The Web of Life
Evolution in Action

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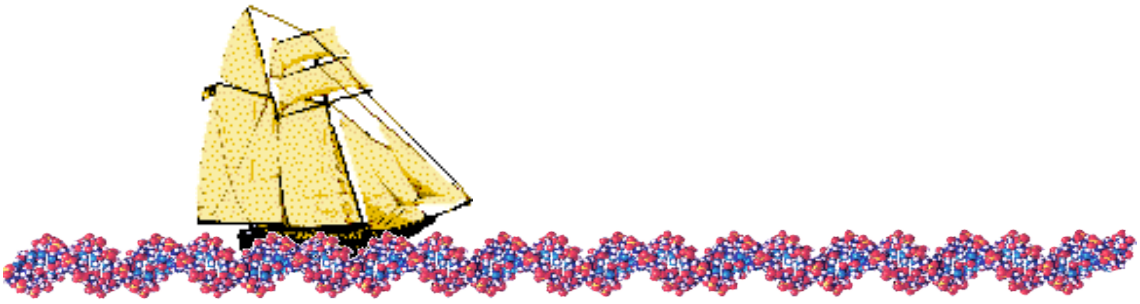

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On Observing Evolution

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Biology teachers sometimes encounter students in their classes who have been primed by anti-evolutionists to challenge any discussion of evolution. Some students even are given specific questions to try to stump their teachers. One creationist argument that is very common is the following: If evolution is true then we should be able to observe it, but we never see one species turn into another, so it must be false. The argument appears in many different guises. If humans evolved from monkeys in the past why don't we see monkeys turning into humans any more? There are many kinds of dogs, a creationist will admit, but you never see a dog turn into a cat, do you? Or, more boldly, creationists may simply assert that no scientist has ever seen any evolutionary change occur whatsoever. One creationist leader tells students to ask "Teacher, were you there?" whenever evolutionary history is explained. Isn't science supposed to deal only with what can be observed? How can evolution be scientific if it is not or cannot be observed. On the face of it, this apparently straightforward criticism might look pretty strong, but there are so many problems with it that it is hard to sort them out.

First, many such criticisms are the result of simple ignorance, faulting evolution for things it does not claim. Criticizing biological evolution because we do not now see monkeys changing into humans is like criticizing linguistic evolution because we don't see Spanish changing into Gujarati. These are current species of language, descended from others, and as they continue to modify we would expect them to develop into new languages, not one into the another. It is a common but erroneous view to think that humans descended from monkeys, which is perhaps why some creationists think that monkeys should still be changing into humans, but the true evolutionary picture is that humans and monkeys are cousins, each species having branched off from a common ancestor. The same holds of dogs and cats, though in this case the common ancestor is even more distant. Convergent evolution, in which similar sorts of traits arise in separate lineages, is possible, and we know that it has occurred in a limited degree in the past under conditions with strong selective pressures from the environment, but convergence of dogs into things that look like cats, say, is so highly unlikely that it is not a serious possibility. It does not make sense to object that we do not observe something that evolutionary theory says we should not expect to occur.

Leaving that aside, what about the claim that evolution cannot be true because scientists never observe any evolutionary development? Let me reply to the challenge in stages. To begin to see what is wrong with this argument against biological evolution let us first look at it how it applies to language evolution. If the argument is good it should apply even more strongly to the evolution of languages, for not only is it true that we have not observed the natural origin of a completely new language, but also those that we have seen originate have all been ones like Esperanto that were purposefully designed by human intelligence. Doesn't this mean that we should conclude that all

languages are intentionally designed and that they did not evolve from one another? Certainly not.

Has a scientist ever observed one language evolve into another? In one simple sense the answer to that question is clearly "No." Even though languages evolve much faster than biological species it is still too slow a process to see a new language emerge in a person's lifetime. However, this does not mean that we cannot know that they have been formed from others by descent with modification. We can know this even without observing it directly because we can observe the evidence for it. Sir William Jones, the Darwin of linguistics, did not observe Sanskrit and the other Indo-European languages evolve from a common source, but he did observe the linguistic homologies that were persuasive evidence of their evolution from a common source, and linguists today extend this evidential comparison using sophisticated statistical methods that bring a precision to the task that he could only have dreamed of. Furthermore, linguists can observe and chart the accumulation of linguistic "mutations" and the other processes of linguistic change and when we put these together with the other evidence we may thereby infer that "language speciation" has occurred and is occurring still. In this sense we observe the evolutionary development of languages all the time. Exactly the same is true for biological evolution.

At this point, creationists are bound to object that this notion of observational inference is not what they mean by "observing evolution." Many creationists seem to hail from the most literalist possible county in Missouri: When they ask biologists to "Show me" evolution, they seem to expect nothing less than to be presented with one species transforming into another, with intermediate forms of each characteristic feature. In his "Back to Genesis" talk, John Morris shows a painting of an armadillo-like creature covered partly with scales but with some of these half-changing into feathers that stick out in odd places as well. If reptiles evolved into birds why do we not observe creatures halfway between the two like this? More often, as we noted, creationists will say that no one (except God) was around to observe when life began or when species originated—and so these topics cannot be scientific.

