope, along with a few lessons learned.

Homo sapiens sapiens has come a long way over the last 10,000 years, moving from hunter-gatherers to today's modern, high-tech society. Despite the many cultural changes our species has gone through, however, the human body and its immune and other systems remain essentially unchanged from those of our early ancestors, says Randolph Nesse, a physician and evolutionary biologist at the University of Michigan–Ann Arbor. "The great mystery of medicine is the presence, in a machine of exquisite

design, of what seem to be flaws, frailties, and makeshift mechanisms that give rise to most disease. The question isn't just how do we get sick, it's why?" The answer, he says, lies in the emerging field of evolutionary medicine.

Nesse and other speakers at the AIBS conference addressed this question. Each arrived at a similar conclusion: Evolutionary biologists and physicians need to join forces to create a new field of Darwinian medicine. "Darwinian medicine is still in its beginning stages," says Richard O'Grady, executive director of AIBS. "But it's evolving at an ever-increasing rate. Evolutionary biology has significance for many areas of health and medicine, not just those that arise from infection." Indeed, speakers at the meeting discussed ways in which evolutionary biologists can collaborate with health-care professionals to better understand diseases like cancer, heart disease, psychiatric disorders, and others.

Darwin's theory of natural selection as the explanation for the functional design of organisms underlies how humans have evolved disease responses. "There are adaptations by which we combat pathogens, adaptations of pathogens that counter our adaptations, maladaptive but necessary costs of our adaptations, and maladaptive mismatches between our body's design and our current environment," Nesse says.

Proximate, or near, questions probe the "what" and "how" of structure and mechanism, while evolutionary questions ask "why" questions about origins and functions. Most medical research seeks proximate explanations about how a part of the body works or how a disease disrupts a function. "The other half of biology, the half that tries to explain what things are for and how they got there," Nesse says, "has been largely neglected in medicine."

"Doctors should be asking, 'Why is a body vulnerable to this or that disease?' and 'Why didn't natural selection make the body less vulnerable?'" Nesse believes. "A lightbulb would go on if they did, and they'd recognize that another entire set of questions needs to be asked about every single disease."

Randolph Nesse introduced the term "Darwinian medicine" with coauthor George Williams in their 1995 book, Why We Get Sick: The New Science of Darwinian Medicine. *He spoke about the relevance of evolutionary biology to human health and the importance of incorporating evolutionary theory into medicine. Photograph: Carroll Photography.*

Decoding the human genome

"It's a spectacular, exciting time to be doing research in human genetics and genomics," said keynote speaker Eric Green, scientific director of the National Human Genome Research Institute's Division of Intramural Research. "Much of this excitement is due to the ability to do more and more powerful sequence-based genome explorations."

The Human Genome Project led to a draft sequence in 2001 and a complete sequence in 2003. "While we marvel at these accomplishments," said Green, "we're also aware in the field of genomics that there's an incredibly tough journey ahead, that of actually interpreting the human genome sequence, something that even at a cursory level is going to take an unknown number of additional years."

A great amount of attention, Green said, is now being focused on studying noncoding regions of the genome. "There's a large [number] of noncoding functional sequences," he said, "that act as regulatory elements to control the expression of genes that mediate chromosome replication, chromosome dynamics, and segregation and that function in ways that aren't even yet described in textbooks."

Darwin knew nothing of DNA and nothing of genomes, Green said. "But he understood that evolution involved this continual tinkering of all species' blueprints, if you will, and a constant attempt to change, to adapt to a change in environment." This tinkering, scientists now know, involved trial-and-error processes that led to major changes in the so-called nonessential, nonfunctional parts of genomes, with the essential, functional components tending to remain the same. "And so, left behind in all existing lifeforms," Green said, "in their genomes, are all sorts of clues about what could and could not be tolerated with respect to change. Evolution has left behind a legacy of successful and failed experiments, all scripted in the genomes of current lifeforms."

Green and his colleagues sequence small, targeted regions of the genome in a large number of vertebrate species. They then systematically compare these sequences to the human reference sequence to identify the most highly conserved regions in the human genome. "We've now targeted over 200 different regions of the human genome for such studies," said Green, "but our flagship target, for which [we have] data from 65 vertebrate species, is a 1.8-megabase region of human chromosome 7. This is the region containing the gene that, when mutated, causes cystic fibrosis." The secrets of this and other diseases may be hidden in the evolution of noncoding regions, Green said.

Besides understanding the importance of the noncoding regions of our genome, Green said, there are some "exciting, new DNA technologies that are going to change the face of sequence exploration...and lead to a whole new revolution of how we might use sequence exploration for answering all sorts of questions."

