Evolution, Health, and Disease

Darwinian Approaches to Medicine

Keynote Speakers: Randolph Nesse (University of Michigan), Paul Ewald (University of Louisville)

Presented by the Center for the Study of Gene Structure and Function at Hunter College and the New York Academy of Sciences

Reported by Don Monroe | Posted May 2, 2007

Overview

The great evolutionary biologist Theodosius Dobzhansky wrote, "Seen in the light of evolution, biology is, perhaps, intellectually the most satisfying and inspiring science. Without that light it becomes a pile of sundry facts, some of them interesting or curious, but making no meaningful picture as a whole."

Evolution's role is equally central in the subset of biology addressing human health and disease. The co-evolution of humans and our pathogens, the rapidly shifting resistance of those pathogens to our antibiotics, and our persistent vulnerability to chronic disease all gain significance when viewed in the context of continuing evolution. These subjects form the core of "Darwinian medicine," also known as "evolutionary medicine."


Sponsorship

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Introduction

"Nothing in biology makes sense, except in the light of evolution," is the oft-quoted title of a 1973 article for biology teachers by the great evolutionary biologist Theodosius Dobzhansky. In it, he writes, "Seen in the light of evolution, biology is, perhaps, intellectually the most satisfying and inspiring science. Without that light it becomes a pile of sundry facts some of them interesting or curious but making no meaningful picture as a whole."

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community convened to discuss issues of evolution, health, and disease, at the 20th Annual International Symposium of the college's Center for Study of Gene Structure and Function. The symposium was organized by professors Michael Steiper, Christopher Braun, and Weigang Qiu, graduate student Jessica Brinkworth, and center director Robert Dottin.

Several speakers emphasized that Darwinian medicine is not "alternative medicine." Instead, it complements the rest of modern medicine by seeking not only proximate causes of diseases—the "how"—but also the longer-term reasons they exist—the "why." If done carelessly, this endeavor degenerates into adaptationism, creating "just-so stories" to explain why "all's for the best in this best of all possible worlds." When the evidence is evaluated critically, however, the evolutionary perspective can provide fundamental insights into the nature of disease and the best ways to treat it.

"Why has natural selection left us so vulnerable to disease?"

The afternoon keynote talk by Randolph Nesse of the University of Michigan helped to frame much of the day's discussion, asking, "Why has natural selection left us so vulnerable to disease?" As central principles of Darwinian medicine, Nesse listed six different explanations for continued disease. These include the limited rate at which we adapt to a changing environment and evolving pathogens, the limited impact that some diseases have on reproduction, and the fact that some unpleasant responses sometimes protect us from more serious problems. Recognizing the evolutionary context of particular diseases is critical to treating them appropriately, he said.

As a possible example of a defensive response, Paul Sherman of Cornell University examined the association between allergy and cancer. For fifty years, he said, there have been hints that allergy sufferers may have less cancer, but the literature is contradictory and inconclusive. Sherman and his colleagues compiled the results of scores of studies, finding that such protective associations predominate. Sherman found that the protective effect was strongest for cancers of tissues that are exposed in some way to the external environment, suggesting that the symptoms themselves may protect sufferers from carcinogens.

Paul Ewald of the University of Louisville has previously made germinal contributions to aspects of Darwinian medicine, for example describing situations where pathogens become more virulent with time. In his morning talk, he focused on the complex interactions between genetic, parasitic, and environmental factors leading to chronic disease. Effective treatment and prevention of disease, he said, depends on identifying the primary cause, as opposed to exacerbating causes. Ewald described in detail what he sees as the primary role of pathogens in atherosclerosis.

Stuart Levy of Tufts University painted an alarming portrait of the growing resistance of bacteria to antibiotics. The selective pressure is enormous, he said, in light of the 35 million pounds of antibiotics produced in this country every year, at least half of it used in animals. We need to recognize that antibiotics are societal drugs, he said, with impacts far beyond the people or animals who are its primary target.

Holly Wichman of the University of Idaho does not study pathogens directly. However, her laboratory experiments on bacteriophages explore the assumptions that underlie current mathematical models for the evolution of microbes, including pathogens. Her team has tracked these viruses over as many as 13,000 generations. They found that, in contrast to the classic theory, mutations in which the fitness changes occur frequently and flow quickly through the whole population.

Steve Mack of the Children's Hospital Oakland Research Institute uses genetic markers in immune-system genes to trace both human migrations and current disease patterns. The human leukocyte antigen region of the genome, which codes for the human versions of the major histocompatibility complexes, shows more variants than any other part of the genome. This polymorphism reflects the evolutionary pressure favoring immune responses to a variety of foreign proteins. The geographic distribution of different variants manifests directly in the distribution of numerous diseases that are associated with this genetic region.

Cristina Gutierrez traced the evolution of the mycobacteria species that causes tuberculosis. This disease remains a major cause of death worldwide, although antibiotics and vaccinations have dramatically reduced the 30% of deaths it caused at the beginning of the last century. Using modern genetic tools, Gutierrez and her colleagues at the Institut Pasteur showed that the classic tuberculosis cluster evolved in close synchrony with humans. A few unusual tuberculosis-causing bacterial strains are closely related to the ancient ancestor of
tuberculosis, dating back almost three million years.

**Arata Kochi**, who recently assumed leadership of the World Health Organization’s Global Malaria Programme, summarized the technical and political issues that have hampered past efforts to control malaria worldwide. He said it is natural for the momentum of such a major effort to flag over decades. Nonetheless, Kochi said, effectively using newly available tools, as well as new funding sources, open the opportunity for renewed progress.

In a talk that went beyond medicine into sociology and politics, **Stephen Bezruchka** summarized the disappointing state of public health in this country. In recent decades, the United States has lost ground relative to other developed countries in public-health measures such as life expectancy and infant mortality. Bezruchka attributes this decline not to absolute wealth, but to unequal distribution of wealth within society. The resulting stress on infants and even fetuses, he said, can affect the health of the population for decades.

This wide-ranging symposium illuminated the exciting advances being made at the intersection between medicine and evolution, both of people and of pathogens. Still, these same opportunities for scientific research into diseases demonstrate how much remains to be done in eliminating or controlling them.

**Why has Natural Selection Left Us So Vulnerable to Disease?**

**Speaker:**
**Randolph Nesse**, University of Michigan

**Highlights**

- Recognizing the role of natural selection in shaping vulnerability to diseases yields profound insights that are useful for medicine.
- Natural selection cannot always keep up with our changing environment or with rapidly evolving pathogens.
- The limits of natural selection leave us vulnerable to disease, as do trade-offs that have advantages as well as disadvantages.
- Natural selection maximizes reproductive success, not the lifespan or health of individuals.
- Defenses such as pain and fever are useful capacities shaped by natural selection, even though they cause suffering and complications in some cases.

**Augmenting medicine with evolutionary insights**

Traditional medical training fails to teach doctors in the profound influence of evolution, said **Randolph Nesse** of the University of Michigan. "Doctors really don't know some of the fundamentals about evolutionary biology."

"We're not asking why some people get sick ... but why all humans are vulnerable to a disease."

Nesse emphasized that evolutionary medicine, also known as Darwinian medicine, is not "alternative medicine," nor does it tell doctors how to practice. Instead, evolutionary medicine addresses not only the immediate mechanism of diseases, but why natural selection has not eliminated aspects of the body that leave it vulnerable to disease. "We're not asking why some people get sick, which is what most medical research asks," Nesse said, "but why all humans are vulnerable to a disease."

The neglect of evolution leads to what Nesse called the "clinician's illusion," in which natural defenses are regarded as defects to be treated. In fact, some responses, like fever and coughing, are protective in some circumstances. Others, like pain and fatigue, can serve as warning indicators. Nesse likened eliminating such symptoms to responding to a car's oil light by clipping the wires rather than by addressing the underlying causes. Fortunately, the body's redundant defenses often protect us from such foolishness, Nesse said, but medicine should more clearly distinguish between these defenses and the true defects that also bring people to doctors.

**Six types of failure**

Natural selection has endowed us with bodies that are flawed in numerous ways, Nesse said, from the appendix
and wisdom teeth to retinal circuitry that blocks light from hitting the retina. "You can design a better body in an afternoon," he asserted. Nonetheless, these flaws can be understood by examining them in an evolutionary context.

Similarly, evolution brings new insights into our continued vulnerability to disease. "Natural selection doesn't just help explain why some things work so well," Nesse said, "it also helps explain why sometimes things work so badly."

Nesse divided evolutionary explanations for disease into six categories. The first two categories reflect the intrinsic sluggishness of natural selection in response to either environmental change or pathogen evolution. Nearsightedness, for example, is clearly a very heritable disease, but it only becomes apparent in cultures that teach young children to read. "It's caused by the modern environment," Nesse observed. "Much disease, and most chronic disease, comes from mismatch with the modern environment." In responding to pathogens, as well, the slow pace of our evolution handicaps us, he said. "We can't outrun them because they evolve so much faster than we do."