This is a serious misunderstanding of how science works and of the nature of observation. First of all, science is much more than a collection of direct observations but also relies on the inference to the best explanation. So, for example, although we may not have direct observations of half-scale/half-feathers, we nonetheless have good evidence of their evolutionary relationship, because we know of mutations in chickens that cause the scales that normally cover their legs to be converted into feathers. Second, there is no clear break between observation and theoretical inference. What we might think of as "direct observation" is rarely so simple. When we observe a microorganism using a microscope, for example, we are not just seeing it through a series of glass lenses but also through the conceptual lens of optical theory. The importance of theory is even more apparent for observations with electron microscopes, which work on completely different theoretical principles than light microscopes. In each case the theory has in a sense been built into the microscope. We do not see with our eyes alone; we see with our brains.

Though we often do not recognize it, such inferential processing is involved in even ordinary situations that are comparable to cases of evolutionary development. Consider what it would take to say that we had observed any sort of gradual development, say of a tree. In my yard is a mighty live oak that is estimated to be well over a hundred years old. In the spring I can observe the tiny green shoots of the new twigs (though hard as I try I can never actually see them grow), and every couple of years I notice that I have to prune a limb that has drooped low enough to scrape the eaves. In the literal "show-me" sense I have never observed that tree grow. In that sense, perhaps, all I have seen is a series of mental snap shots taken at different times. In the inferential sense, however, it is quite reasonable to say that I have seen the tree grow for I can mentally "connect the dots," as it were, of those snap shots. I was also not around to see that tree when it was a seedling newly sprouting from an acorn (probably no one observed that acorn fall and sprout), but given what I know of the process of growth, and having seen other trees in other stages of growth I can conclude with a high degree of confidence that that was what happened. The growth of the tree of languages took centuries longer and the growth of Darwin's tree of life took longer still by many orders of magnitude so these are harder for us to see in our mind's eye. Nevertheless, by taking the time to review the evidence we can connect the dots of the linguistic and biological observational data and here too observe evolutionary change continuing to occur around us. To close one's eyes to this as creationists do and insist upon the special creation of each language and each species of plant and animal is as absurd as insisting upon the special creation of each individual tree and twig because we did not observe its origin directly.

Once we are attuned to the nature of observation and understand what evolutionary theory actually claims, it becomes clear that scientists have observed evolution in as clear a manner as one could desire both in the lab and in nature. Aside from observations from many lab experiments and field studies like the Grants' finch research, scientists have also observed, for example, how insects have evolved resistance to various pesticides and how disease-causing bacteria have evolved resistance to penicillin and other antibiotics. (This last example involves a serious issue in public health, and understanding the evolutionary processes that lead to resistant strains has recently helped the medical profession begin to change the way it prescribes antibiotics so as to not further accelerate their evolution. Interestingly, pharmaceutical companies are beginning to use a form of Darwinian engineering to help develop more powerful drugs.) Biologists even know of cases of speciation in the wild within the last half of the twentieth century. In the plant genus *Tragopogon*, for example, two new species (*T. mirus* and *T. miscellus*) have evolved by a process known as allopolyploidy. Most *Tragopogon* species are diploid, which means that they have two sets of chromosomes. The new species were formed when one species accidentally fertilized a different one and produced an offspring with four sets of chromosomes. This mutation resulted in an interfertile tetraploid that could not fertilize or be fertilized by either of its two parent species types and thus qualified as a different species by being reproductively isolated.[1] In plants, allopolyploids have often evolved into distinct phyletic lines. It is even possible to induce allopolyploid speciation in lab settings, in

some cases, by exposing plants to the chemical colchicene. One could easily extend this list of observational evidence indefinitely.

A good science teacher does not simply give students a series of scientific facts to memorize, but teaches the about the nature of science as a method of finding out things about the world. Science does not simply collect a series of observations. Rather, scientific hypotheses are confirmed by a combination of observation and reasoning. In particular, one tests hypotheses by checking their *observational consequences*. A teacher can explain this basic method of reasoning using examples from chemistry, physics, geology and any other science, and show that evolutionary biology is no different. So, if a student asks a question like "Teacher, were you there?" take it as an excellent opportunity to teach something about the nature of scientific evidence.

[The above is a slightly modified except from *Tower of Babel: The Evidence against the New Creationism*. MIT Press, 1999.]

DefendingEvolution

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Most educators would probably agree that it is important to know why students think something they are teaching is inaccurate. Yet when it comes to their students rejecting their teaching of evolution, many educators just chalk it up to students being creationists and do not explore their reasons any further. However, the label *creationist*, while often useful for categorizing the wide variety of people who reject evolution, is much too broad to give educators an appropriate understanding of the numerous rationales students have for rejecting the underlying theory of biology.

In Charles Darwin's time, the "creationist" label generally was used to refer to someone who believed that the human soul was not inherited from the parents but was a special creation for each individual. However, the day after the *Origin of Species* became public, Darwin began writing letters using the term creationist to refer to anti-evolutionists. The term as it is used today has come to mean specific types of evolution rejection, which vary greatly depending on who you read or with whom you talk.