Emerging viruses

Edward Holmes of Penn State University reported that the ultimate reservoir of the SARS (severe acute respiratory syndrome) virus is, in fact, the horseshoe bat. In his talk on the evolution of emerging viruses, Holmes said that SARS is "an archetypical emerging virus.

It's a new pathogen that caused a new disease. And its ultimate reservoir was not a human. It's not the first, however, to develop in this way, and it won't be the last."

The science of looking at emerging viruses began in the 1980s with AIDS, Holmes said. "As an evolutionary biologist, my interest in these viruses is, are there rules we can develop to understand why some of them have emerged in humans, while others haven't? Why do we have these particular ones and not the myriad of other infectious diseases that circulate in the animal kingdom?"

In fact, he said, there are rules. The first, and simplest, is that almost all emerging infectious diseases caused by viruses are RNA viruses. "That's important because RNA viruses evolve extremely quickly. They lack any kind of error correction mechanism. When they mutate, those errors are perpetuated. And their evolution rates, their mutation rates, are maybe six [orders of magnitude] higher than you see in mammals like humans....That incredible evolutionary mutational power must in some way allow them to jump boundaries and get going in new hosts."

The second rule, he said, is that if you look closely at a list of emerging viruses, they can be categorized by how successful they've been in a new host species. When they jump from an animal to a human, how successful are they in a human? Evolution is the reason, said Holmes, "for why lots of things cross over into humans, but very few establish themselves as proper human pathogens" with human-to-human transmission. AIDS is one of those that did.

There's an ecological factor in why AIDS became an epidemic, Holmes said. "The logging industry in West Africa exposed people to primates that carry the [viral] relative to HIV. And that change in proximity allowed HIV to jump from nonhuman primates to humans. There's always an ecological aspect to these emergences that we must know about" to understand these viruses. Then there are genetic factors determining why some viruses can emerge and some can't, like host susceptibility.

AIBS President Douglas Futuyma (left), professor in the Department of Ecology and Evolution at the State University of New York in Stony Brook, conducted the meeting and introduced speakers, including Edward Holmes (center) and Eric Green. Photograph: Carroll Photography.

"It turns out there's a very strong rule—the closer in evolutionary distance the donor and the recipient species are, the more likely the virus will spread from one to the other and successfully emerge.... Fewer mutations are needed for a primate virus to recognize cells in humans and get itself going. So phylogeny is really critical in understanding emergence."

Holmes also said that with changing ecology, "like deforestation and megacities, more and more [pathogens] will get into human populations.... If there's one thing we learned from SARS, it's that we have to have active disease surveillance and global cooperation.... That virus was knocked out very quickly" because it was controlled so well. "SARS was an advertisement for global cooperation on disease."

Rustom Antia of Emory University used the example of the myxoma virus in rabbits in Australia to talk about how pathogens emerge and why they harm their hosts. The rabbits were introduced into Australia by European settlers. The rabbit population exploded, said Antia, and changed the ecology of the area by eating much of the native vegetation. "Then someone found that the same European rabbit species brought to South America rapidly died of a myxoma infection," he said. "So there was a suggestion that this virus could be used to control [the rapidly expanding] rabbit populations in Australia." So the myxoma virus was introduced there.

A decline in Australia's rabbit population took place, but the virus rapidly evolved. As was shown in this virus in rabbits and in subsequent modeling studies of other viruses in other hosts, Antia said, "the within-host dynamics of a pathogen can be modeled as a sort of race between the pathogen growing and the immune system [response that] it elicits, controlling the pathogen. The pathogen elicits immunity, and immunity controls the pathogen.

"This basic framework shows the interaction between the pathogen and the immune system, in the transmission of a pathogen between an infected host and an uninfected host. The slowly growing pathogen grows and then gets killed by the immune response before it reaches a high density. A very fast-growing pathogen, however, grows fast and then kills the host. Transmission seems to happen most often at the intermediate levels of virulence. At this level, the pathogen grows to a high density but doesn't kill the host," increasing the chances for transmission.

Very simple models, he said, have helped scientists look at the importance of evolutionary changes in driving the emergence of pathogens. "Next we have to bridge immunology and epidemiology," Antia said. "That bridge will help us understand the evolution of virulence in pathogens and the emergence of things like drug resistance." No matter what the pathogen, whether myxoma or influenza, he said, "we need to link within-host dy-

Robert Fleischer (left), head of the Center for Conservation and Evolutionary Genetics at the National Zoo, and Carlos Bustamante (center) listen as Douglas Wallace answers a question during the discussion session on genes and genomics. Photograph: Carroll Photography.

namics to the transmission of a virus in a population to understand why parasites harm their hosts."

