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A New Germ Theory

The dictates of evolution virtually demand that the causes of some of humanity's chronic and most baffling "noninfectious" illnesses will turn out to be pathogens -- that is the radical view of a prominent evolutionary biologist

by Judith Hooper

A LATE-SEPTEMBER heat wave enveloped Amherst College, and young people milled about in shorts or sleeveless summer frocks, or read books on the grass. Inside the red-brick buildings framing the leafy quadrangle students listened to lectures on Ellison and Emerson, on Paul Verlaine and the Holy Roman Empire. Few suspected that strains of the organism that causes cholera were growing nearby, in the Life Sciences Building. If they had known, they would probably not have grasped the implications. But these particular strains of cholera make Paul Ewald smile; they are strong evidence that he is on the right track. Knowing the rules of evolutionary biology, he believes, can change the course of infectious disease.

In a hallway of the Life Sciences Building an anonymous student has scrawled above a display of glossy photographs and vitae of the faculty, "We are the water; you are but the sponge." This is the home of Amherst's biology department, where Paul Ewald is a professor. He is also the author of the seminal book *Evolution of Infectious Disease* and of a long list of influential papers. Sandy-haired, trim, and handsome in an all-American way, he looks considerably younger than his forty-five years. Conspicuously outdoorsy for an academic, he would not seem out of place in an L. L. Bean catalogue, with a golden retriever by his side. Ewald rides his bike to the campus every day in decent weather -- and in weather one might not consider decent -- from the nearby hill village of Shutesbury, where he lives with his wife, Chris, and two teenage children in a restored eighteenth-century house.

As far as Ewald is concerned, Darwin's legacy is the most interesting thing on the planet. The appeal of evolutionary theory is that it is a grand unifying principle, linking all organisms, from protozoa to Presidents, and yet its essence is simple and transparent. "Darwin only had a couple of basic tenets," Ewald observed recently in his office. "You have heritable variation, and you've got differences in survival and reproduction among the variants. That's the beauty of it. It has to be true -- it's like arithmetic. And if there is life on other planets, natural selection has to be the fundamental organizing principle there, too."

These Darwinian laws have led Ewald to a new theory: that diseases we have long ascribed to genetic or environmental factors -- including some forms of heart disease, cancer, and mental illness -- are in many cases actually caused by infections. Before we take up this theory, we need to spend a moment with Ewald's earlier work.

Paul Ewald

Ewald began in typical evolutionary terrain, studying hummingbirds and other creatures visible to the naked eye. It was on a 1977 field trip to study a species called Harris's sparrow in Kansas that a bad case of diarrhea laid him up for a few days and changed the course of his career. The more he meditated on how Darwinian principles might apply to the organisms responsible for his distress -- asking himself, for instance, what impact treating the diarrhea would have on the vast populations of bacteria evolving within his intestine -- the more obsessed he became. Was his diarrhea a strategy used by the pathogen to spread itself, he wondered, or was it a defense employed by the host -- his body -- to flush out the invader? If he curbed the diarrhea with medication, would he be benefiting the invader or the host? Ewald's paper outlining his speculations about diarrhea was published in 1980, in the *Journal of Theoretical Biology.* By then Ewald was on his way to becoming the Darwin of the microworld.

"Ironically," he says, "natural selection was first recognized as operating in large organisms, and ignored in the very organisms in which it is especially powerful -- the microorganisms that cause disease. The time scale is so much shorter and the selective pressures so much more intense. You can get evolutionary change in disease organisms in months or weeks. In something like zebras you'd have to wait many centuries to see it."

For decades medical science was dominated by the doctrine of "commensalism" -- the notion that the pathogen-host relationship inevitably evolves toward peaceful coexistence, and the pathogen itself toward mildness, because it is in the germ's interest to keep its host alive. This sounds plausible, but it happens to be wrong. The Darwinian struggle of people and germs is not necessarily so benign. Evolutionary change in germs can go either way, as parasitologists and population geneticists have realized -- toward mildness or toward virulence. It was Ewald's insight to realize what we might do about it.

Manipulating the Enemy

SAY you're a disease organism -- a rhinovirus, perhaps, the cause of one of the many varieties of the common cold; or the mycobacterium that causes tuberculosis; or perhaps the pathogen that immobilized Ewald with diarrhea. Your best bet is to multiply inside your host as fast as you can. However, if you produce too many copies of yourself, you'll risk killing or immobilizing your host before you can spread. If you're the average airborne respiratory virus, it's best if your host is well enough to go to work and sneeze on people in the subway.

Now imagine that host mobility is unnecessary for transmission. If you're a germ that can travel from person to person by way of a "vector," or carrier, such as a mosquito or a tsetse fly, you can

afford to become very harmful. This is why, Ewald argues, insect-borne diseases such as yellow fever, malaria, and sleeping sickness get so ugly. Cholera uses another kind of vector for transmission: it is generally waterborne, traveling easily by way of fecal matter shed into the water supply. And it, too, is very ugly.

"Here's the [safety] hood where we handle the cholera," Jill Saunders explained as we toured the basement lab in Amherst's Life Sciences Building where cholera strains are stored in industrial refrigerators after their arrival from hospitals in Peru, Chile, and Guatemala. "We always wear gloves." A medical-school-bound senior from the Boston suburbs, Saunders is one of Ewald's honor students. As she guided me around, pointing out centrifuges, -80 degree freezers, and doors with BIOHAZARD warnings, we passed a closet-sized room as hot and steamy as the tropical zones where hemorrhagic fevers thrive. She said, "This is the incubation room, where we grow the cholera."