For example, many science instructors believe that anyone who rejects evolution must be a religious literalist fundamentalist and/or someone with a conservative political agenda. However, polls show that about half of Americans choose options other than evolution to explain how humans arose on earth. These figures indicate that more persons than just religious fundamentalists (let alone literalist fundamentalists) or political conservatives choose nonevolutionary options. A Gallup poll reports that about 56% of conservatives, 42% of moderates, and 36% of liberals choose the survey option "God created human beings pretty much in their present form at one time within the last 10,000 years or so." Gallup also reports that about half of Republicans and half of Democrats choose this view as well, leading us to believe that the rejection of evolution is bipartisan.

Many students who reject evolution *do* have rationales for their objections. Some of these rationales are well thought out, while others border on the affective domain -- responses that stem from emotion. The cognitive rationales range from what most people would consider to be purely religious rationales to rationales that may strike many as nonreligious. The vast majority of students, however, hold some combination of religious and nonreligious rationales for their rejections.

Instructors should be aware of students' conceptions in order to help them learn the science of evolution better and to understand why the scientific community agrees that evolution is the only scientific theory to explain the diversity of life. Otherwise, it will be difficult, if not impossible, to productively address students' misconceptions about evolution. Additionally, to better understand why many students (and nonstudents) contend that the evolutionary science we teach is inaccurate, it is illustrative to examine some of the religious and non-religious rationales underpinning their thinking. In this

presentation we will look at some of these specific yet greatly varied religious and non-religious rationales that students typically give for their rejection of evolution.

[The above is a slightly modified excerpt from *Defending Evolution in the Classroom,* 2001, Jones & Bartlett Press, Boston..

Humans as the World's Greatest Evolutionary Force

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In addition to altering global ecology, technology and human population growth also affect evolutionary trajectories, dramatically accelerating evolutionary change in other species, especially in commercially important, pest, and disease organisms. Such changes are apparent in antibiotic and human immunodeficiency virus (HIV) resistance to drugs, plant and insect resistance to pesticides, rapid changes in invasive species, life-history change in commercial fisheries, and pest adaptation to biological engineering products. This accelerated evolution costs at least $33 billion to $50 billion a year in the United States. Slowing and controlling arms races in disease and pest management have been successful in diverse ecological and economic systems, illustrating how applied evolutionary principles can help reduce the impact of humankind
on evolution.

Human impact on the global biosphere now controls many major facets of ecosystem function. Currently, a large fraction of the world's available fresh water, arable land, fisheries production, nitrogen budget, CO2 balance, and biotic turnover are dominated by human effects (1). Human ecological impact has enormous evolutionary consequences as well and can greatly accelerate evolutionary change in the species around us, especially disease organisms, agricultural pests, commensals, and species hunted commercially. For example, some forms of bacterial infection are insensitive to all but the most powerful antibiotics, yet these infections are increasingly common in hospitals (2). Some insects are tolerant of so many different insecticides that chemical control is useless (3). Such examples illustrate the pervasive intersection of biological evolution with human life, effects that generate substantial daily impacts and produce increasing economic burden.

Accelerated evolutionary changes are easy to understand—they derive from strong natural selection exerted by human technology. However, technological impact has increased so markedly over the past few decades that humans may be the world's dominant evolutionary force. The importance of human-induced evolutionary change can be measured economically, in some cases, and is frequently seen in the exposure of societies to uncontrollable disease or pest outbreaks. Attempts to slow these evolutionary changes are widespread but uncoordinated. How well do they work to slow evolution? Can successes from one field be generalized to others?

The Pace of Human-Induced Evolution

Paul Muiiller's 1939 discovery that DDT killed insects won him the 1948 Nobel Prize, but before the Nobel ceremony occurred, evolution of resistance had already been reported in house flies (3, 4). By the 1960s, mosquitoes resistant to DDT effectively

prevented the worldwide eradication of malaria (5), and by 1990, over 500 species had evolved resistance to at least one insecticide (6). Insects often evolve resistance within about a decade after introduction of a new pesticide (7), and many species are resistant to so many pesticides that they are difficult or impossible to control (3). Similar trajectories are known for resistant weeds (8), which typically evolve resistance within 10 to 25 years of deployment of an herbicide (Table 1).

Bacterial diseases have evolved strong and devastating resistance to many antibiotics. This occurs at low levels in natural populations (9) but can become common within a few years of the commercial adoption of a new drug (Table 1). For example, virtually all Gram-positive infections were susceptible to penicillin in the 1940s (2, 10) but in hospitals today, the vast majority of infections caused by important bacterial agents like Staphylococcus aureus are penicillin-resistant, and up to 50% are resistant to stronger drugs like ethicillin (11). Treatments that used to require small antibiotic doses now require huge concentrations or demand powerful new drugs (10). But such solutions are short-lived. For example, vancomycin, one of the only treatments for methicillin-resistant infections, has been overcome by some of the most frequent infectious agents in hospitals (2, 12). Antibiotics also generate evolution outside hospitals. Resistant strains are common on farms that use antibiotics in livestock production (13) and have been found in soils and groundwater affected by farm effluents (14).