Computational methods for gene mapping

How can scientists take in all the genetic variation they see within and between species and begin to patch it together to understand the rules of how form and function have come together in various species? To address this question, Carlos Bustamante of Cornell University analyzed human polymorphisms, and divergence data between humans and chimps, to identify genes that appear to be rapidly evolving and might be involved in recent human molecular evolution.

"Humans share a most recent common ancestor, somewhere on the order of about 100,000 years ago, give or take," said Bustamante. "And if we walk back five million years ago, we'd find ourselves in a population very much like present-day chimpanzees. So how is it that we go from these hairy-looking things to things that look like my wife and daughter, at a real level?"

The question, he said, "is really daunting from a computational view, because there are so many changes, even from our closest recent ancestors. So which mutations and which kinds of genes are responsible for the adaptive molecular evolution of our species? How much of the genetic variation that we see within human populations is functionally important? How much of it is neutral? How much is deleterious? And what types of changes and what types of genes may be involved in human disease?"

If humans and chimps are roughly one percent divergent, said Bustamante, "that translates to somewhere on the order of 30 million nucleotide differences. That's 300,000 changes just in protein coding genes, 100,000 of which are amino acid differences. And 100,000 amino acids is something you can't look at one by one." Then there's the complication that no one can guess how much of noncoding DNA is important.

"So how do we do this? We need computational methods. Likewise, if we just focus on humans, a pair of human chromosomes [is] on the order of 99.9 percent identical, but it's the different one-in-a-thousand base pair that translates to on the order of 10 million variable nucleotide sites in the human genome." A person can't figure out what every amino acid change means, said Bustamante, and computational methods are the only answer.

A mitochondrial paradigm of disease

Each one of us, though we think of ourselves as a single individual, is, in fact, a colony of a hundred trillion individual cells. And our cells have taken the evolutionary strategy, said Douglas Wallace of the University of California–Irvine, of creating a differentiation multicellularity, while inside each of these individuals there is a colony of bacteria, known as mitochondria. "So, in fact, the important concept," Wallace said, "is to not think of ourselves as an entity, but to think of these different organisms as they relate to achieving their ultimate evolutionary goal, which is to optimize the probability that their genetic lineage will be retained from generation to generation."

Until now, said Wallace, "modern medicine—classical medicine—has been based on the structural paradigm of diseases: tissue-specific functions, tissue-specific disease. But now we can say that there is another organism. This is the mitochondrial organism, which has an energy paradigm. This is a holistic effect but has differential tissue-specific effects."

By studying energy flow through mitochondria, Wallace developed an evolutionary paradigm to understand medicine at both the structural and the energetic level. "So the mitochondria are about energy, and life is about the interplay between structure, energy, and information. We humans have what we might call an energy anatomy," a way of looking at our organs and our tissues, through the lens of energy flow through mitochondria. Human degenerative diseases, like cancer or diabetes, and aging are intimately linked to our mitochondria, Wallace said.

"A significant part of our mitochondrial DNA must have been adaptive," he said, "allowing human ancestors to occupy new environments. But some of these same variants, it's beginning to turn out, are now important risk factors for a wide range of common diseases."

In our distant past, we needed to eat large amounts of hard-to-find salt and sugar to survive. Today, eating the amount of salt and sugar we're still "programmed for" can lead to high blood pressure, or to diabetes and metabolic syndrome. Our mitochondrial DNA didn't get the memo: most of us aren't hunter-gatherers any longer.

Genetic variation and adaptation in Africa

Because it's thought that we all originated in Africa, said Sarah Tishkoff of the University of Maryland, "it's critical for reconstructing our human origins to study disease processes there. We know that there is a huge amount of infectious disease in Africa, with HIV, TB, and malaria the three biggest killers. So if we want to identify those variants that are associated with either risk or protection from these diseases, we need to look in Africa."

If we also want to find more effective treatments for ethnically diverse populations, she said, "we need to be studying variants of genes in African populations. Think of it as a footprint that's left behind when there is a strong selection for one of these variants. If we can find those regions that are under selection, maybe we can narrow down some of the variants that are important in disease."

"For the past six years or so we've been going to Africa and collecting samples. We now have about 6500 samples that we've isolated from about 100 different ethnic groups," she said. "We obtain detailed ethnographic information about each individual, but in addition, we're quite interested in obtaining phenotypic information so that we can connect genotype with phenotype and try to map some of these interesting traits."