**Six Reasons Why Diseases Exist**

- **Selection is slow**
  1. Mismatch: body in a novel environment
  2. Competition with fast evolving organisms

- **Selection is constrained**
  3. Every trait is a trade-off
  4. Constraints on natural selection

- **We misunderstand**
  5. Organisms shaped for R/S, not health
  6. Defenses and suffering

Evolutionary medicine identifies six reasons why natural selection leaves us susceptible to disease.

Two other categories follow the traditional explanation that "selection can't do everything," Nesse said. Adaptations are not free, and will not occur unless the benefits exceed the costs. Such inherent tradeoffs may result in body functions that look surprisingly maladaptive. For example, the uric acid that sometimes leads to gout, and the bilirubin that sometimes causes childhood jaundice, Nesse said, are both potent antioxidants. In addition, selection must make use of available tools, which often depend on historical accidents. We are still living with the poor retina arrangement that arose some 150 million years ago, although the octopus eye shows that a better structure is quite feasible, Nesse said. "It's just bad luck." Still, he said, "no trait in the body can be perfect, because all are compromised by the needs of other traits."

The final two categories are not really flaws in natural selection, Nesse said, but reflect our misunderstandings about it. First, natural selection shapes organisms for reproductive success, not necessarily for health. Nesse suggested the higher death rate for men as an example of this pressure. "For every woman who dies in early adulthood, three men die." Finally, Nesse devoted much of his talk to the sixth category, which concerns the suffering caused by natural defense mechanisms.

**The smoke-detector principle**

"General medicine is mostly blocking natural defenses," Nesse said. "Nausea, vomiting, diarrhea, fever, cough, fatigue, anxiety: They're painful but they're useful," unlike true defects like cancer or stroke.

These defenses may often be deployed when they serve no purpose, however. Drawing from the engineering theory of signal detection, Nesse said that a defense makes sense if the "cost" of the defense is less than the expected damage from the disease. This expected damage, in turn, is the product of the probability that the danger is actually present and the damage it would cause if it were. Thus, an improbable but horrible outcome may justify a
mildly unpleasant defense. "If the defense is cheaper than the danger, do the defense," he said.

"If natural selection is so great, how can we get away with blocking these responses all the time?"

Nesse and his longtime colleague George Williams called this the "smoke-detector principle," Nesse said. "You put up with your smoke detector and all of its false alarms, because you want something to go off every single time there's a fire." In many cases the response will be unnecessary, he said, "but it's perfectly normal."

This perspective helps explain why widespread symptomatic treatment is not killing us, Nesse said. It answers the question, "If natural selection is so great, how can we get away with blocking these responses all the time?"

In some cases, like some immune disorders, the defense response seems to cause more damage than the infection itself. One origin for this flaw, Nesse said, can be seen from the analysis of graded responses. It may seem natural that when the defense is optimal it will cost the same as the cost of the infection. However, depending on the mathematical details, the optimum defense may be more costly, just like the cost of responding to an improbable threat that turns out to be a false alarm.

These examples illustrate the power of evolutionary or Darwinian medicine for explaining not just how, but why the body goes bad. This perspective has been adopted in studies of infectious disease and genetics, Nesse said, but it should be part of the mainstream of medical research and practice. "There's so much more left to do," he argued.

Allergies and Cancers: Are the Complex Relationships Comprehensible?

Speaker:
Paul Sherman, Cornell University

Highlights

- Darwinian medicine suggests that troublesome bodily responses can persist if they sometimes protect the body from much more serious problems.
- Previous studies have sometimes indicated an association between allergies and cancer, but not consistently.
- Combining results from many studies shows that allergies correlate more often with lower cancer risk than with higher risk.
- The reduced risk is strongest for cancers of tissues that are exposed to the environment, supporting the idea that allergic responses directly reduce exposure to carcinogens.

What could be useful about allergies?

Paul Sherman of Cornell University emphasized that Darwinian medicine and traditional medicine are complementary, not alternative approaches. Instead of focusing on proximate causes and how to ameliorate them, he said, Darwinian medicine asks "Why are the symptoms there in the first place, and should they always be ameliorated?"

"What could possibly be useful about such annoying and costly symptoms?"

The possible usefulness of responses like fever—killing germs—and pain—avoiding further injury—seems clear, in spite of their unpleasantness. Even the discomfort of morning sickness may help protect the developing embryo: Sherman previously showed that women who suffer nausea are less likely to have a miscarriage. The irritating symptoms of allergy, however, on which Americans spend some $18 billion a year, seem to be side-effects of a hyperactive immune system. "What could possibly be useful about such annoying and costly symptoms?" Sherman asked.

Conflicting data, conflicting hypotheses
According to Sherman, "for fifty years there has been a persistent hint in the literature that there's some relationship—in fact, almost a protective relationship—between allergies and certain sorts of cancers." Still, major reviews of this topic have found the results to be contradictory and inconclusive. "No consensus has yet emerged," Sherman concluded.

Sherman reviewed three hypotheses that connect allergies and cancer. The "antigenic-stimulation" hypothesis suggests that persistent inflammation and cell growth during allergic responses opens the door for mutations, so that allergies would increase cancer.

In contrast, the "immunosurveillance" hypothesis posits that a hair-trigger immune system that leads to allergies is also more effective at eliminating carcinogens, so that cancer would decrease as a side-effect.

The third hypothesis, "prophylaxis," would also explain how allergic responses also decrease cancer. Rather than being a side effect, however, in this view the allergic responses are favored by natural selection because of their tendency to reject foreign material, which may include carcinogens. Sherman and his colleagues proposed an extension of immunosurveillance to include behavior changes to avoid things that had previously caused a reaction, as in the "smoke detector" principle discussed by Randolph Nesse.

To test these hypotheses, Sherman's team assembled "the most comprehensive database yet available" on allergies and cancers, including the results of 407 studies in 119 publications. The studies looked for associations between various types of cancer and either general or specific allergic responses. Overall, Sherman said, "there is an excess of inverse relationships" between allergies and cancer. Although the results do not completely eliminate the antigenic-stimulation hypothesis, in which allergic responses promote cancer, it favors the other two hypotheses.

A defensive response?

The observed inverse relationship could result from either a hyperactive immune response or a direct protective effect of allergies. To distinguish these immunosurveillance and prophylaxis hypotheses, Sherman looked more closely at particular types of cancer. Specifically, if allergic responses are truly defensive, as in the prophylaxis hypothesis, they should best protect from cancer those tissues having direct contact with the external environment. In contrast, the immunosurveillance hypothesis supposes the symptoms to be unfortunate byproducts of a zealous immune system, so all cancers should be equally affected.

Comparing cancer in different tissues, "the proportion of inverse relationships is much higher," Sherman said, for cancers that "interface directly with the external environment." However, two cancers do not fit this pattern: glioma and pancreatic cancer show a strong inverse relationship although they affect internal tissues. At first, Sherman said, this observation "caused us to rethink the whole thing and think that maybe we were wrong."

A "very strong relationship" emerges between allergies and cancer.

On further evaluation, however, they concluded that both glia (whose stem cells are exposed to chemicals from the nasal epithelium) and pancreatic cells (which can be exposed to intestinal contents if the intervening sphincter malfunctions) should be regarded as special cases. "Both the glia and the pancreas are unusual internal [structures] in that they have, essentially, a direct connection with the external environment," Sherman said. With this reclassification, "a very, very strong relationship emerges" between allergies and cancer in environmentally exposed tissues, Sherman concluded. "Suddenly this maze of conflicting claims starts to parse out a little bit." These results support the prophylaxis hypothesis, in which the allergic responses have a direct role in protecting tissues from the external environment.

Further implications

This hypothesis suggests other relationships. For example, among allergies, "asthma is unusual in that it causes bronchial constriction, and the inability to expel mucus," Sherman said. "It's almost the opposite of normal allergy symptoms," which increase expulsion. The prophylaxis hypothesis (although not its aversive behavior variant) would suggest that asthma could promote cancer, and Sherman's results agree. "When we look at the studies of asthma only, in relation to lung cancer, a larger proportion show positive relationships than show inverse
relationships," in contrast to other allergies.

Even a large meta-analysis is unlikely to resolve all questions, but can suggest ways to focus further research. Sherman's classification of tissues as external or internal, for example, could eliminate a variable that confounded earlier studies. For example, the prophylaxis hypothesis suggests that the association with cancers should be strongest for allergies of externally exposed tissues. The data support this relationship.

People who expressed immunoglobulin E and allergy symptoms were less likely to have toxic chemicals in their bodies.