Cholera invaded Peru in 1991 and quickly spread throughout South and Central America, in the process providing a ready-made experiment for Ewald. On the day of my tour Saunders had presented to the assembled biology department her honors project, "Geographical Variations in the Virulence of *Vibrio cholerae* in Latin America." The data compressed in her tables and bar graphs were evidence for Ewald's central thesis: it is possible to influence a disease organism's evolution to your advantage. Saunders used a standard assay, called ELISA, to measure the amount of toxin produced by different strains of cholera, thus inferring the virulence of *V. cholerae* variants from several Latin American regions. Then she and Ewald looked at figures for water quality -- what percentage of the population had potable water, for example -- and looked for correlations. If virulent strains correlated with a contaminated water supply, and if, conversely, mild strains took over where the water was clean, the implication would be that *V. cholerae* becomes increasingly mild when it cannot use water as a vector. When the pathogen is denied easy access to new hosts through fecal matter in the water system, its transmission depends on infected people moving into contact with healthy ones. In this scenario the less-toxic variants would prevail, because these strains do not incapacitate or kill the host before they can be spread to others. If this turned out to be true, it would constitute the kind of evidence that Ewald expected to find.

The dots on Saunders's graphs made it plain that cholera strains are virulent in Guatemala, where the water is bad, and mild in Chile, where water quality is good. "The Chilean data show how quickly it can become mild in response to different selective pressures," Ewald explained. "Public-health people try to keep a disease from spreading in a population, and they don't realize that we can also change the organism itself. If you can make an organism very mild, it works like a natural vaccine against the virulent strains. That's the most preventive of preventive medicine: when you can change the organism so it doesn't make you sick." Strains of the cholera agent isolated from Texas and Louisiana produce such small amounts of toxin that almost no one who is infected with them will come down with cholera.

Joseph Schall, a professor of biology at the University of Vermont, offers a comment on Ewald's work: "If Paul is right, it may be that the application of an evolutionary theory to public health could save millions of lives. It's a stunning idea. If we're able to manipulate the evolutionary trajectory of our friends -- domestic animals and crops -- why not do the same with our enemies, with cholera, malaria, and HIV? As Thomas Huxley said when he read Darwin, "How stupid of me not to have thought of that before." I thought when I heard Paul's idea, "Gee, why didn't *I* think of that?"

Ewald put forward his virulence theories in *Evolution of Infectious Disease*. Today his book is on the syllabus for just about every college course in Darwinian medicine or its equivalent. "I regard him as a major figure in the field," says Robert Trivers, a prominent evolutionary biologist who holds professorships in anthropology and biology at Rutgers University. "It is a shame his work isn't better known to the public-health and medical establishments, who are willfully ignorant of evolutionary logic throughout their training." While praising Ewald's boldness and originality, some of his peers caution that his data need to be independently corroborated, and others object that his hypotheses are too crude to capture the teeming complexity of microbial evolution. "Evolutionary biologists have had very poor success in explaining how an organism evolves in response to its environment," says James Bull, an evolutionary geneticist at the University of Texas. "Trying to understand a two-species interaction should be even more complicated."

Recently, in any case, Ewald has adopted a new cause, far more radical but equally rooted in evolution. Let's call it Germ Theory, Part II. It offers a new way to think about the causes of some of humanity's chronic and most baffling illnesses. Ewald's view, to put it simply, is that the culprits will often turn out to be pathogens -- that the dictates of evolution virtually demand that this be so.

The Case for Infection

GERM Theory, Part I, the edifice built by men like Louis Pasteur, Edward Jenner, and Robert Koch, took medicine out of the Dark Ages. It wasn't "bad air" or "bad blood" that caused diseases like malaria and yellow fever but pathogens transmitted by mosquitoes. Tuberculosis was famously tracked to an airborne pathogen, *Mycobacterium tuberculosis,* by Robert Koch, the great German scientist who in 1905 won a Nobel Prize for his work. Koch also revolutionized medical epidemiology by laying out his famous four postulates, which have set the standard for proof of infectivity up to the present day. The postulates dictate that a microbe must be (a) found in an animal (or person) with the disease; (b) isolated and grown in culture; (c) injected into a healthy experimental animal, producing the disease in question; and then (d) recovered from the experimentally diseased animal and shown to be the same pathogen as the original.

By the early twentieth century the whole landscape had changed. Most of the common killer diseases, including smallpox, diphtheria, bubonic plague, flu, whooping cough, yellow fever, and TB, were understood to be caused by pathogens. Vaccines were devised against some, and by the 1950s antibiotics could easily cure many others. Smallpox was actually wiped off the face of the earth (if you don't count a few strains preserved in laboratories in the United States and Russia).

By the 1960s and 1970s the prevailing mood was one of optimism. Ewald is fond of quoting from a 1972 edition of a classic medical textbook: "The most likely forecast about the future of infectious disease is that it will be very dull." At least in the developed world, infectious diseases no longer seemed very threatening. Far scarier were the diseases that the medical world said were not infectious: heart disease, cancer, diabetes, and so on. No one foresaw the devastation of AIDS, or the serial outbreaks of deadly new infections such as Legionnaire's disease, Ebola and Marburg

hemorrhagic fevers, antibiotic-resistant tuberculosis, "flesh-eating" staph infections, hepatitis C, and Rift Valley fever.

The infectious age is, we now know, far from over. Furthermore, it appears that many diseases we didn't think were infectious may be caused by infectious agents after all. Ewald observes,"By guiding researchers down one path, Koch's postulates directed them away from alternate ones. Researchers were guided away from diseases that might have been infectious but had little chance of fulfilling the postulates." That is, just because we couldn't readily discover their cause, we rather arbitrarily decided that the so-called chronic diseases of the late twentieth century must be hereditary or environmental or "multifactorial." And, Ewald contends, we have frequently been wrong.

Germ Theory, Part II, as conceived by Ewald and his collaborator, Gregory M. Cochran, flows from the timeless logic of evolutionary fitness. Coined by Darwin to refer to the fit between an organism and its environment, the term has come to mean the evolutionary success of an organism relative to competing organisms. Genetic traits that may be unfavorable to an organism's survival or reproduction do not persist in the gene pool for very long. Natural selection, by its very definition, weeds them out in short order. By this logic, any inherited disease or trait that has a serious impact on fitness must fade over time, because the genes that spell out that disease or trait will be passed on to fewer and fewer individuals in future generations. Therefore, in considering common illnesses with severe fitness costs, we may presume that they are unlikely to have a genetic cause. If we cannot track them to some hostile environmental element (including lifestyle), Ewald argues, then we must look elsewhere for the explanation. "When diseases have been present in human populations for many generations and still have a substantial negative impact on people's fitness," he says, "they are likely to have infectious causes."