Retroviruses with RNA genomes evolve even more quickly than bacteria (15). Every year, vaccinations against influenza must be reformulated, making prediction of next year's viral fashion one of preventative medicine's chief challenges (16). The virus that causes AIDS, human immunodeficiency virus –1, evolves so quickly that the infection within a single person becomes a quasi-species consisting of thousands of evolutionary variants (15). Over the course of months or years after HIV infection, the virus continually evolves away from immune system suppression (17, 18). Evolution in the face of antiviral drugs is just as rapid. For example, the drug nevirapine reduces viral RNA levels for only about 2 weeks (19). Thereafter, mutations in the HIV reverse transcriptase gene quickly arise that confer drug resistance, and the HIV mutants have a doubling time of 2 to 6 days (19). This rapid evolution is repeated with virtually all other antiretroviral drugs when given singly, including the inexpensive antiviral drugs zidovudine (azidothymine, AZT), lamivudine (3TC), didanosine (ddI) and protease inhibitors like indinavir (20–24).

Rapid evolution caused by humans is not restricted to disease or pest species. Under heavy fishing pressure, fish evolve slower growth rates and thinner bodies, allowing them to slip through gill nets (25, 26). In hatchery populations of salmon, there is strong selection for dwarf males that return from sea early, increasing their survival (25). Invading species, transported by humans, have been known to rapidly change to match local selection pressures (27). For instance, house sparrows, introduced to North America in 1850, are now discernibly different in body size and color throughout the United States (28). In some cases, species introduced by humans induce evolution in species around them. For example, after the subtidal snail Littorina littorea invaded coastal New England in the late 1800s, native hermit crabs [Pagurus longicarpus (Say)]

quickly evolved behavioral preference for their shells. The crabs also evolved body and claw changes that fit them more securely in these new, larger shells (29). Even more quickly, introduced predatory fish have caused rapid evolution of life-history traits and color pattern in their prey species (30, 31). Rates of humanmediated evolutionary change sometimes exceed rates of natural evolution by orders of magnitude (30).

Causes of Evolution

These examples demonstrate pervasive and rapid evolution as a result of human activity. In most cases, the causes of this volutionary pattern are clear: if a species is variable for a trait, and that trait confers a difference in survival or production of offspring, and the trait difference is heritable by offspring, then all three requirements of evolution by natural selection are present. In such cases, the evolutionary engine can turn, although evolutionary directions and speed can be influenced by factors such as drift, conflicting selection pressure, and correlated characters (31). The overwhelming impact of humans on evolution stems from the ecological role we now play in the world, and the industrialization of our agriculture, medicine, and landscape. Successful pesticides or antibiotics are often produced in massive quantities. DDT, for example, was first used by the Allied Army in Naples in 1943, but by the end of World War II, DDT production was proceeding on an industrial scale. Currently, we use about 700 million pounds of pesticide a year in the United States (7). Antibiotic production is also high, with 25 to 50% going into prophylactic use in livestock feed (13).

Inefficient use of antibiotics has been cited as a major cause of antibiotic resistance. Partial treatment of infections with suboptimal doses leads to partial control of the infecting cell population and creates a superb environment for the evolution of resistant bacteria. Up to one-third of U.S. pediatricians report overprescribing antibiotics to assuage patient concerns, particularly in cases of viral childhood congestions that cannot respond to the drug (32). Failing to complete a course of antibiotics is associated with increased emergence of resistant tuberculosis and HIV infections (33, 34), and differences in antibiotic use may partly explain differences among nations in antibiotic resistance rates (2).

Spread of antibiotic resistance has been accelerated by transmission of genes between bacterial species (13). Recently, biotechnology has applied this acceleration to other species as well, and a new humanmediated mechanism for generating evolutionary novelty has emerged—insertion of exogenous genes into domesticated plants and animals. Taken from bacteria, plants, animals, or fungi, these genes convey valuable commercial traits, and they are placed into new host genomes along with genes that control expression and in some cases allow cell lineage selection (35, 36). Exmples include the insertion of genes for insecticidal proteins (37), herbicide tolerance (38, 39) or novel vitamins (40) into crop plants; growth hormone genes into farmed salmon (41); and hormone production genes into livestock "bioreactors" (42). These efforts effectively increase the rate of generation of new traits—akin to increasing the rate of macromutation. When these traits cross from domesticated into wild species, they can add to the fuel of evolution and allow rapid spread of the traits in natural populations

(43). Genetic exchange from crops has already enhanced the weediness of wild relatives of 7 of the world's 13 most important crop plants (44), although no widespread escape of an engineered gene into the wild has been reported yet.

The Economics of Human-Induced Evolution

Evolution is responsible for large costs when pests or disease organisms escape from chemical control. Farmers spend an estimated $12 billion on pesticides per year in the United States (7). Extra costs due to pest resistance, such as respraying fields, may account for about 10% of these direct expenditures (45, 46). Despite the heavy use of chemical pesticides, 10 to 35% of U.S. farm production is lost to pest damage (45). If even 10% of this loss is due to activities of resistant insects (and the figure may be far higher), this represents a $2 billion to $7 billion yearly loss for the $200 billion U.S. food industry. The development of resistance in diamondback moths to Bacillus thuringiensis (Bt) toxin in 1989 (47) foreshadows the decline in use of the world's largest selling biopesticide and the need for new approaches. The price of developing a single new pesticide, about $80 million in 1999 (7), is an ongoing cost of agricultural business. Even higher development costs (about $150 million per product) are incurred by pharmaceutical companies [p. 157 in (7)]. In both sectors, evolution sparks an arms race between human chemical control and pest or disease agent, dramatically increasing costs that are eventually paid by consumers (7, 11). For example, the new drugs linezolid and quinupristin-dalfopristin were recently approved by the U.S. Food and Drug Administration (FDA) for use on vancomycinresistant infections (48). Previously, vancomycin had been used to overcome methicillin resistance (10), and methicillin was itself a response to the failure of penicillin treatment (13). This development cascade has been ongoing since the birth of the chemical-control era and represents a poorly quantified cost of evolution.