In a more direct test of the mechanism, if allergies are directly protective, people who have them should have lower levels of environmental carcinogens. "The data on this are very sparse," Sherman acknowledged. The two known studies support this relationship, however, finding that "people who expressed immunoglobulin E and allergy symptoms were less likely to contain dioxins, PCBs, and other known carcinogens."

Finally, if allergy symptoms are themselves protective, Sherman said, then "suppression of the symptoms via desensitization or antihistamines should result in greater vulnerability to cancers." In this case, the few existing studies looking at this very direct test do not fully address the hypothesis, because they mainly focused on internal cancers that would not be protected according to the prophylaxis hypothesis. Moreover, the studies were small and aimed at other questions, however. "I regard this as an open question, not obviously supporting the prophylaxis hypothesis, but not rejecting it either," Sherman said.

Sherman stressed that allergies are only one aspect of a hierarchy of defenses against cancers. However, these results suggest that allergic reactions may join the lists of annoying responses that survive natural selection because they provide a greater direct benefit. Sherman concluded that "further studies have to begin to consider the benefits of allergies as well as the costs," and should reconsider the idea that "allergies are simply immune-system disorders that can be suppressed with impunity."

Gene/Environment Interaction and the Causes of Atherosclerosis

Speaker:
Paul Ewald, University of Louisville

Highlights

- Three types of causes—genetic, pathogenic, and environmental—all contribute to most diseases.
- Researchers should isolate the primary cause of a disease from secondary causes that make it worse but are not required.
- The ε4 allele of the gene for apolipoprotein E is clearly associated with atherosclerosis, but also with stroke, Alzheimer's disease, and multiple sclerosis.
- If a bacterium such as Chlamydia pneumoniae is the primary cause of atherosclerosis, many paradoxes are resolved.
- For diseases caused by pathogens, interventions can be very effective.

A balanced perspective

Most diseases, especially chronic diseases, involve complex interactions between a variety of factors. Unfortunately, said Paul Ewald of the University of Louisville, researchers who are predisposed toward a particular cause for a disease tend to discount evidence pointing to other causes, as exemplified by the skepticism about the bacterial origins of peptic ulcers. To counter this tendency, Ewald advocates "a perspective that keeps everything on the table."

To illustrate this perspective, Ewald uses a triangular diagram. "There are three categories of disease causation," Ewald asserted. "There are genetic causes, parasitic causes, and there's everything else." He acknowledged that lumping all non-parasitic factors, such as diet lifestyle, chemicals, and radiation, into a single "environment category is "a little bit cheating." Still, Ewald said, the patterns and interactions of factors are characteristic for
"To really understand the disease you have to think about the exacerbating effects of infection."

Although much research has focused on identifying risk factors for disease, Ewald said, "this doesn't take us very far." To make real progress, he suggested, researchers need to think in terms of causation. In particular, they should distinguish between primary causes that initiate the disease process and secondary causes that exacerbate it. This does not mean that secondary causes can be ignored, Ewald cautioned. "Diseases often can only be understood if we think about exacerbation."

For example, cystic fibrosis is, in a primary sense, a genetic disease, since without a well-known point mutation it will not occur. Nonetheless, Ewald noted, "to really understand the disease you have to think about the exacerbating effects of infection."

In contrast, for chronic diseases like cardiovascular disease, cancer, diabetes, and Alzheimer's, Ewald said, "I doubt that we're going to get some very conclusive experiment" proving the cause. Because the development of these diseases often takes decades, he said, "this is an area where we really have to use our minds."

Ewald focused on atherosclerosis, "the main contributor to deaths from heart attacks and strokes as a result of blockage of blood vessels." He pointed out that "the pathology of atherosclerosis begins in the teenage years and the early 20s, yet people die of heart attacks in their 40s, 50s, 60s, and 70s." In contrast to the "old view" that fat and cholesterol deposit on the inside of blood vessels, he said, it is now clear that these substances accumulate within the artery wall. "Whatever the primary cause of atherosclerosis is, it has to explain why this is an early stage," he asserted.

Genetics is clearly an important contributor to atherosclerosis, Ewald said. The primary genetic risk factor is a specific "ε4" allele of the gene that codes for apolipoprotein-E, which transports fat and cholesterol.

"We have to reject the 'thrifty-allele' hypothesis" of atherosclerosis.

One popular hypothesis maintains that the ε4 allele is a holdover from pre-agricultural human history, and that it is simply too good at its job in a modern, nutrient-rich culture. Over time, other alleles are replacing ε4, but it is still rather common. Still, although this allele is less common in populations with a long agricultural heritage, Ewald said, even in these cultures agriculture is too recent to explain the observed frequencies. "We really have to reject the thrifty-allele hypothesis that argues that it was the agricultural setting that was responsible for the shift away from ε4."

An additional clue, Ewald said is that ε4 "is the major risk factor not only for atherosclerosis and stroke, but also for sporadic Alzheimer's and multiple sclerosis." The fat transport that influences atherosclerosis is a completely different chemical property than the formation of protein plaques in Alzheimer's or the myelin-sheath destruction in multiple sclerosis. "The idea that ε4 would be bad in all of these different ways," Ewald said, "is really stretching it."

The case for infection

Another possibility, Ewald said, is that "the genetic vulnerability is really a vulnerability to infection: some pathogen could be tracking ε4." In fact, he said, "if we look at atherosclerotic lesions, we see a lot of pathogens in there: Chlamydia pneumoniae, Porphyromonas gingivalis," and others. Moreover, C. pneumoniae, an intracellular parasite, "is strongly associated with multiple sclerosis, and it's also associated with sporadic Alzheimer's disease."

Ewald cited a neglected, nearly decade-old study by Alan Hudson's group, which compared the frequency of the ε4 alleles in people who had various bacteria in the fluid of their joints with people who did not. Although for most bacteria the frequency was unchanged from the 13% background, for C. pneumoniae, "the ε4 frequency is way above the background, almost 65%" with a p-value less than 0.01. "This suggests" Ewald said, "that people who are ε4-positive may be particularly vulnerable to C. pneumoniae," which is a candidate primary cause for atherosclerosis.
Very recently, in fact, Hudson's group has elucidated the specific mechanism by which \textit{C. pneumoniae} "hitchhikes" into cells on the ε4 version of apolipoprotein-E. Altogether, Ewald asserted, this "gets close to what we might call a proof, that \textit{C. pneumoniae} is causally involved in the pathogenesis of atherosclerosis."

**Paradoxes up in smoke**

When infection is viewed as the primary cause of atherosclerosis, Ewald said, "a lot of other paradoxes just start falling into place." Although he alluded to many other examples, he described in detail the increased risk of atherosclerosis associated with smoking.

This risk is often ascribed to direct damage to arteries by toxic compounds in smoke. Although it is surprising that such compounds could lead to damage inside the artery walls, Ewald said, the "really big paradox" involves the increased risk of so-called "second-hand smoke."

A heavy smoker doubles his or her risk of cardiovascular events. Merely living with a smoker, however, increases that risk by one third, although the smoke exposure is smaller than that of a smoker by a factor of a hundred. "Everything just looks wrong in terms of explaining the increased risk of passive smokers in terms of direct damage from the smoke," Ewald said. "There just doesn't seem to be enough smoke."

"If you live with a smoker, you're more likely to get the type of infections that are primary candidates for causing atherosclerosis."

This paradox vanishes, however, if the primary cause of atherosclerosis is infection. "One thing we know is that smoking increases vulnerability to these infections in the lungs," Ewald said, or, for \textit{P. gingivalis}, in the mouth. "The effect of second-hand smoke, then, is that "if you live with a smoker you're more likely to get infections from the kinds of pathogens that are primary candidates for causing atherosclerosis."

Other chronic diseases show a similar pattern, Ewald asserted. "When you look at infections, all sorts of paradoxes evaporate. Things start making sense" when known risk factors are seen as interacting with infection, rather than simply adding together to determine the risk of disease.

The view that many of the big killers are primarily caused by parasites is "very exciting," Ewald said. "When we find out that disease is caused by infections, our track record is that we can almost always do something important. If we can block the initial stage of infection, then we are able to have tremendous numbers of people who are able to live much longer lives."

**The Ecology of Antibiotic Resistance**

**Speaker:**
**Stuart Levy**, Tufts University

**Highlights**

- Bacteria have many mechanisms for exchanging genetic information, including that which confers resistance to antibiotics.
- Most bacteria have strains that are resistant to more than one class of antibiotics; some have strains that are resistant to everything available.
- Antibiotics should be viewed in terms of their impact on society, not just on individual people or animals.
- At least half of the antibiotics used in the United States are for animals, and four-fifths of these are given in low doses to speed weight gain.
- Much resistance develops, not in the patients given antibiotics, but in the surrounding environment.