Although its fitness-reducing dimensions are difficult to calculate, the ordinary stomach ulcer is the best recent example of a common ailment for which an infectious agent -- to the surprise of almost everyone -- turns out to be responsible.

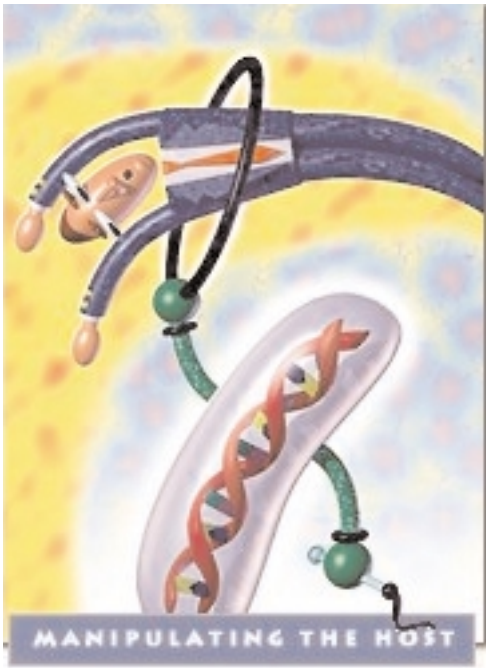
When I visited him one afternoon, Ewald pulled off his shelves a standard medical textbook from the 1970s and opened the heavy volume to the entry on peptic ulcers. We squinted together at a gray field of small print punctuated by subheads in boldface. Under "Etiology" we scanned several pages: *environmental factors ... smoking ... diet ... ulcers caused by drugs ... aspirin ... psychonomic factors ... lesions caused by stress.* In the omniscient tone of medical texts, the authors concluded, "It is plausible to hypothesize a wealth of these factors.... " There was no mention of infection at all.

In 1981 Barry J. Marshall was training in internal medicine at the Royal Perth Hospital, in Western Australia, when he became interested in incidences of spiral bacteria in the stomach lining. The bacteria were assumed to be irrelevant to ulcer pathology, but Marshall and J. R. Warren, a histopathologist who had previously observed the bacteria, reviewed the records of patients whose stomachs were infected with large numbers of these bacteria. They noticed that when one patient was treated with tetracycline for unrelated reasons, his pain vanished, and an endoscopy revealed that his ulcer was gone.

An article by Marshall and Warren on their culturing of "unidentified curved bacilli" appeared in the British medical journal *The Lancet* in 1984, and was followed by other suggestive studies. For years, however, the medical establishment remained deaf to their findings, and around the world ulcer patients continued to dine on bland food, swear off stress, and swill Pepto-Bismol. Finally Marshall personally ingested a batch of the spiral bacteria and came down with painful gastritis, thereby fulfilling all of Koch's postulates.

There is now little doubt that *Helicobacter pylori,* found in the stomachs of a third of adults in the

United States, causes inflammation of the stomach lining. In 20 percent of infected people it produces an ulcer. Nearly everyone with a duodenal ulcer is infected. *H. pylori* infections can be readily diagnosed with endoscopic biopsy tests, a blood test for antibodies, or a breath test. In 90 percent of cases the infections can be cured in less than a month with antibiotics. (Unfortunately, many doctors still haven't gotten the news. A Colorado survey found that 46 percent of patients seeking medical attention for ulcer symptoms are never tested for *H. pylori* by their physicians.)



Antibiotics Against Heart Disease?

EWALD closed the medical textbook on his knee. "This was published twenty years ago," he said. "If we looked up 'atherosclerosis' in a textbook from ten years ago, we'd find the same kind of things -- stress, lifestyle, lots about diet, nothing about infection."

Heart disease is now being linked to *Chlamydia pneumoniae,* a newly discovered bacterium that causes pneumonia and bronchitis. The germ is a relative of *Chlamydia trachomatis,* which causes trachoma, a leading cause of blindness in parts of the Third World. *C. trachomatis* is perhaps more familiar to us as a sexually transmitted disease that, left untreated in women, can lead to scarring of the fallopian tubes, pelvic inflammatory disease, ectopic pregnancy, and tubal infertility.

Pekka Saikku and Maija Leinonen, a Finnish husband-and-wife team who have evoked comparisons to the Curies, discovered the new type of chlamydial infection in 1985, though its existence was not officially recognized until 1989. Saikku and Leinonen found that 68 percent of Finnish patients who had suffered heart attacks had high levels of antibodies to *C. pneumoniae,* as did 50 percent of patients with coronary heart disease, in contrast to 17 percent of the healthy controls. "We were mostly ignored or laughed at," Saikku recalls.

While examining coronary-artery tissues at autopsy in 1991, Allan Shor, a pathologist in Johannesburg, saw "pear-shaped bodies" that looked like nothing he'd ever seen before. He mentioned his observations to a microbiologist colleague, who had read about a new species of chlamydia with a peculiar pear shape. The colleague referred Shor to an expert on the subject, Cho-Chou Kuo, of the University of Washington School of Public Health, in Seattle. After Shor shipped Kuo the curious coronary tissue, Kuo found that the clogged coronary arteries were full of *C. pneumoniae.* Before long, others were reporting the presence of live *C. pneumoniae* in arterial plaque fresh from operating tables. Everywhere the bacterium lodges, it appears to precipitate the same grim sequence of events: a chronic inflammation, followed by a buildup of plaque that occludes the opening of the artery (or, in the case of venereal chlamydia, a buildup of scar tissue in the fallopian tube). Recently a team of pathologists at MCP-Hahnemann School of Medicine, in Philadelphia, found the same bacterium in the diseased sections of the autopsied brains of patients who had had late-onset Alzheimer's disease: it was present in seventeen of nineteen Alzheimer's patients and in only one of nineteen controls.