Tishkoff and colleagues have studied four of the hundred or so ethnic groups in Africa: pygmies from Cameroon, East African pastoralists, East African hunter-gatherers, and a Bantu-speaking group. "They live in very different environments," said Tishkoff, "and have very different diets. They've been exposed to distinct pathogens, so we have every reason to think there could be very distinct adaptation going on in these different populations, both for traits that are associated with disease and those that aren't."

Evolutionary dynamics of cancer

Is genetic instability an early event and the driving force of cancer progression, asks Martin Nowak of Harvard University, or a late-stage by-product? "This is one of the biggest questions in cancer genetics at the moment," said Nowak. "I want to analyze mathematically the evolution that actually initiates the cancer process, and chromosomal instability is very likely an extremely early event that actually drives the process. I'm asking, What is the optimal mutation rate of a cancer cell on the way to cancer progression? Optimum for the cancer, that is, not for the host."

Pictured (from left) are discussion panelist Stephen O'Brien, of the National Cancer Institute, and plenary speakers Rustom Antia, Carlos Bustamante, Sarah Tishkoff, and Martin Nowak. Photograph: Carroll Photography.

All our high-risk tissues, Nowak said, have developed in a way that allows us to avoid or delay the onset of cancer. Evolution has devised an attempt at sidestepping cancer: We have a large number of cells that divide, but these cells are only replenished from a small number of cells in a hierarchy—the stem cells. "Conventional cancer chemotherapy kills all cells that divide," said Nowak. "So you kill the cancer. And often you kill the patient. But you want to help the patient to survive a tremendous amount of poison.

"So now we have molecular targeted therapy that's directed only at the cancer cells. And imatinib, or Gleevec, is the first molecular targeted anticancer therapy drug.... It's highly effective as a treatment of chronic myeloid leukemia." Unfortunately, however, the leukemia stem cell population is somehow spared by Gleevec. "There's no decline of the cancer cell population that drives the disease," Nowak said. "The probability of resistance is determined by the stem cell population size at the start of therapy. The number of cell divisions that generates the leukemia...leads to much higher levels of resistance. Then it depends on the mutation rate and the selective advantage of resistance mutations—even prior to treatment."

Which brings us back to his thesis "that the major stake in the evolution of multicellularity was to make sure that cancer does not happen too early, that cells do what they're supposed to do and don't just go crazy and divide."

Melding evolutionary biology and medicine

Regarded as a founder in the field of Darwinian medicine, Neese said the field is really flowering now. "I think this meeting may be looked back upon as a

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milestone," he said. Evolution is the foundation for all biology, Nesse explains, and its contributions to understanding infectious disease and genetics are widely recognized, but its full potential for use in medicine has yet to be realized. Training in evolutionary thinking, he maintains, can help both biologists and physicians ask important questions they might not otherwise pose.

In his talk, Nesse related a tale of a hospital whose medical staff clearly needed to better understand evolutionary medicine. "Several hospitals were rotating antibiotics, so they'd use one for six months, then they'd all agree to use another for the next six months, and another one for the next six months. This is the ideal way to create antibiotic resistance as fast as you can."

Although anatomy, physiology, biochemistry, and embryology are recognized as basic sciences for medicine, evolutionary biology has not been. Future doctors, Nesse says, are generally not taught evolutionary explanations for why our bodies are vulnerable to certain kinds of failure. The narrowness of the birth canal, the existence of wisdom teeth, and the persistence of genes that cause bipolar disease and senescence all have their origins in our evolutionary history.

In an entire array of clinical and basic science challenges, evolutionary biology is turning out to be crucial. The evolution of antibiotic resistance is becoming more widely recognized, "but few appreciate how competition among bacteria has shaped an evolutionary arms race that has been going on for hundreds of millions of years," wrote Nesse, Stephen Stearns of Yale University, and Gilbert Omenn of the University of Michigan in an editorial in *Science,* "Medicine Needs Evolution" (24 February 2006). "There is a growing recognition that cough and fever are useful responses shaped by natural selection, but knowing when to block them will require studies grounded in an understanding of how selection shaped the systems that regulate such defenses, and the compromises that had to be struck."

What actions would meld evolutionary biology and medicine? Nesse lists three: first, include questions about evolution on medical licensing tests, which would motivate medical school curriculum committees to include evolutionary medicine courses; second, ensure evolutionary expertise in agencies that fund biomedical research; and third, incorporate evolution into every relevant high school, undergraduate, and graduate course.

These changes would help physicians and biomedical researchers understand that both the human body and its pathogens are not perfectly designed machines, but are evolving biological systems shaped by selection under the constraints of trade-offs—trade-offs that produce specific compromises and vulnerabilities. Nesse offers a new twist on Theodosius Dobzhansky's well-known observation: Nothing in *medicine* makes sense except in the light of evolution.

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