**A growing problem**

"You'll often hear that antibiotic resistance is inevitable," said **Stuart Levy** of Tufts University, "and it probably is." Nonetheless, the ubiquity of resistance genes, in both pathogenic and benign bacteria, is not by itself a problem.
The resistance problem occurs because of the selective pressure caused by widespread use of antibiotics. "Unfortunately, we aren't changing to deal differently with resistant bacteria," Levy said. By modifying our antibiotic use to better account for resistance, he said, "we can prevent it from becoming a resistance problem."

By modifying our antibiotic use, "we can prevent it from becoming a resistance problem."

Resistance genes can appear through mutations within a species. In addition, however, "bacteria have evolved fantastic ways of exchanging genes to make up for what they might be missing in their chromosomes," Levy said. Bacteriophages, transposons, plasmids, and even naked DNA can transfer resistance between even distantly related species. "Resistance is not stationary," Levy commented, because both bacteria and resistance genes can move between populations.

The selective pressure encouraging resistance is enormous. "An estimated 35 million pounds of antibiotics are produced and used in this country yearly," Levy said. "This is an enormous amount of drug being used, not just for humans but also for animals and agriculture."

In fact, more than half of these antibiotics are used in agriculture. Some are used prophylactically, in part to counter high animal densities. However, "the most disturbing," Levy said, "is the use of these antibiotics in low amounts for growth promotion." This usage accounts for 80% of the antibiotics given to animals in this country, and includes drugs like streptomycin, tetracycline, and penicillins that are still used for people.

**Local treatment, global impact**

The development of resistance depends not only on the amount of antibiotic used, but on how widely it is distributed, a factor Levy calls the "selection density." "If you distribute the same amount of antibiotic among 10 times more people or animals, they all become factories," he said of antibiotic resistant bacteria.

Abundant data show the connection between human antibiotic usage and resistance, at the level of the hospital ward or in the larger community. One study comparing entire European countries, Levy said, concluded that "the more antibiotic used, the more resistance you see."

Antibiotic use therefore directly affects the wider community. "The thing about antibiotics that's different from any other therapeutic is that these are societal drugs," Levy said. "The treatment of the individual really affects the members of the family and the community."

"Antibiotics are societal drugs."

Many bacteria are also developing simultaneous resistance to many antibiotics. The best known example is MRSA, which initially meant "methicillin-resistant S. aureus, but now the "MR" can also mean "multidrug-resistant." Unfortunately, "there are also other organisms that are becoming resistant to two, three, or four different antibiotics," Levy said. "We're dealing, in this particular era, with multidrug resistance."

Hospitals have long been recognized as a breeding ground for resistant bacteria because of their extensive antibiotic use, but strains resistant to multiple drugs are now arising elsewhere. For example, community-associated (or acquired) MRSA, Levy said, "is a new, very dangerous, very upsetting problem," resulting from the widespread use of antibiotics. "This is a phenomenon that emerged not in the hospitals but in the community. We don't know why. We don't know how." (For more information on MRSA, see the eBriefing [SuperStaph: Tracking a Virulent New Community-Bred MRSA.](#))

**Out in the world**

Levy suggested that resistance frequently arises in bacteria other than the intended target. "I'm not convinced that the first stage of the antibiotic usage, that is in the treatment of a person, is where resistance emerges, because it's very rare in a patient." Instead, he said, it emerges "when these drugs and these bacteria meet out in the environment."

Resistance may develop when drugs and bacteria meet in the environment.
For example, Levy described a study in which patients taking erythromycin quickly developed skin flora that were resistant to the drug. Although this is not surprising, the study found that other people in the same house had a similar change in their skin flora. This resistance selection, he said, can be viewed as resulting from exposure to "second-hand antibiotics."

He and his colleagues also compared farm chickens that were given low doses of antibiotics with others who were not. The chickens developed resistance within two weeks. More disturbingly, "farm workers showed the same thing twelve weeks later," even though they weren't taking the antibiotic. "There's an enormous impact of antibiotics on food animals," Levy said, and "resistant bacteria can move from animals to people very easily."

Such findings are also particularly disturbing in view of the widespread use of "antibacterials" in consumer products from soaps to chopsticks. These products typically use triclosan, whose target is the same as one of the drugs of choice for tuberculosis.

Researchers have learned a great deal about antibiotic resistance, Levy said. For example with enough antibiotic use, resistance will eventually appear, and it will not disappear immediately when antibiotics are stopped. The development also occurs in steps, and bacteria tend to accumulate additional resistances. These lessons will not solve the problems of antibiotic resistance, however, unless people learn how to use antibiotics differently.

**Experimental Evolution in a Virus Model System**

**Speaker:**
Holly Wichman, University of Idaho

**Highlights**

- Experimental testing is critical to understanding how pathogens evolve.
- The adaptation of bacteriophages to a novel environment occurs through a series of waves in which a mutation spreads throughout the population.
- Parallel evolution, in which similar starting organisms evolve in similar ways, occurs surprisingly often.
- In contrast to the classic adaptive walk described by Fisher, the laboratory system often takes large steps in fitness.
- Close collaboration between experimental biologists and mathematicians leads to rapid refinement of models.

**13,000 generations of evolution**

The microorganisms that cause disease are continually evolving: developing resistance to antibiotics, finding new ways to evade the immune system, and switching between different animal hosts. To understand these phenomena, "we would like to have a predictive theory about pathogen evolution," said Holly Wichman of the University of Idaho. Such a theory will build on decades of research in population genetics.

"We're now in a position to test some of the assumptions behind these theories for the first time." Wichman said. She and her colleagues are exploring evolution experimentally, using the bacteriophage ΦX174. "There are a lot of complexities in evolutionary theories that are best addressed in an experimental system," she observed.

Complexities in evolutionary theories "are best addressed in an experimental system."

This virus system has many advantages for exploring evolution, Wichman said. "Bacteriophages evolve rapidly, they're very cheap to work with, and they're safe." Although they are not human pathogens, the principles that drive their evolution should be more broadly applicable. In addition, they have huge populations. "We can pump through the equivalent of the human population of the earth every few minutes or hours," she observed, running the virus through cycles of replication in a closed chemostat. "The longest experiment we've done is about 13,000 generations," accumulating a genetic difference comparable to that between humans and chimps. "We can push evolution pretty far in these kinds of systems."
In addition, the phage's simple genome, comprising only 11 genes, makes it relatively easy to genetically modify and repeatedly sequence. The small genome allows the researchers to connect genetic changes more easily to phenotype and to fitness. Wichman commented, "It's fairly easy to do evolution with this experimental system and characterize it."

### Adaptive Sweeps

The versatile phage system has demonstrated several unexpected aspects of evolution, Wichman said. "The system, despite the fact that it is simple, never fails to surprise me."

For example, "in most of our experiments, evolution can be characterized as a series of external sweeps," Wichman said. By repeated genetic sequencing, the researchers monitored the prevalence of a new mutation among their viruses. "In general, a substitution would arise and sweep through" until the mutation was shared by virtually the entire population.

Different experimental runs of phage systems shared many of the same mutations.

"The other thing that really did surprise us was the amount of parallel evolution," Wichman said. The researchers found that experimental runs under different conditions shared many mutations—about half of the changes were the same between two different runs. "The same changes occurred independently," she said.

In addition, these mutations were dominated by substitutions that code for different amino acids. "This doesn't look anything like comparisons that you would get if you were looking at random organisms from the wild, because there's this huge excess of nonsynonymous substitutions," she observed.

Nonetheless, the researchers found that the specific amino-acid substitutions at which evolution was occurring in the lab were also frequently observed when they sequenced organisms from the wild. "There are a fair number of shared changes," Wichman said. Significant changes occurred in two genes, one for the lysis protein that disrupts the host cells and the other for the major protein of the viral coat.

### Exploring the mutational landscape

![Mutations moving the organism closer to the optimum are beneficial.](image)

In the classic Fisher model, adaptation towards optimal fitness is dominated by small-fitness changes, since large changes overshoot the optimum. The virus experiments disagree with this model.

In a typical experiment, Wichman's team takes a phage that is well adapted to one environment or host cell and expose it to a completely novel environment or host. As the viruses evolve to become better adapted to their new situation, their fitness, as measured by their doubling rate, often increases dramatically in a single mutation. "We found extremely huge fitness effects," Wichman said.
This observation contrasts sharply with Fisher's classic model for adaptation. In this model, the fitness "landscape" is viewed as a surface whose altitude is lowest for the most fit organisms. Upon finding itself far from the optimum, an organism will evolve by mutations that take it to other points on the landscape. According to Fisher, the mutational steps should individually have a small effect on the fitness. "We don't see small effects in the lab," Wichman said. In practice, however, the most interesting features of pathogen evolution, such as host switching or drug resistance, are also not small effects. These large size of the fitness jumps the researchers see, she said, "doesn't fit in with population genetic theory at all."