By the mid-1990s a radical new view was emerging of atherosclerosis as a chronic, lifelong arterial infection. "I am confident that this will reach the level of certainty of ulcer and *H. pylori,*" says Saikku, who estimates that at least 80 percent of all coronary heart disease is caused by the bacterium. Big questions remain, of course. Studies show that about 50 percent of U.S. adults carry antibodies to *C. pneumoniae* -- but how many will develop heart disease? Even if heart patients can be shown to have antibodies to *C. pneumoniae,* and even if colonies of the bacteria are found living and breeding in diseased coronary arteries, is it certain that the germ *caused* the damage? Perhaps

it's an innocent bystander, as some critics have proposed; or a secondary, opportunistic infection.

But suppose that a *Chlamydia pneumoniae* infection during childhood can initiate a silent, chronic infection of the coronary arteries, resulting in a "cardiovascular event" fifty years later. Could antibiotics help to address the problem?

A few early studies suggest they might. Researchers in Salt Lake City infected white rabbits with *C. pneumoniae,* fed them a modestly cholesterol-enhanced diet, killed them, and found thickening of the thoracic aortas, in contrast to the condition of uninfected controls fed the same diet. Additionally, treatment of infected rabbits with antibiotics in the weeks following infection prevented the thickening. Saikku and colleagues reported a similar finding, also in rabbits. Coronary patients in Europe who were treated with azithromycin not only showed a decline in antibodies and other markers of infection but in some studies had fewer subsequent cardiovascular events than patients who were given placebos. (These findings are preliminary; in a few years we may know more. The first major clinical trial is under way in the United States, sponsored by the National Institutes of Health and the Pfizer Corporation: 4,000 heart patients at twenty-seven clinical centers will be given either the antibiotic azithromycin or a placebo and followed for four years to gauge whether the antibiotic affects the incidence of further coronary events.)

Smoking, stress, cholesterol, and heredity all play a role in heart disease. But imagine if our No. 1 killer -- with its vast culture of stress-reduction theories, low-fat diets, high-fiber cereals, cholesterol-lowering drugs, and high-tech bypass surgery -- could in many instances be vanquished with an antibiotic. Numerous precedents exist for long-smoldering bacterial infections with consequences that appear months or years later. Lyme disease, leprosy, tuberculosis, and ulcers have a similar course. Ewald is confident that the association of *C. pneumoniae* and heart disease is real. He doesn't believe that the germ is an innocent bystander. "It reminds you a lot of gonorrhea in the 1890s," he says. "When they saw the organism there, people said, 'Well, we don't know if it's really causing the disease, or is just living there.' Every month the data are getting stronger. This is a smoking gun, just like *Helicobacter.*"

Evolutionary Byways

Gregory Cochran

I HAVE a motto," Gregory Cochran told me recently. "'Big old diseases are infectious.' If it's common, higher than one in a thousand, I get suspicious. And if it's old, if it has been around for a while, I get suspicious."

The fact that Ewald has dared to conceive of a big theory for the medical sciences owes much to Cochran's contributions. A forty-five-year-old Ph.D. physicist who lives in Albuquerque with his wife and three small children, Cochran makes a living doing contract work on advanced optical systems for weaponry and other devices. Whereas Ewald is an academic insider, with department meetings to attend and honors theses to monitor, Cochran is a solo player, with an encyclopedic mind (he is a former College Bowl contestant) and a manner that verges on edginess. These days he spends a lot of time at his computer, as rapt as a conspiracy theorist, cruising Medline for new data on infectious diseases and, one imagines, almost cackling to himself when he finds something really good. Cochran's background in a field dominated by grand theories and universal laws may serve as a valuable counterpoint to the empirical and theory-hostile universe of the health sciences.

Ewald and Cochran encountered each other serendipitously, after Cochran decided to pursue a certain line of thinking about a very sensitive subject. "I was reading an article in *Scientific American* in 1992 about pathogens manipulating a host to get what they want," Cochran recalls. "It described a flowering plant infected by a fungus, and the fungus hijacks the plant's reproductive machinery so

that instead of pollen it produces fungal spores. I thought, *Could it be?*" Cochran strayed from his field to try his hand at writing an article on biology -- elaborating an audacious theory that human homosexuality might result from a "manipulation" of a host by a germ with its own agenda. He sent his draft to a prestigious biology journal, which sent it out to three scientists for peer review. Two were unconvinced, even appalled; the third was Paul Ewald, who thought the article was flawed but who was nonetheless impressed by the logic of the idea. The article was rejected, but Ewald and Cochran began their association.

To illustrate his thinking about infectiousness and disease, Cochran not long ago gave me a tour of his conceptual bins, into which he sorts afflictions according to their fitness impact. Remember that fitness can be defined as the evolutionary success of one organism relative to competing organisms. Only one thing counts: getting one's genes into the future. Any disease that kills host organisms before they can reproduce reduces fitness to zero. Obviously, fitness takes a major hit whenever the reproductive system itself is involved, as in the case of venereal chlamydia.

Consider a disease with a fitness cost of one percent -- that is, a disease that takes a toll on survival or reproduction such that people who have it end up with one percent fewer offspring, on average, than the general population. That small amount adds up. If you have an inherited disease with a one percent fitness cost, in the next generation there will be 99 percent of the original number in the gene pool. Eventually the number of people with the disease will dwindle to close to zero -- or, more precisely, to the rate produced by random genetic mutations: about one in 50,000 to one in 100,000.

We were considering the bin containing diseases that are profoundly antagonistic to fitness, with a fitness cost of somewhere between one and 10 percent by Cochran's calculations. My eye took in a catalogue of human ills -- some familiar, some exotic, some historically fearsome but close to extinct, some lethal in the tropics but of little concern to inhabitants of the temperate zones. This list also showed prevailing medical opinion about cause. Each name of a disease was trailed by a lower-case letter: *i* (for infectious), *g*(genetic), *g+*(genetic defense against an infectious disease), *e* (caused by an environmental agent), or *u* (unknown). I read, "Atherosclerosis (*u*), ... chlamydia (venereal) (*i*), cholera (*i*), diphtheria (*i*), endometriosis (*u*), filariasis (*i*), G6PD deficiency (*g+*), ... hemoglobin E disease (*g+*), hepatitis B (*i*), hepatitis C (*i*), hookworm disease (*i*), kuru (*i*), ... malaria (vivax) (*i*), ... pertussis (*i*), pneumococcal pneumonia (*i*), polycystic ovary disease (*u*), scarlet fever (*i*), ... tuberculosis (*i*), typhoid (*i*), yellow fever (*i*)."