More direct expenses stem from the increase in drug payments and hospitalization necessary to treat resistant diseases. There are approximately 2 million hospital-acquired infections in the United States each year [data from 1995 (11, 49)], a quarter of which are caused by antibiotic-resistant S. aureus (2). Half of these are penicillin-resistant strains that require treatment with methicillin at a cost of $2 billion to $7 billion (11, 49). The other half are methicillin-resistant infections, and they cost hospitals an estimated $8 billion per year to cure (11). Community-acquired, antibiotic-resistant staph infections more than double these costs (49, 50). These figures are for a single type of infection and do not include other well-known drug-resistant bacteria. For example, in the United States up to 22% of hospital-acquired infections of Enterococcus faecium are resistant to vancomycin, and combating such infections drives the price of evolution even higher.

Similar conservative tabulations can be made for the cost of HIV treatment. The current standard of care in the United States is to treat HIV with massive doses of at least three drugs (51). Because treatment with the inexpensive antiretroviral drug AZT would successfully halt HIV if it did not evolve resistance, the need for more powerful drugs is due to HIV evolution. Drug and treatment prices vary but have recently been estimated

at $18,300 per year per patient in the United States (52). If half the 700,000 HIV patients (53) in the United States receive this level of care, these costs amount to $6.3 billion per year (52). Costs of lost labor, disruption of health services, development of new drugs, and medical research are not included in this figure, and so the actual cost of HIV evolution is far higher.

The annual evolution bill in the United States approaches $50 billion for these examples (Table 2), and probably exceeds $100 billion overall. However, the social price of evolution is far higher. Skyrocketing costs of treating resistant diseases create a situation
where effective medical treatment may be economically unattainable for many people. Thus, evolution expands the class of diseases that are medically manageable but economically incurable.

Ways of Slowing Evolution

Responding to the pervasive reach of evolution in medicine and agriculture, health specialists and agricultural engineers have developed an impressive series of innovative methods to slow the pace of evolution.
A large body of theory guides deployment of some of these attempts (54–59). Other methods, circulated as guidelines for clinical practices or farming strategies, often appear to be developed through a combination of trial and error and common sense. Independent of their theoretical underpinnings, the following examples show that successful methods often slow evolution for clear evolutionary reasons and that these approaches may be generalizable to other systems.

Drug overkill and HIV triple-drug therapy. Overkill strategies, the combination of treatments to kill all infectious or invading pests, are common. For example, treatment with a drug cocktail that includes a protease inhibitor and two different reverse transcriptase inhibitors is the Cadillac of AIDS treatment strategies (51). This approach has been successful longer than any other, because it not only reduces viral levels but also slows the evolution of resistance. The evolutionary biology hidden in this strategy is simple: a strong, multiple-drug dose leaves no virus able to reproduce, and so there is no genetically based variation in fitness among the infecting viruses in this overwhelming drug environment. Without fitness variation, there is no evolutionary fuel, and evolution halts. Lack of HIV variation for growth in this regime is responsible for reduced evolutionary rate and probably drives the current success of triple-drug treatment. However, sequential treatment with single drugs or voluntary drug cessation can foster the evolution of drug resistance (33), which appears to be increasing (60, 61). This suggests that the triple-drug overkill strategy will not halt HIV evolution forever but may provide only a brief window for the development of more
permanent solutions, such as HIV vaccines.

Overkill strategies have been echoed in pesticide management programs, where they are often termed "pyramiding" (62), and in treatment of bacterial infections (11). However,

their use is limited by drug toxicity: extreme doses can have physiological or ecosystem side effects.

Direct observation therapy. Tuberculosis infects one-third of the world's population (10, 34), and is difficult to treat because it requires 6 months of medication to cure. Partial treatment has resulted in evolution of multidrug resistance (34). To combat this, drug doses are brought individually to patients, who are observed while they take the drugs. This direct-observation therapy has been used to improve patient compliance during the whole treatment regimen, reducing evolution of resistance by ensuring a drug dose long enough and severe enough to completely eradicate the infection from each person. Direct-observation therapy has been credited with snuffing out emerging tuberculosis epidemics and dramatically reducing costs of medical treatment (10).

Withholding the most powerful drugs. The antibiotic vancomycin has been called the "drug of last resort," because it is used only when other, less powerful antibiotics fail (10). Withholding the most powerful drugs lengthens their effective life-span (11), because overall selection pressure exerted by the drug is reduced, slowing the pace of evolution. Although successful in reducing the evolution of resistance to vancomycin by some bacteria, the strategy depends on low use rates in all sectors of the antibiotic industry, including livestock and prophylactic use (13). Failure to include these sectors in the strategy will engineer its failure.