**Refining the models**

Wichman has assembled an interdisciplinary team to use the experimental data to help develop and refine population-genetic theories, building on the mutational-landscape model of Gillespie and Orr. A key insight of those models is that a complete description of how fitness depends on genetic makeup is too hard. "We have this totally unpredictable distribution of fitness effects that's really hard to model mathematically," Wichman said. The small fraction of mutations that make the virus better, however, represent an extreme tail of the distribution, and can be modeled using a technique called extreme-value theory. This kind of theory, she said, "gives us testable predictions."

Indeed, in a careful series of experiments Wichman's team identified nine adaptive mutations of the phage, all of which affected similar positions in the virus structure. The frequencies of the various mutations did not at first agree very well with the predictions from extreme value theory. The agreement improved, however, when the researchers accounted for the fact that transversions, which interchange of purine and pyrimidine bases, occurs more slowly than transitions that do not.

"If we want a really good predictive model, we have to test the underlying assumptions."

One risk of the experimental approach is that it tends to emphasize large changes in fitness. Wichman's team compensated for this problem by normalizing all jumps to the smallest one observed. They also found ways to pool data across experiments to increase the statistical power. Without such techniques, Wichman said, replicating the experiment is likely to simply find "the same thing over and over."

Finally, the researchers also found disagreement with a key assumption when the previous model was applied to two experimental data sets. It remains to be determined how such violations will affect predictions that have been made based on these models.

These experimental studies, and the close collaboration with mathematical modelers, subject the theory of evolution to rigorous tests that have practical implications for pathogen evolution. Previous theoretical understanding depended on unvalidated assumptions, leading Wichman to advise, "If we want a really good predictive model, we have to test the underlying assumptions."

**Using the Human Major Histocompatibility Complex to Study Disease**

**Speaker:**
Steven J. Mack, Children's Hospital Oakland Research Institute and Roche Molecular Systems

**Highlights**

- **Human leukocyte antigen (HLA),** the human version of the major histocompatibility complex (MHC), is coded by the most variable region in the human genome, with hundreds of variants at some loci.
- **The genetic diversity of this region is preserved by "balancing selection," presumably because multiple MHC alleles can present a more diverse set of antigens to generate an immune response to changing pathogens.
- **The high prevalence of nasopharyngeal cancer in Chinese and Taiwanese populations is associated with a specific allele at one HLA locus, which appears to impede the binding of a virus-related peptide.**
- **Various combinations of HLA alleles are associated with large changes in risk for type 1 diabetes, but the relationship is complex.**
The brain of the immune system

The adaptive immune system lets vertebrates respond to a tremendous variety of assaults by identifying foreign peptides and activating a T-cell response to them. Short peptides from either inside or outside of cells are presented at the cell surface within a pocket of the Class I or Class II Major Histocompatibility Complex (MHC), respectively.

The genes coding for the MHC in humans are in a region on chromosome 6 designated HLA, for human leukocyte antigen. "It's the most polymorphic region of the genome," said Steve Mack of Children's Hospital Oakland Research Institute. Most of the variation occurs in six specific loci, referred to as A, B, C (or Class I MHC), DP, DQ, and DR (or Class II).

"In the HLA region, we have to contend with 830 alleles across populations."

The extent of the variation is "really quite amazing," Mack commented. As of last fall, for example, researchers had identified 830 distinct alleles in the B locus, with other regions also featuring of hundreds of possible variants. "Many people are interested in SNPs," or single-nucleotide polymorphisms, Mack said, where researchers track "one common allele and one less-common allele. In the HLA region, we have to contend with 830 alleles across populations." Many of these alleles are rather rare, however.

The polymorphic loci of HLA region code for the protein that forms the pocket that binds the peptide and presents it to T-cell receptors. The genetic diversity thus plays a direct role in the immune system's ability to respond to diverse threats. "A given amino-acid change," Mack said, "can really affect the nature of the pocket that's formed, and affect the specificity of what peptide can be presented."

Recent advances in technology, using arrays of immobilized, sequence-specific DNA probes, give Mack and his colleagues a "bar code that tells you what the HLA genotype is for a given individual." The technique also identifies both of the alleles that are present when an individual is heterozygous in a given locus.

The new tools are much more powerful than traditional, serological methods of HLA classification. For the DR locus, for example, the antibodies used in the older technique are primarily sensitive to the N-terminal ends of the molecule. The serological method can only distinguish 25 variations, in contrast to the 541 alleles that genotyping reveals.

Valuing diversity

We see balancing selection, which favors diversity of alleles, in almost all populations and in most HLA genes.

The importance of diversity in immune response has a profound effect on the evolution of the HLA region. Mack and his colleagues examined in detail the probabilities of finding pairs of identical alleles for HLA in various populations. In cases where a particular allele is advantageous, such homozygous pairs become increasingly likely over time. In contrast, they conclude that the natural selection has favored different alleles, in what is known as balancing selection. "This can result from the interaction of genotype and disease," as when multiple alleles allow for a more diverse set of responses to infection.

"We see balancing selection in almost all populations around the world," Mack concluded. One notable exception occurs in isolated populations in Java, presumably in response to the prevalence of a specific pathogen. The trend towards diversity applies throughout the HLA region of the genome. "For most HLA loci, the overall trend is toward balancing selection," Mack said. As a result of this balancing selection, the distribution of alleles around the world makes HLA a special window into the historical human migration patterns.

A simple connection to a cancer

"HLA is associated with a wide variety of diseases," Mack said, although generally other factors are also important. These diseases include not only infectious diseases and others that are clearly tied to the immune
system, such as type 1 diabetes and multiple sclerosis, but also some types of cancer.

The connection to HLA is particularly straightforward for nasopharyngeal carcinoma, or NPC, which Mack described as "the most common cancer that you've never heard of." Although rare in most parts of the world, he said, this cancer is very common in China and Taiwan. The cancer is associated with the ubiquitous Epstein-Barr virus, and also with some chemical exposures.

Among Chinese populations, this cancer is associated with the HLA alleles that are serologically identified as A2. In European populations, however, the A2 serotype is not associated with NPC. The resolution of this puzzle lies in the failure of the serological technique to make important distinctions between genotypes. The increased risk associated with A2 in Chinese populations actually arises from a particular genotype of A2 that is rare in European populations.

Interestingly, the increased risk is associated with a single amino-acid change in the A locus, which affects the affinity of the binding pocket. "The change is reducing to a very great extent the ability to present Epstein-Barr co-proteins to the T-cell receptor," Mack comments. The inability to mount an immune response to the Epstein-Barr virus, together with other factors, increases the risk of NPC.

The prevalence of NPC in China directly reflects the prevalence of certain HLA alleles, Mack said. "The disease is regionally distributed because the polymorphism is regionally distributed."

A complex connection to diabetes

HLA is also a major factor in type 1 diabetes, which is an autoimmune response to insulin-producing cells in the pancreas. Genome scans consistently associate markers in the HLA region with type 1 diabetes, Mack said, with very high confidence levels. "Every study we do, the strongest factor is the HLA region."

In every study of type 1 diabetes, the "strongest factor is the HLA region."

The relationship is not as simple as that in NPC, however. Genotyping shows that patients who developed the disease as infants or small children are likely to be heterozygous, with a mixed DR3/DR4 genotype. Other specific genotypes give an increased chance of developing diabetes later in life.

One concern with such studies is that the genetic signature that seems to implicate the HLA genes could simply be a marker for another nearby gene. If the genes are close enough, they will tend to be found together, or linked, as part of the same haplotype. Detailed analysis, however, shows that the alleles at two separate HLA loci contribute to the effect in a complicated interaction. "It's not simply that there's one marker that is responsible for conferring risk and may be linked to something nearby. There are two markers working together somehow," Mack commented.

The details of how specific haplotypes affect the presentation of peptides such as those derived from insulin remains unclear. However, the geographical distribution of diabetes risk around the world, Mack said, clearly reflects the distribution of various HLA haplotypes.

The highly variable HLA region therefore provides important information about the prevalence and distribution of diseases, as well as historical insight into human origins and migration.

Parallel Origin and Diversity of Tuberculosis Agents and Humans

Speaker:
Cristina Gutierrez, Institut Pasteur

Highlights

- Modern genetic tools have clarified the relationships among the different species in the Mycobacterium genus that cause tuberculosis.
- Tuberculosis did not arise from cattle, because human, bovine, and other species that make up the M. tuberculosis "cluster" share a common ancestor some 35,000 years ago.
The rare tuberculosis-causing bacteria that grow in smooth cultures are genetically very distinct from one another and from the classic tuberculosis cluster, and probably derive from a common "prototuberculosis" species that arose about three million years ago.