Of the top forty fitness-antagonistic diseases on the list, thirty-three are known to be directly infectious and three are indirectly caused by infection; Cochran believes that the others will turn out to be infectious too. The most fitness-antagonistic diseases must be infectious, not genetic, Ewald and Cochran reason, because otherwise their frequency would have sunk to the level of random mutations. The exceptions would be either diseases that could be the effect of some new environmental factor (radiation or smoking, for example), or genetic diseases that balance their fitness cost with a benefit. Sickle-cell anemia is one example of the latter.

Though sickle-cell anemia is strictly heritable according to Mendelian laws, it is widely believed to have persisted in the population in response to infectious selective pressures. It heads the list of genetic diseases that Ewald dubs "self-destructive defenses," in which a disease fatal in its homozygous form (two copies of the gene) carries an evolutionary advantage to heterozygous carriers (with one copy), protecting against a terrible infection: in this case falciparum malaria, common in Africa. Similarly, cystic fibrosis, some argue, evolved in northern Europe as a defense against *Salmonella typhi,* the cause of typhoid fever. Infection thus explains why these deadly genetic diseases have remained in the human gene pool when they should have died out.

But what about something like atherosclerosis? I asked. Leaving aside the evidence concerning *C.*

pneumoniae, it is not apparent why a genetic cause for atherosclerosis should be dismissed out of hand on evolutionary grounds. If it hits people in midlife or later, after they have launched their genes, how could it possibly affect fitness?

Cochran's response illustrates some of the intricacies of evolutionary thinking. "Well, obviously, it's not as bad as a disease that kills you before puberty, but I think it does have a fitness cost. First of all, it's *really* common. Second, people think that all you have to do to pass your genes along is have children, but that's not true. You still need to raise the offspring to adulthood. In a hunter-gatherer or subsistence-farming culture, the fitness impact of dying in midlife might be considerable, especially during bad times, like famines. You've got to feed your family. Also, cardiovascular disease is a leading cause of impotence, and any disease that makes males impotent at age forty-five has got to affect reproduction somewhat."

But fifty-year-olds? Sixty-year-olds?

Grandmothers do a large proportion of the food-gathering in some tribal cultures, according to recent anthropological reports. "They aren't hampered by babies anymore, and they don't have to go around chucking spears like the men," says George C. Williams, a professor emeritus of ecology and evolution at the State University of New York at Stonybrook, and one of the pillars of modern evolutionary biology. "They contribute substantially to the family diet." If long-lived elders historically have made a difference by fostering the survival of their descendants, and therefore their genes, Cochran figures, then a disease that kills sixty-year-olds could have a fitness impact of around one percent.

The Cause-and-Effect Conundrum

KNOW what that is?" Ewald asked. We were standing in the main corridor of the Life Sciences Building, gazing up at a decorative metalwork frieze that runs along the walls just above door height. A pair of hummingbirds chase each other in a circle. A human eye and an octopus eye face off. A human hand is juxtaposed with a chimpanzee hand. Ewald pointed to something that looked like a daddy longlegs with a video camera for a head. "Some kind of insect?" I ventured. "It's a virus," he said. "See, it's like a spaceship. That" -- he pointed at the head -- "is its DNA. It injects it inside the cell."

There is something unsettling and fascinating about a virus, an organism that is neither strictly alive nor strictly inanimate, and that replicates by sneaking inside a host cell and commandeering its machinery. "Viruses are essentially bits of nucleic acid -- either DNA or RNA -- wrapped in a protein capsule," Ewald explained. "A retrovirus, like HIV, is an RNA virus with a protein called reverse transcriptase built into it, and once it gets into a cell, it uses the reverse transcriptase to make a DNA copy of its RNA. This viral DNA copy can insert itself into our DNA, where it can be read by our protein-making machinery the same way our own instructions are read."

The modus operandi of the world's most feared virus, HIV, is clever, killing its hosts very, very slowly. A sexually transmitted pathogen, without the luxury of being spread through sneezes or coughs, must await its few opportunities patiently; if those infected have no symptoms and don't know they are sick, so much the better. A mild, chronic form of AIDS had in all likelihood been around for centuries in Africa, according to Ewald. Suddenly in the 1970s -- owing to changing patterns of sexual activity and to population movements -- deadly strains spread in the population of Central and East Africa.

HIV has an extremely high mutation rate, which means that it is continually evolving, even within a single patient, producing competing strains that fight for survival against the weapons produced by the immune system. If selective pressures -- in this case a high potential sexual transmission -- have

forced the virus to evolve toward virulence, the opposite selective pressures could do the reverse. Conceivably, we could "tame" HIV, encouraging it to evolve toward comparative harmlessness. It was already known that preventive measures such as safe sex, fewer partners, clean needles, and so forth could curb the spread of the disease. But Ewald pointed out early on that social modification was a far more potent weapon than anyone realized. Once HIV was cut off from easy access to new hosts, milder strains would flourish -- ones that the host could tolerate for longer and longer periods. Indeed, Ewald argues, given limited public-health budgets, it might make sense to put more money into transmission-prevention programs and less into the search for vaccines. (He also has strong opinions about how drugs should be used to treat AIDS. He asserts that every time we use an antiviral drug like AZT, we produce an array of AZT-resistant HIVs in the population; if viral evolution is taken into account, antiviral drugs can be used more judiciously.)

Ewald's theories tilt him decidedly toward the optimistic camp. Even in the absence of a vaccine the AIDS epidemic will not inevitably worsen; it can be curbed without reducing transmission to zero. A natural experiment now occurring in Japan, he says, could be a test case for his theories. In the early 1990s highly virulent strains of HIV from Thailand took root in Japan, but Ewald predicts that low rates of sexual transmission in that country -- due to widespread condom use and other factors -- will act as a selective pressure on these strains so that they evolve toward mildness. If this is true, the trend should become evident over the next ten years.