Screening for resistance before treatment. Screening infections for sensitivity to particular antibiotics before treatment allows a narrow-range antibiotic to be used instead of a broad-spectrum antibiotic. Reduced use of broad-spectrum antibiotics slows evolution of resistance as in the mechanism above. Genotyping of viruses in an HIV infection and prediction of the antiviral drugs to which they are already resistant improves drug usefulness (63). Similarly, farmers are advised to check their fields after pesticide treatment and then to change the chemical used in the next spraying if many resistant individuals are discovered. Screening for pest susceptibility reduces use of chemicals for which resistance has begun to evolve.

Cyclic selection due to changing chemical regimes. Farmers are encouraged to follow several simple rules to reduce herbicide resistance: (i) do not use the same herbicide 2 years in a row on the same field, and (ii) when switching herbicides, use a new one that has a different mechanism of action (64). These guidelines slow evolution through a rapid alteration of selection pressure that sequentially changes the selective landscape. Mutants favored in one generation are not favored in the next, because one mutation is not likely to provide resistance to two herbicides with different mechanisms. Similar cyclic selection regimes have been proposed to limit resistance in intensive-care units (11, 59) and agricultural fields (62). Mosaic selection, in which different chemicals are used in different places at the same time (65) is a spatial version of this tactic.

Integrated pest management. Integrated pest management (IPM) may include chemical control of pests, but does not rely on it exclusively, and is credited with better pest control and with slower evolution of resistance (62). Slow evolution can come from two

sources. First, the multiple control measures used in IPM reduce reliance on chemical treatments, thereby reducing selection for chemical resistance. Second, physical control of populations (e.g. through baiting, trapping, washing, or weeding) reduces the size of the population that is exposed to chemical control. Smaller populations have a reduced chance of harboring a mutation, thereby slowing the evolution of resistance. The term IPM is common only in insect management, but the strategy has appeared independently in hospitals where hand-washing, instead of prophylactic antibiotic use, is encouraged and in weed management, where resistant weeds are pulled by hand.

Refuge planting. Biotechnology has introduced insecticidal toxin genes into numerous crop species, but resistance to toxins produced by these genes has already evolved in pests, threatening the commercial use of this technology (66–68). To reduce the potential
for evolution, crop engineers have instituted a program of refuge planting to slow the success of resistant insects (69). If farmers plant a fraction of a field with non-toxin-producing crop varieties, and allow these to be consumed by insects, a large number of nonresistant pests are produced. These can then mate with the smaller number of resistant
individuals emerging from fields of plants producing insecticidal proteins, greatly reducing the number of offspring homozygous for the resistance alleles. In cases where resistance is recessive, refuges slow the spread of resistant alleles (69), although they require high crop losses in the refuge plantings. This mechanism functions by reducing the inheritance of resistance through increases in the proportion of breeding individuals without resistance alleles.

Engineering evolution. Using evolution to our advantage may also be possible, although this is seldom attempted [p. 215 in (70)]. One illustrative exception is the use of the drug 3TC to slow the mutation rate of HIV and thereby, perhaps, to limit its ability to rapidly evolve resistance to other drugs (24). An ongoing use of evolutionary theory is the prediction of which influenza strains to use for future vaccines (15). Another is the use of chemical control where resistance includes a severe metabolic cost, making resistant individuals less fit when the chemicals are removed (71). In such cases, the potential of evolution to lower pest fitness in the absence of a pesticide may be a method of using the power of evolution to our advantage. An unintended evolutionary outcome may be the escape of antibiotic, herbicide, or pesticide resistance genes to natural populations, possibly making them less susceptible to pesticides in the environment. In some agricultural settings, artificial selection for pesticide resistance has been used to protect populations of beneficial insects (72).

This summary shows that successful control of evolution has followed many different strategies, and that the methods currently used impact all three factors driving evolutionary change. However, seldom have all three evolutionary prerequisites been manipulated in the same system, and seldom has the engineering of the evolutionary process been attempted in a systematic way. Instead, in every new case, human-mediated evolution tends to catch us by surprise, and strategies to reduce or stop it are invented from scratch. For example, cyclic selection has been invented at least three

times (for control of insects, bacteria, and HIV), IPM at least three times (insects, weeds, and bacteria), and drug overkill at least twice (HIV and tuberculosis).

Overall, three ways to adjust selective pressures are widely used in pest and health management: application of multiple simultaneous chemicals or "pyramiding," cyclic application of different chemicals, and using different chemicals in different places or "mosaic application." Although the principles are exactly the same in all fields, seldom has the literature from one field been used to inform the other (73). Some strategies that are very successful in one arena have not been tried in others (e.g., no direct-observation therapy has been tried on farms). Yet, the commonality of successful methods suggests that lessons in evolutionary engineering from one system may be useful in others and that it may be possible to control evolution far more successfully than is currently practiced. Mathematical models of evolutionary engineering provide some guidance about practical field methods (54, 62), but this exchange between prediction and practice has only been common in pest management (65) and antibiotic resistance (59). A critical need is the inclusion of evolutionary predictions in the current debate on global HIV policy. Most important, it is seldom realized that a pivotal goal is slowing the evolution of resistance and that, without this, all successful pest and disease control strategies are temporary (62, 70, 74).