The genetic relationships among strains of tuberculosis mirror the relationships among people deduced from mitochondrial DNA, suggesting that they arose and evolved together.

**Whence tuberculosis?**

Human tuberculosis is a very ancient disease, said Cristina Gutierrez of the Pasteur Institute, referred to in the Old Testament and found in Egyptian and Peruvian mummies. The bacterium *Mycobacterium tuberculosis*, the causative bacterium, has been found only in humans. The disease spreads directly between people through the air.

The death rate from tuberculosis has declined significantly due to antibiotics and vaccination since the 19th century, when it was the major killer worldwide. "At the beginning of the last century, more than 30% of deaths were due to this disease in the world," Gutierrez said. Even today, roughly one-third of Earth's population serves as the only reservoir for the bacterium, nine million new cases appear every year, and drug-resistant strains have emerged.

"It is very clear that *M. bovis*, which infects cattle, is not the origin of *M. tuberculosis.*"

Closely related species of the *Mycobacterium* genus are found in cattle, goats, mice, and sea lions. Together these species comprise the *Mycobacterium tuberculosis* complex, or MTBC. The last common ancestor of the species in the MTBC is only about 35,000 years old. "For a long time," Gutierrez said, "the hypothesis was that the origin of tuberculosis was transmission from cattle to humans during the development of agriculture," perhaps 8000 or 9000 years ago.

Since the 1990s, however, molecular methods have changed this picture. Researchers have sequenced the entire genome of *M. tuberculosis*, and have found many molecular markers, including mutations, deletions, variable-number tandem repeats, and insertion sequences. "For each strain," said Gutierrez, "we are able to recognize a bar code using these molecular markers."

Using this information, researchers assembled a complete evolutionary tree for the MTBC. "It is very clear that *M. bovis* [the species that infects cattle] is not the origin of *M. tuberculosis*, because both share a last common ancestor," Gutierrez said. To explain the diversity in the complex, that ancestor must date to about 70,000 years ago. There are no signs of genomic exchange between the branches, she added. "This is really a clone, a clone that expanded very aggressively" about 35,000 years ago.

**Following human migrations**

Using the genetic markers, the researchers also tracked the more recent history of the bacterium. "There are eight main genetic groups of *M. tuberculosis*," Gutierrez said, and these groups are distributed differently around the world. For example, the "Beijing family" is widespread in Asia, but "virtually absent in other parts of the world. We can see this variability with all the molecular markers that we analyze," she said.

"The reservoir for tuberculosis corresponds to one third of the global population."

Combining this molecular information into a phylogenetic tree shows a global population structure for tuberculosis. "What is really surprising," Gutierrez said, is that each of the branches of the tuberculosis family tree has a specific geographic distribution, based on the origin of the patients from whom the bacteria were isolated. The most ancient bacteria, those most closely related to the common ancestor appear in East Africa and Asia, hinting that the diversity of *M. tuberculosis* mirrors the migration patterns of early humans.

**A window into the ancient past**

To further explore the development of the tuberculosis complex, Gutierrez and her colleagues explored the very
rare human tuberculosis-causing species, *M. canetii*. This species, first isolated more than 30 years ago in a patient from Madagascar, "was described as the first to diverge from the last common ancestor," Gutierrez said. The reality turned out to be even more profound.

*M. canetii* is distinctive because it forms smooth, glossy colonies in culture. "This is completely different than all the *M. tuberculosis* we know," Gutierrez observed. She and her colleagues collected a small group of 37 samples of similar, smooth tuberculosis bacteria, mostly from patients who lived in East Africa or had traveled there. "In the beginning," she said, "we thought these were just this bacterium, *M. canetii."

"The genomic distances among these smooth-culturing bacteria are much larger than for the traditional tuberculosis cluster."

Molecular markers, however, showed that these bacteria were very different from one another. "Some were like the *canetii* variant, but others were completely different." By analyzing a group of housekeeping genes, her team found that "the genomic distance among these bacteria is much larger than for the traditional cluster," the MTBC. Also, instead of a tree, the relationships showed a net-like topology, indicating significant genetic exchange between them.

Based on this analysis, Gutierrez suggests that the smooth variants are related to a much more distant ancestor of the species in the tuberculosis cluster. She estimates the age of the divergence from this ancestor, dubbed *M. prototuberculosis*, at 2.6–2.8 million years. This is the period when the first hominids were starting to evolve.

Gutierrez suggests that, "like man, tuberculosis bacteria came from East Africa," about three million years ago. "These bacteria recombined and gave the last common ancestor for the TB complex. After that, this complex expanded with the human emigration wave all around the world, around 35,000 years ago." The evolution and spread of tuberculosis and of man thus appear to be intimately entwined.

### A New Approach to Fighting Malaria

**Speaker:**
**Arata Kochi**, World Health Organization

**Highlights**

- A major effort in the 1950s eradicated malaria in much of the world.
- Declining attention has left malaria a major problem in tropical Africa, the Indian subcontinent, Southeast Asia and the Caribbean.
- There may be 350–500 million cases worldwide, and 1.2 million deaths, but the numbers are uncertain because there is no clear definition.
- To limit the development of drug-resistant strains, single drugs should not be used against malaria.
- Potential vaccines should be measured against simple prophylactic measures, in particular bed nets infused with long-lasting insecticide.

**A measure of success**

Although malaria is not as serious a threat as it once was, especially in developed countries, it remains a significant problem. For **Arata Kochi**, however, who took over the malaria program at the World Health Organization (WHO) in late 2005 after years of fighting tuberculosis, the major challenge is to use tools that are already available more effectively.

"Many parts of the world succeeded to eradicate malaria" in the years after World War II.

In the years following World War II, Kochi said, "many parts of the world succeeded to eradicate malaria." This success was mainly due to spraying with DDT and to new medicines. Since the 1970s, however, deaths have risen in Africa as the population swelled and the parasite developed resistance to existing drugs.

The reduced enthusiasm for malaria control was natural, Kochi said. For one thing, malaria had basically
disappeared in the rich countries. In addition, he said, it is difficult to concentrate on an issue for decades. "People start to get tired, or bored." Nonetheless, effectively using newly available tools and funds—sources like The Global Fund to Fight AIDS, Tuberculosis, and Malaria—could create new opportunities for progress.

**Technical and political challenges**

Kochi said the best estimate is about 1.2 million deaths from malaria each year. But he complained that the small, static, and fractious malaria community has no consensus on how to define malaria, particularly in tropical Africa where it is most active. "There is no strong leadership in terms of epidemiology," Kochi said, so "I cannot take any responsibility for this figure."

"In the history of malaria disease, we lost all the single drugs by drug resistance."

Previous efforts to reinvigorate the malaria effort, such as the Roll Back Malaria campaign begun in 1998, have met with mixed results, Kochi said. The campaign's targets included widespread access to treatment within 24 hours of the first symptoms. This is hard to measure, but treatment is often much slower. Although half of children are treated, Kochi said, "it cannot be considered 'prompt and effective treatment.'" The results fell short of other goals as well, although there was a "clear success" in reducing reported cases as well as deaths.

An important reason why the targets were missed, Kochi said, was weak WHO leadership, both technical and political. For example, the best current treatments for malaria are clearly artemisinin-based combination therapies, or ACTs, which were develop in the early 1990s. These drugs exploit the effectiveness of artemisinin, to which resistance has not yet developed, but combine it with older antibiotics to sustain this effectiveness. However, powerful countries wanted to continue using older drugs, in spite of growing evidence of resistance. In the face of this pressure, Kochi said, "WHO couldn't take a position very clearly."

A similar conflict slowed the distribution of insecticide-treated bed nets, which are known to be very effective. The U.S. Agency for International Development, a major donor, advocated distribution through commercial channels, although the $5–$10 cost is too high for many African families. "This kind of a conflict, based on ideology or philosophy, is still prevailing," Kochi said.

Indoor residual spraying, generally with DDT, also faced opposition, Kochi observed. "Until very recently, WHO wasn't very keen to promote DDT, even though the data form southern Africa is very clear that effective use of DDT can reduce deaths by about 70%–80%.

In contrast, for tuberculosis, "there is a agreement" about the best approaches, Kochi claimed. "Everybody does it the same way. Thus we can make them accountable for what they are doing."

**New approaches, new tools**

"We have to use all available cost-effective tools in our arsenal," Kochi said. The most feasible intervention is long-lasting insecticidal bed nets," or LLINs, Kochi said, in which insecticide is embedded in the fibers. "They last five years, and they're quite effective." Over the last year or two, production backlogs have been solved, so the nets are available in the needed quantities.