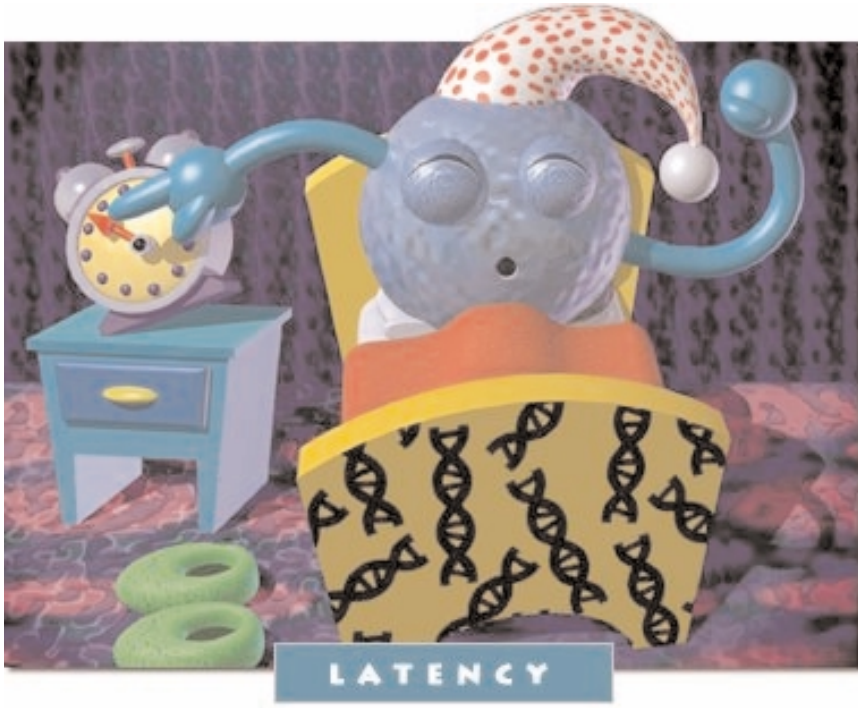
Like HIV, many other viruses have an indolent course, with a long latency between infection and the development of symptoms. Herpes zoster, the agent of chicken pox, lingers in the body forever, capable of erupting as painful shingles decades later. There are also so-called hit-and-run infections, in which a pathogen or its products disrupt the body's immunological surveillance system; once the microbes are gone (or when they are present in such low frequency as to be undetectable), the immune response stays stuck in the "on" mode, causing a lingering inflammation. By the time symptoms occur, the microorganism itself has disappeared, and its genome will not be detectable in any tissue.

"The health sciences are still grappling with the masking effects of long delays between the onset of infection and the onset of disease," Ewald says. "Any time you have hit-and-run infections, slow viruses, lingering or relapsing infections, or a time lag between infection and symptoms, the cause and effect is going to be very cryptic. You won't find these newly recognized infections by the methods we used to find old infectious diseases. We have to be ready to think of all sorts of new, clever ways to identify pathogens. We will have to abandon Koch's postulates in some cases."

The Great Synthesizer

AS of this writing, the ideas at the core of Germ Theory, Part II, have been presented by Ewald mostly in the form of lectures, and in communications with colleagues. The papers in which the ideas will be formally articulated are in preparation. Given Ewald's prominence, the ideas are bound to cause a stir. They will also draw criticism. In the medical sciences, where "theory" is a bad word and "Stick to the data" is the reigning motto, Ewald will come under particular scrutiny because his hypothesis arrives detached from a vast corpus of laboratory data. It is helpful to think of Ewald as continuing the tradition of the great scientific synthesizers. Darwin himself was a synthesizer extraordinaire, who composed the thesis of *The Origin of Species* largely out of hundreds of odds and ends contributed by others, from pigeon breeders to naturalists. "Professor So-and-so has observed ... " is a recurring motif in Darwin's book.

Ewald's theory about evolution and infectiousness provides a framework that potentially unites diverse research on the front lines of various afflictions. Ulcers and heart disease have already been mentioned. Here are two more: cancer and mental illness.



In 1910 a man named Peyton Rous discovered the eponymous Rous sarcoma virus, demonstrating that chickens infected with it developed cancer. Over the years many other cancer viruses have been discovered in animals. And yet until 1979, despite broad hints from the animal world, not a single human cancer was generally accepted as infectious. Rous had been lucky: his chickens became sick only two weeks after infection. Human cancers follow a more languorous course, which means that by the time symptoms show up, any infectious causation may well be buried under a lifetime of irrelevant risk factors.

In 1979 HTLV-1, a retrovirus endemic in parts of Asia, Africa, and the Caribbean, and transmitted either sexually or from mother to child, was linked to certain leukemias and lymphomas; the cancer appeared decades after infection. The Epstein-Barr virus (the agent that causes mononucleosis) has now been associated with some B-cell lymphomas, with a nasopharyngeal cancer common in south China, and with Burkitt's lymphoma, a deadly childhood cancer of Africa. Some 82 percent of all cases of cervical cancer have been associated with the sexually transmitted human papilloma virus, a once relatively innocent-seeming pathogen responsible for genital warts.

H. pylori, the ulcer pathogen, confers a sixfold greater risk of stomach cancer, and accounts for at least half of all stomach cancers. Also, the lymphoid tissue of the stomach can produce a low-grade gastric lymphoma under the influence of this bacterium. Early reports indicate that the lymphoma is cured in 50 percent of cases by resolving the *H. pylori* infection -- which may mark the first time in medical history that cancer has been cured with an antibiotic.

Hepatitis B and C, two of the ever-growing alphabet soup of hepatic diseases, have been linked to liver cancer. Herpes virus 8 has recently been discovered to be the cause of Kaposi's sarcoma. "There is no reason to believe that this flurry of discovery has now completed the list of infectious agents of cancer," Ewald says.