Conclusions and Prospects

Rapid evolution occurs so commonly that it is, in fact, the expected outcome for many species living in human-dominated systems (62). Evolution in the wake of human ecological change should be the default prediction and should be part of every analysis of the impact of new drugs, health policies, pesticides, or biotechnology products. By admitting the speed and pervasiveness of evolution, predicting evolutionary trajectories where possible, and planning mechanisms in advance to slow evolutionary change, we can greatly reduce our evolutionary impact on species around us and ameliorate the economic and social costs of evolution (70). Ignoring the speed of evolution requires us to play an expensive catch-up game when chemical control agents and medications fail. Because our impact on the biosphere is not likely to decline, we must use our knowledge about the process of evolution to mitigate the evolutionary changes we impose on species around us.

Note added in proof: In two recent papers (76, 77), the genetic basis of resistance to BT toxins has been discovered in nematodes and lepidopterans. In both cases, mutations at single genes appear to confer substantial resistance, and might also provide cross resistance to different BT toxins. Without efforts to mediate this evolutionary potential, strong selection in diverse plant pests at a single locus may generate field resistance to transgenic Bt-producing crops or to commercially used sprays of Bt toxin.

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Evolution in Our Lives

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One challenge of teaching evolution is demonstrating to our students how evolution is relevant to their lives. One easy way to do this is through medical examples. Many students, even at the high school level, aspire to medical professions, and everyone has had the experience of being sick.

Emerging diseases are one of the biggest challenges facing medicine today. These are diseases which, though previously rare, unknown, or relatively harmless, are now a threat to public health. The most notorious of these and biggest public health crisis is AIDS, or acquired immune deficiency syndrome, which is caused by the HIV virus. Cases of HIV infection began to be reported in the U.S. only twenty years ago, and now, as many as a million people may be infected in the U.S. Worldwide, perhaps 30 million people are infected and infection rates continue to climb. Why did HIV begin to infect so many people? Why is it so hard to make a vaccine to HIV? Why do drugs work against HIV for a while, and then stop working? The answer to all these questions is - evolution by natural selection.

HIV/AIDS as a Model System for Teaching Evolution

Studying HIV/AIDS is made immensely easier by access to databases that contain DNA sequences of many varieties of HIV. The increase of internet access in high school classrooms means that teachers and students can access the latest in national and international genetic databases. By comparing the DNA sequences, students can see for themselves the way that mutation and selection act to inhibit development of HIV vaccines.

Genetic Variation is Fundamental

The fundamental requirement for evolution is not natural selection, but genetic variation. Darwin emphasized how important it was that there were different varieties of a given trait, and that these varieties must be heritable, that is, genetic. All genetic variation comes from mutation. The reason that HIV is difficult to vaccinate against is in part because the mutation rate is very high. This causes the virus to evolve quickly.

All mutations are random. However, not all mutations are the same. Because of the way the genetic code works, some mutations cause a change in the proteins of the virus, while others do not. By looking at the DNA sequence, we can predict which mutations will change proteins. And, we can compare how often mutations that change proteins happen, versus those that do not.

Molecular biology caused a fundamental change in the way researchers think about evolution. Biologists were able to recognize that the heritable variation they were

observing was caused by changes to the DNA. We can look at a collection of DNA sequences and see the footprints of evolution by natural selection. We can use this evidence to suggest which genes are important in evolution, even if the functions of these genes are unknown. For example, vaccines work by teaching the body to recognize proteins on the outside of a virus or bacteria. HIV only has a few genes, some of which code for proteins that are on the outside of the virus. By comparing the rates of DNA sequence evolution of the different genes in HIV, including those that code for the outer coat and those that do not, we can see that the proteins on the outside evolve most quickly. This is why developing a vaccine for AIDS is so difficult.

The same mutational process that drives the evolution of the outside of the virus is responsible for the way that the virus can evolve resistance to new drugs. These mutations are also responsible for the change in the virus's host, from monkeys to humans. Further, these mutations are the same kind that cause evolution at higher scales, including generating new species. By demonstrating the power of evolution over short time scales, or microevolution, we can challenge students to think about evolution's potential power over longer time scales, or macroevolution. Simultaneously, we can use the example of HIV to teach details about the genetic code, to demonstrate some of the scientific resources on the internet, and to bring home the importance of evolution to our students' lives.

Putting the Scientific Method into Biological Taxonomy – Teaching the Phylogenetic System

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Introduction: In teaching the practice of science, we usually cite the scientific method, with its objective repeatable observations and falsifiable hypotheses, as its essence. In biological education, however, there is often a chasm between the scientific method and the body of knowledge that we spend much of our time conveying. That this gulf is conspicuous in biological taxonomy, the ordering of the diversity of life, is not altogether surprising. The traditional Linnean system of taxonomy did not arise from a consistent application of the scientific method. Rather, it is an accretion of observations, intuitions, and conventions established over two and a half centuries by people using organizing principles as contradictory as Aristotelian essentialism and Darwinian evolution.