"The most feasible intervention is long-lasting insecticidal bed nets."

Kochi also advocates indoor spraying with residual insecticide, including DDT. "The technology is there and the tool is there, and it's very simple to use." Other new tools are rapid diagnostic tests, or RDTs, that permit prompt, effective treatment.

Although ACTs are the most effective drugs, Kochi said, they must be used with care to prevent the development of resistance. To this end, he has strongly encouraged companies to eliminate treatments that contain only a single drug. "You've got to protect the effectiveness of the very important drugs. In the history of malaria disease, we lost all the single drugs by drug resistance, some of them in less than one year," he said. "Once we use artemisinin, it will probably take more than ten years before a new drug comes."

Although research naturally focuses on possible vaccines, Kochi suggested that they be compared with LLINs.
This tool is "highly efficacious," he said, reducing deaths by 20% if they are widely distributed. "We can deliver this with one contact," using the same distribution channels currently use for immunizations, he said. "Unless [the] coming vaccine is better than this, I don't know if it's worthwhile to produce it or not."

**Targeting Childhood Development to Make the Nation Healthy Again**

*Speaker: Stephen Bezruchka, University of Washington*

**Highlights**

- Despite spending half of the world's health-care budget, the United States compares poorly with other developed countries in terms of life expectancy and other public-health measures.
- Poor public health appears to correlate with economic inequality, rather than absolute poverty level.
- The public-health impact of inequality may arise in part because of higher stress, both in adults and in children.
- Since prenatal and early childhood environment influence health throughout life, it may take decades for any changes to have an effect.

**The health of a nation**

"Individual behaviors," said Stephen Bezruchka of the University of Washington, "may not be the really important determinants of the health of populations." Japan, for example, has the highest prevalence of (male) smokers, but has the highest life expectancy of any country in the world. In contrast, Bezruchka said, "The United States is not very healthy compared to other countries," generally ranking 30th or worse. The infant mortality rate in this country is dramatically higher than that in other industrialized countries.

"The United States is not very healthy compared to other countries."

It has not always been so. After World War II, U.S. health was among the world's best by these measures. Although the U.S. has improved, other countries have improved much more. At this point, "the life-expectancy gap between us and the healthiest country in the world is significant," even though "we spend half the worlds' health-care bill," Bezruchka said. "Whatever it's buying us, it's not buying us a healthy, long life." He also cited other behaviors, such as teenage birth rates and murder rates, in which the United States fares poorly compared to other countries.

**Income versus income distribution**

"If you take anything away" from his talk, Bezruchka said, it is the simple concept that "poorer people have poorer health." In sub-Saharan Africa, where AIDS is prevalent, as well as in the former Soviet Union, overall health has actually been declining since the 1990s. "Health has been improving," Bezruchka observed, "but not everywhere."

Bezruchka's central thesis, however, concerned not the role of absolute poverty, but that of income distribution within a society. Since the pioneering 1992 paper by Richard Wilkinson in *BMJ*, many researchers have looked at the effect of societal inequality on measures of public health. Currently, Bezruchka said, "We have close to 200 studies linking income distribution and health, and about 70% of them are supportive of this relationship," that inequality degrades health.

"We have close to 200 studies linking income distribution and health, and about 70% of them are supportive" of the idea that inequality degrades health.

Within the United States, Bezruchka said, there is "tremendous disparity" in life expectancy, from a range of 70 to 90 years in different counties. Individual states with more income inequality also have lower life expectancy. "This suggests some relationship between some measure of hierarchy in a state and its mortality rate," Bezruchka said. As a country, wealth in the U.S. is more unevenly distributed than in most other countries, which may explain the short life expectancy in spite of high average income.
How could income distribution affect health, and so profoundly? "I would suggest that what's impacting all of these behaviors and the mortality outcomes is chronic stress in society," Bezruchka said. The disempowering effects of hierarchy on society's weakest members, he asserted, induce self-destructive and life-shortening behavior, which the mortality statistics reflect.

**Lasting effects of childhood stress**

More profoundly, Bezruchka asserted, "it's early life where hierarchy matters most." The best study of this issue so far, he said, is the 1958 British birth-cohort study, which tracked a complete cross-section of Britons born in the first week of March 1958. Researchers concluded that early life experiences continue to influence the self-assessed health of these subjects even at age 33. Issues such as birth weight, growth to age 7, early social and emotional status, and schooling and parenting, Bezruchka said, are at least as important as things that happened later in life. That suggests, he said, that health is governed by "very important factors that come to light before we really make any conscious choices about our lives."

"Conditions that affect growth *in utero* have profound effects on your health in your 50s, 60s, and 70s."

Bezruchka also described studies showing the profound effects of maternal health during pregnancy, which he suggested reflected the damaging effects of stress. One study, for example, found that "conditions that affect growth *in utero* have profound effects on your health in your 50s, 60s, and 70s," including coronary heart disease, hypertension, and type 2 diabetes.

Bezruchka concluded that policies aimed at mothers and infants should be a high public-health priority. Such policies include more aggressive spending on childhood poverty and education, as well as paid maternity leave policy; the U.S. is one of only a handful of countries without such a policy. "Secure attachment in early childhood, I think, is the most important thing that societies can promote." Bezruchka said. Still, he cautioned, the persistent effects of childhood environment suggest that "if we're going to see changes in population health over long periods of time, we're going to have to play up through generations."

**Open Questions**

How well does laboratory bacteriophage evolution resemble pathogen evolution?

Can antibiotics or vaccines prevent atherosclerosis?

Do antihistamines cause cancer?

Why is a poor nation's health more dependent on inequality than on absolute poverty?

Will the new initiatives against malaria succeed?

Will widespread use of antibacterials create resistance to the preferred antibiotic for tuberculosis?

What will it take to bring evolutionary perspectives into the medical mainstream?

How do the complex genotypes associated with diabetes affect immune response?

Why doesn't every genetically susceptible person develop disease when exposed to risk factors?

Will tuberculosis again become a dominant killer because of antibiotic resistance?

Will humankind survive longer than tuberculosis agents?

**Media**

Slides & Audio
Darwinian Medicine: Why has Natural Selection Left Us So Vulnerable to Disease?

Gene/Environment Interaction and the Causes of Atherosclerosis

The Ecology of Antibiotic Resistance

Experimental Evolution in a Virus Model System

Using the Human Major Histocompatibility Complex to Study Disease, Natural Selection, and Human Evolution

Parallel Origin and Diversity of Tuberculosis Agents and Humans

A New Approach to Fighting Malaria

Targeting Childhood Development to Make the Nation Healthy Again

Symposium Introduction

Introduction to Morning Session

Introduction to Afternoon Session

Web Sites

Center for the Study of Gene Structure and Function at Hunter College
A consortium based at Hunter College that brings together biologists, chemists, biopsychologists, biophysicists, and bioanthropologists working within the CUNY system. Additional information about this conference is available on their Web site: Evolution, Health & Disease.

Alliance for the Prudent Use of Antibiotics
A nonprofit organization dedicated to promoting proper antibiotic use and curbing antibiotic resistance worldwide.

**Evolution and Medicine Network**  
A resource for scientists and medical professionals working at the interface of evolutionary biology and medicine.

**The Global Fund to Fight AIDS, Tuberculosis, and Malaria**  
A partnership between governments, civil society, the private sector and affected communities organized to coordinate efforts and leverage resources to fight these diseases.

**The Global Malaria Programme at the World Health Organization**  
Lots of information here about malaria and the WHO's efforts to prevent its spread.

**Institut Pasteur**  
A non-profit private foundation which contributes to the prevention and treatment of disease, primarily infectious diseases, through research, education, and public health activities.

**National Evolutionary Synthesis Center (NESCent)**  
A collaborative effort of Duke University, The University of North Carolina at Chapel Hill, and North Carolina State University working to facilitate synthetic research into fundamental questions of evolutionary biology.

**Population Health Forum at the University of Washington**  
Stephen Bezruchka leads this organization of health activists whose mission is to raise awareness and initiate dialogue about the ways in which political, economic, and social inequalities interact to affect the overall health status of our society.

**Program on Disease Evolution**  
The interdisciplinary graduate program at the University of Louisville, bringing an evolutionary perspective to the study of health and disease.

**The SITVIT Database**  
Molecular markers database for *Mycobacterium tuberculosis* at the Pasteur Institute.

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**Books**


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**Journal Articles**

Darwinian Medicine: Why has Natural Selection Left Us So Vulnerable to Disease?