Among the many known animal cancer viruses is a closely studied retrovirus known as mouse mammary tumor virus (MMTV), which causes mammary-gland cancer in mice. This virus is transmitted from mother to offspring through mother's milk, lying latent in the daughter's mammary tissue until activated by hormones during her own lactation. Could such a virus be a factor in human breast cancer? In the mid-1980s researchers announced that they had found in malignant human breast tumors a DNA sequence resembling MMTV, but the excitement waned when the same sequence was found in normal breast tissue as well. Interest has been revived by the research of Beatriz G-T. Pogo, a professor in the departments of medicine and microbiology at Mount Sinai School of Medicine, in New York. Examining some 400 to 500 breast-cancer samples, she has found DNA sequences resembling MMTV that are not present in normal tissue or in other human cancers. She remains guarded about the implications.

Can You "Catch" Schizophrenia?

MICROBES obviously can cause mental disorders -- as syphilitic dementia, to name but one example, makes brutally clear. But most post-Freudian discussions of psychiatric dysfunction have tended not to invoke infection. Recently, however, some cases of childhood obsessive compulsive disorder (OCD) have hinted at a new set of possibilities. Children who have this disease may compulsively count the crayons in their book bags over and over again, or meticulously avoid each crack in the pavement, in order to ward off some imagined evil. Susan E. Swedo, of the National Institute of Mental Health, in Bethesda, Maryland, noticed strong resemblances between OCD and a disease called Sydenham's chorea, formerly known as Saint Vitus's dance, which, like rheumatic heart disease, is a rare complication of an untreated streptococcal infection. Streptococcal antibodies find their way into the brain and attack a region called the basal ganglia, causing characteristic clumsiness and arm-flapping movements along with obsessions, compulsions, senseless rituals, and *idées fixes.* Could some cases of childhood OCD be a milder version of this illness? The hunch paid off. In the early 1990s a new syndrome, known as PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcus), was recognized.

Some children with OCD get better when they are given intravenous immunoglobulin or undergo therapeutic plasma exchange to remove the antibodies from their blood. It is not known whether adult-onset OCD -- whose most famous avatar was the germ-phobic Howard Hughes -- also results from some sort of infection. But it is certainly provocative that a mental disorder can result from a lingering immune response. The phenomenon makes some people wonder about schizophrenia.

For years, amid the smorgasbord of theories about the etiology of schizophrenia, there has been recurring speculation about a schizophrenia virus. Karl Menninger wondered in the 1920s if schizophrenia might result from a flu infection. Later researchers pointed to data that showed seasonal and geographic patterns in the births of schizophrenics, suggestive of infection -- though it must be said that the viral theorists were largely regarded as inhabiting the fringe. Genetic theories grabbed center stage, and by the 1990s most researchers were pinning their hopes on the genetic markers being identified in the Human Genome Project.

In Ewald and Cochran's view, evolutionary laws dictate that infection must be a factor in schizophrenia. "They announced they had the gene for schizophrenia, and then it turned out not to be true," Cochran said one day when I mentioned genetic markers. "I think they found and unfound the gene for depression about six times. Nobody's found a gene yet for any common mental illness. Maybe instead of the Human Genome Project we should have the Human Germ Project." Cochran is endorsing a suggestion made by several scientists in a recent issue of *Nature.* "I don't mean to say that the Human Genome Project isn't worthwhile for many reasons, but all the genes we've found have been for *rare* diseases. I don't think the common diseases are going to turn out that way."

Schizophrenia affects about one percent of the population, and thus in Ewald and Cochran's scheme is too common for a genetic disease that profoundly impairs fitness. As noted, the background mutation rate -- the ratate which a gene spontaneously mutates -- is typically about one in 50,000 to one in 100,000. Not surprisingly, genetic diseases that are severely fitness-impairing (for example, achondroplastic dwarfism) tend to have roughly the same odds, depending on the gene. (In a few cases, however, the gene involved may be especially error-prone, resulting in a higher frequency of mishaps. One of the most common genetic diseases, Duchenne's muscular dystrophy, afflicts boys at a rate of one in 7,000, reflecting the fragility of an uncommonly long gene.)

From the fitness perspective, schizophrenia is a catastrophe. It is estimated that male schizophrenics have roughly half as many offspring as the general population has. Female schizophrenics have roughly 75 percent as many. Schizophrenia should therefore approach the level of a random mutation after many generations. (To explain this away, some genetic theorists have proposed that in hunter-gatherer cultures schizophrenics were the tribal shamans -- desirable as sexual partners -- and thus did not incur a reproductive disadvantage.)

No one has found a schizophrenia virus yet, but some think they may be close. Following a tip from Ewald and Cochran, I typed "Borna virus" into my online search engine and ended up with a stack of scientific papers. Borna virus was first recognized as the cause of a neurologic disease in horses, and can infect nearly all warm-blooded animals, from birds to primates. Horses and other animals infected with Borna virus may exhibit depressed or apathetic behavior, weakness of the legs, abnormal body postures, or a staggering gait. Borna-infected laboratory rats exhibit learning disorders, exaggerated startle responses, and hyperactivity, among other things.

Royce Waltrip, an associate professor of psychiatry at the University of Mississippi with an expertise in virology, studies Borna virus. Despite being leery of a rash of inconsistent studies associating Borna virus with schizophrenia, Waltrip believes that "there is something there, though I don't know if it's a perinatal infection or an adult infection or what." When he started looking for antibodies to Borna in mental patients, he found that 14 percent of the schizophrenic patients had antibodies to two or three Borna proteins, whereas none of the healthy controls did. Waltrip speculates that Borna virus is not *the* cause of schizophrenia. "I think that schizophrenia is an etiologically heterogeneous disease," he said. "I think there are a finite number of ways the brain can respond to injury. There are probably different routes to schizophrenia, and there is probably more than one infectious pathway." One route, he hypothesizes, is Borna virus.

Ewald and Cochran do not doubt that multiple pathogens or multiple factors may be implicated in some broad disease syndromes, among them schizophrenia. But they worry, in general, that the "multifactorial"argument has become too facile a response. "That's what they *always* say when they don't know the cause of a disease," Cochran said on the phone. "They say it's *multifactorial.* Ulcers and heart disease were supposed to be multifactorial. But they're infections! Tuberculosis was supposed to be multifactorial. It's an infection!"

I happened to be visiting Ewald in his office when Cochran called, so we were having a three-way conversation, with Cochran's voice echoing over the static on a speaker phone. Outside the window

the scene was shifting subtly into mid-autumn. Patches of orange and rust speckled the blue-green flanks of the Holyoke hills, and the students on the playing fields were wearing sweatpants.

But what about random accidents in utero as a cause of schizophrenia? I asked. Some kind of damage to the wiring?

"You'd have to say what caused the damage," Ewald responded, pointing out that the word "random" is often used to refer to something we haven't been able to understand. He noted once again how widespread schizophrenia is. "At this frequency -- one percent of the population -- we'd expect that natural selection would have led to protective mechanisms."

The same holds true for severe depression, Ewald believes. A tendency toward suicide doesn't make evolutionary sense in a world of organisms driven by the twin urgencies of survival and reproduction. The relentless engine of natural selection should have eliminated any genes that infringed on them. So why are these fitness-antagonistic traits still around?

This leads to a subject that Ewald is not shy about bringing up in discussions with colleagues and in professional lectures: homosexuality. Various pieces of evidence have been adduced in recent years, by prominent researchers, for some sort of genetic component to homosexuality. The question arises as to whether natural selection would sustain a homosexual trait in the gene pool for any length of time. The best estimates of the fitness cost of homosexuality hover around 80 percent: in other words, gay men (in modern times, at least) have only 20 percent as many offspring as heterosexuals have. Simple math shows how quickly an evolutionarily disadvantageous trait like this should dwindle, if it is a simple genetic phenomenon. The researchers Richard Pillard, at the Boston University School of Medicine, and Dean Hamer, at the National Cancer Institute, are not persuaded that natural selection would necessarily have eliminated a homosexual trait, and offer ingenious counterarguments. (And they note that historically the fitness cost may not have been very high, when gay men stayed in the closet, married, and had children.)

No one, of course, has ever isolated a bacterium or a virus responsible for sexual orientation, and speculations about the manner in which such an agent would be transmitted can be nothing more than that. But Ewald and Cochran contend that the severe "fitness hit" of homosexuality is a red flag that should not be ignored, and that an infectious process should at least be explored. "It's a very sensitive subject,"Ewald admits, "and I don't want to be accused of gay-bashing. But I think the idea is viable. What scientists are supposed to do is evaluate an idea on the soundness of the logic and the testing of the predictions it can generate."

The Search for Telltale Signs

AFTER I had spent time talking to Ewald and Cochran and reading back issues of the journal *Emerging Infectious Diseases*, everything began to look infectious to me. The catalogue of suspected chronic diseases caused by infection, according to David A. Relman, an assistant professor of medicine, microbiology, and immunology at Stanford University, now includes "sarcoidosis, various forms of inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, Wegener's granulomatosis, diabetes mellitus, primary biliary cirrhosis, tropical sprue, and Kawasaki disease." Ewald and Cochran's list of likely suspects would include all of the above plus many forms of heart disease, arteriosclerosis, Alzheimer's disease, many if not most forms of cancer, multiple sclerosis, most major psychiatric diseases, Hashimoto's thyroiditis, cerebral palsy, polycystic ovary disease, and perhaps obesity and certain eating disorders. From an evolutionary perspective, Cochran says, anorexia is strikingly inimical to the survival principle. "I mean, *not to eat* -- what would cause that?"

"In all these situations you look for little signs of infectious spread," Ewald said in his office. "Is there geographic variation? Temporal variation? Does it go up or down across decades? Multiple sclerosis seems pretty clearly infectious, because you have these island populations where there was no MS and then you see it spread like a wave through the population. And you have this latitudinal gradient ... "

"Yes!" Cochran burst from the speaker phone. "The farther you get from the Equator, the more common it is. It's three to four times more common if you grow up in Ontario than if you grow up in Mississippi. Some people have tried to say that's because Canadians are genetically different from Americans."

I downloaded a paper about extremely high rates of multiple sclerosis in the Shetland and Orkney Islands and other regions of Scotland, and I made a mental note of the many Canadian Web sites devoted to MS. Like other autoimmune diseases, MS looks suspiciously infectious for a number of reasons: epidemiological evidence of childhood exposure to disease agents, geographic clusters, abnormal immune responses to a variety of viruses, resemblances to animal models and human diseases with a relapsing-remitting course. And, in fact, a virus has been nominated: the human herpes virus 6, the agent of roseola infantum, a very mild disease of childhood. The connection, however, is by no means proved.

"No doubt everywhere people look there will be more and more examples of chronic diseases with infectious etiology," says Stephen S. Morse, an expert in infectious diseases at the Columbia University School of Public Health. "*Helicobacter* is probably the tip of the iceberg." Although we have wielded the tools of microbial cultivation for a hundred years, much of the microbial world is still as mysterious as an alien planet. "It has been estimated that only 0.4 percent of all extant bacterial species have been identified," David Relman has written. "Does this remarkable lack of knowledge pertain to the subset of microorganisms both capable of and accomplished in causing human disease?" Even the germs that inhabit our bodies -- the so-called "human commensal flora," such as the swarming populations of organisms that live in the spaces between our teeth -- are largely unknown, he points out. Most of them are presumably benign, up to a point. There are disquieting suggestions in the literature of a link between bacteria in dental plaque and coronary disease.

"Some people think it's scary to have these time bombs in our bodies," Ewald says, "but it's also encouraging -- because if it's a disease organism, then there's probably something we can do about it. The textbooks say, In 1900 most people died of infectious diseases, and today most people don't die of infectious disease; they die of cancer and heart disease and Alzheimer's and all these things. Well, in ten years I think the textbooks will have to be rewritten to say, "Throughout history most people have died of infectious disease, and most people continue to die of infectious disease."