**Allergies and Cancers: Are the Complex Relationships Comprehensible?**


**Gene/Environment Interaction and the Causes of Atherosclerosis**


**The Ecology of Antibiotic Resistance**


**Experimental Evolution in a Virus Model System**


Using the Human Major Histocompatibility Complex to Study Disease, Natural Selection and Human Evolution


Parallel Origin and Diversity of Tuberculosis Agents and Humans


Targeting Childhood Development to Make the Nation Healthy Again


Speakers
Randolph Nesse is professor of psychiatry, professor of psychology, and research professor at the Research Center for Group Dynamics at the Institute for Social Research at the University of Michigan. He also directs Michigan's Evolution and Human Adaptation Program and is a founder of the field of Darwinian medicine. His early research was on the neuroendocrinology of anxiety and the treatment of anxiety disorders. Currently he is dedicated to advancing the field of Darwinian medicine, with special attention to implications for psychiatry. His specific research now focuses on the evolutionary origins of emotions, especially mood and moral emotions that make committed relationships possible.

Paul W. Sherman, PhD

Paul Sherman teaches courses and seminars in behavioral ecology, animal behavior, and Darwinian medicine at Cornell University. In 2005 he was appointed an S. H. Weiss Presidential Fellow in recognition of "effective, inspiring, and distinguished teaching." He was a Sigma Xi National Lecturer in 2004–06, and was elected a Fellow of the Animal Behavior Society in 2004.

Sherman's research has contributed to scientific understanding in six general areas: altruism, kin recognition, eusociality, sexual selection, conservation biology, and Darwinian medicine. He has studied birds, insects, and mammals, including an insect-like mammal, the naked mole-rat.

Sherman completed his doctoral studies at the University of Michigan, followed by a Miller Postdoctoral Fellowship at the University of California, Berkeley. He joined the Cornell faculty in 1981, was awarded tenure in 1985, and was promoted to full professor in 1991.

Paul W. Ewald, PhD

Paul Ewald is a professor of biology and director of the Program on Disease Evolution at the University of Louisville. He holds appointment in the Department of Biology at the Academic campus and the Department of Microbiology and Immunology at the School of Medicine. Professor Ewald received his PhD from the University of Washington with a specialization in evolutionary biology. He was the first recipient of the Smithsonian Institution's George E. Burch Fellowship in Theoretic Medicine and Affiliated Sciences. Prior to joining University of Louisville, Ewald was on the faculty at Amherst College, where he achieved full professorship and was the Dominic Paino Professor of Global Environmental Studies. During this time he also held and adjunct appointment at the University of Massachusetts.

Ewald was a principle founder of the discipline evolutionary medicine, by virtue of the papers and books he has published from 1980 onwards. He is the author of Evolution of Infectious Disease (Oxford) which is widely acknowledged as the watershed event for the emergence of this discipline. His second book Plague Time (Free Press & Anchor) integrated many of these ideas with our emerging understanding of the broad role of germs as causes of chronic diseases. In addition to his work for scientific journals, Ewald has also written widely for popular magazines and newspapers, has lectured extensively around the world, and has made approximately 200 television appearances.

Stuart B. Levy, MD

Tufts University
Stuart Levy is the director of the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine and Staff Physician at the New England Medical Center. He also serves as president of the Alliance for the Prudent Use of Antibiotics. He is a past president of the American Society for Microbiology and cofounder and chief scientific officer of Paratek Pharmaceuticals, Inc.

In addition to his papers on antibiotic use and resistance for scientific journals, Levy has edited four books and two special journal editions on the subject, including *The Antibiotic Paradox: How Miracle Drugs Are Destroying the Miracle*. In his research, he led the discovery of the first characterized energy-dependent antibiotic efflux mechanism and efflux protein, that for tetracycline resistance. His interests have expanded to the phenomenon of multidrug resistance in bacterial and mammalian cells.

Levy is a fellow of the American College of Physicians, Infectious Disease Society of America, and the American Academy of Microbiology. He has organized and chaired several significant committees on drug resistance and consults to many prominent international and national organizations. He is an editor of Plasmid and serves on editorial boards for a number of journals, including *Antimicrobial Agents & Chemotherapy*. He has been a lecturer for the American Society for Microbiology Foundation and the Australia Society for Microbiology. He has served twice as a member of the Comite Scientifique d'Evaluation of the Pasteur Institute, Paris. Among his awards are the Hoechst-Roussel Award for esteemed research in antimicrobial chemotherapy by the American Society for Microbiology and honorary degrees in biology from Wesleyan University and Des Moines University.

Holly A. Wichman, PhD

*University of Idaho*

[web site] [publications]

Holly Wichman is a professor in the Department of Biological Sciences at the University of Idaho. In her recent work she is conducting experimental studies of bacteriophages aimed at understanding the rules of viral evolution. Recognizing that short-term evolution contributes to health problems such as drug resistance and host switching, researchers in Wichman's laboratory study short-term adaptation at the molecular level to ask whether it is possible to learn the rules of molecular evolution on this time scale. She also teaches courses in genetics and experimental approaches in the biological sciences.

Steven J. Mack, PhD

*Children's Hospital Oakland Research Institute*

*[e-mail]* [publications]

Steven Mack earned his PhD in molecular and cell biology in Allan Wilson's laboratory at the University of California, Berkeley in 1996, studying the molecular evolution of mitochondrial DNA and MHC genes in Native American populations. He then completed a postdoc position with Henry Erlich at Roche Molecular Systems, studying the population genetics and molecular evolution of MHC in human populations. From 1999 to 2005, he co-chaired the anthropology and human genetic diversity components of the 13th and 14th international histocompatibility workshops, and served on the histocompatibility committee of the National Marrow Donor Program. Mack is now an assistant staff scientist at the Children's Hospital Oakland Research Institute.

Cristina Gutierrez, MD, PhD

*Institut Pasteur*

*[e-mail]* [publications]

Cristina Gutierrez obtained her medical degree and her PhD in molecular biology, both from the University of Santiago de Compostela, Spain. In 1996, she received her specialty in medical microbiology from the Spanish Ministry of Education. She is presently a senior researcher at the Institut Pasteur, Paris. Gutierrez has worked to develop molecular methods for characterizing the agents of tuberculosis and other mycobacteria, and has studied the molecular evolution of tuberculosis agents and their diversity in different human populations. Recently, on the basis of her experience with mycobacteria, she and her collaborators have challenged the hypothesis of a
recent origin for human tuberculosis.

Gutierrez has worked as deputy director at the French National Reference Center for Mycobacteria, was a founder-member of the European network for surveillance of multidrug-resistant tuberculosis, and since 2000 has taught at the Institut Pasteur School for Post-graduate Training. She is active in national and international mycobacteriology societies, and is a scientific advisor for the French High Council of Public Health.

Arata Kochi, MD, PhD

World Health Organization

e-mail | web site | publications

Arata Kochi is director of the Global Malaria Programme at the World Health Organization. Previously, he served in several key leadership posts at WHO, including leading efforts to revise and strengthen its programs to control the global tuberculosis (TB) epidemic. Because of new control practices he initiated, nearly 60% of TB patients now receive this quality treatment and care. In 2001, Kochi became the director of WHO's HIV Department and initiated AIDS treatment in poor countries which lead to the "3 by 5" initiative.

Kochi was trained as a medical doctor at Japan's Tohoku University Medical School, where he also obtained a PhD in social medicine. He also holds MPH and MS degrees from the Harvard School of Public Health. He has extensive field experience, having worked for UNICEF as a health and nutrition expert in Myanmar and Afghanistan.

Stephen A. Bezruchka, MD

University of Washington

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Stephen Bezruchka is a senior lecturer in the Department of Health Services at the University of Washington School of Public Health and Community Medicine. He set up and facilitated the introductory component of their Community Oriented Public Health Practice MPH curriculum, creating learning opportunities for students to study problems in groups rather than learning by lecture. He received the 2002 Outstanding Teacher Award in the School of Public Health. Bezruchka's main interest is to disseminate information about population health and for this purposes he maintains a web site. He also runs a forum at the University of Washington to advance understanding of population health concepts. He is currently helping to develop curricula on population health for middle and high schools, and speaks widely to groups including the homeless, teachers, student groups, church organizations, unions, and political action networks.

Bezruchka continues to practice medicine as an emergency physician both in the United States and abroad. He has also worked in Nepal for over ten years in community health projects, setting up remote district hospitals as teaching institution for Nepali family practice doctors and supervising them in their rotations there. He currently works with Nepali doctors there to improve surgical services in remote hospitals.

Bezruchka graduated from Stanford Medical School in 1973 after completing a master's in mathematics at Harvard. He also has a master's in public health from Johns Hopkins University.

Don Monroe

Don Monroe is a science writer based in Murray Hill, New Jersey. After getting a PhD in physics from MIT, he spent more than fifteen years doing research in physics and electronics technology at Bell Labs. He writes on biology, physics, and technology.

The Center for the Study of Gene Structure and Function at Hunter College