Roughly forty years ago, evolutionary biologists began experimenting with alternatives to this system that would embody the methodological rigor of the scientific method and a consistent organizing principle. From these explorations, a new system of taxonomy, the Phylogenetic System, has risen to prominence. This system, based on the cladistic algorithm of phylogeny reconstruction, employs the branching pattern of evolutionary history as its exclusive organizing principle. The phylogenetic system was embraced by historical evolutionists in the 1980s and became common in undergraduate education during the 1990s. To date, however, it has made few inroads into K-12 curriculum. This is regrettable, because the new system offers compelling connections between the rigor of the scientific method, the fact of evolution, and our body of evolutionary knowledge. Above all, in its simple clarity, the Phylogenetic System is well within the grasp of motivated secondary school students.

Weaknesses of the Linnean System: The Linnean system has played an indispensable role in the organization of a rapidly expanding body of biological knowledge for over two centuries. No one's decision to abandon it is made lightly. Nevertheless, it embodies paradoxes that cannot be resolved with reference to biological reality. Two conundra that might easily be posed by an attentive high school student illustrates them.

1. What is the difference between a reptile and a bird? - It is universally accepted among evolutionists that birds are descended from reptiles, probably theropod dinosaurs. In the Linnean view, at some point, creatures cease being reptiles and become birds. Looking at living organisms, this is a clear-cut distinction. Birds could be defined by a list of characteristics like feathers and a wish bone. When we consider extinct organisms, however, the picture blurs. Creatures like *Allosaurus*, *Caudipteryx*, *Archaeopteryx*, and *Ichthyornis* each possess some, but not all of these "avian" features To decide which are actually birds, we must somehow designate one characteristic as

"key." Unfortunately, no repeatable objective criterion exists for choosing key characters in such circumstances. Consequently, whatever criterion we pick will inevitably be arbitrary, and yet the Linnean approach requires us to make such a choice.

2. How are alligators like oysters? - Both the groups Alligatoridae, alligators, and Ostreidae, oysters, have the rank of family in the Linnean system, suggesting that they are somehow biologically equivalent. Many measures of equivalence can be imagined, including geologic age, species diversity, or morphological disparity, however none is an acknowledged standard. In practice, families, like other taxonomic ranks give structure to Linnean taxonomy as an information retrieval system, but do not consistently convey a biological meaning.

The Phylogenetic System directly addresses these shortcomings. The tree of evolutionary history, with its bifurcating branches of evolving lineages, is its organizing principle. An internested set of taxonomic groups is defined based on descent from common ancestors represented by lineage bifurcations. Taxonomic groups, by definition, include all of the descendants of a given common ancestor. From the phylogenetic perspective, reptiles do not cease being reptiles when they evolve into birds. Rather, the group Aves is nested within a more inclusive Reptilia. Such definitions need not rely on any arbitrary criterion. Instead, they are grounded in something biologically real - common ancestry. Additionally, no effort is made to establish artificial ranks across large ranges of groups. Above all, in their strict evolutionary hierarchy, phylogenetically defined groups offer the student a constant reminder of the evolutionary tree upon which its taxonomy based.

The scientific method: Phylogenetic systematists use the cladistic method to reconstruct the history of life. Simply stated, this algorithm examines a "matrix" or table of organisms and their characteristics in which the data in each cell indicate whether an organism has the ancestral or derived state of a characteristic. The cladistic algorithm sequentially constructs every possible tree arrangement, mapping the minimum number of character state changes onto each tree and counting them. The alternative trees are then evaluated according to parsimony, or "Occam's razor:" The preferred hypothesis of evolutionary history requires the fewest character state changes. Like all scientifically repeatable observations, the matrix data can be reviewed by others, and revised. Like any scientifically falsifiable hypothesis, the preferred hypothesis of evolutionary history can be tested by the addition of new information, in the form of new organisms or newly recognized characters, to the analysis.

Simple, illustrative cladistic analyses can be performed with pencil and paper, however with inexpensive analytical software, more detailed student analyses are perfectly feasible. Furthermore, several academic institutions maintain web sites, and even consortia of sites, phylogenetically describing the tree of life and disseminating recent discoveries, so in addition to learning about the scientific basis for the new taxonomy, students who understand its cladistic basis can explore the evolutionary tree directly.

Educators should have no illusions about the immutability of the Phylogenetic System. In the last twenty years, researchers have reached broad consensus on the general pattern of evolution, especially for vertebrates, but many details remain controversial. Many invertebrate groups have barely been examined. Thus, one should expect continuing revisions. This intensity, of course, is part of what distinguishes active science from static revealed wisdom. Educators who embrace the Phylogenetic System will give their students the opportunity to witness, first hand, the connection between the scientific method and the coherent body of knowledge it generates, and watch that body grow.

SNPs : Why all the excitement?

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The year 2000 marks a milestone in the study of genetics with the announcement of the completion of a working draft of the human genome sequence. Among the most important outgrowths of the human genome project are a collection of powerful new approaches to the understanding of human diversity and the underlying genetic basis of complex diseases. At the foundation of the most heralded approaches, and an increasing presence in the popular press and other media as well, are Single Nucleotide Polymorphisms or SNPs.

As their name implies, SNPs are single base changes in the DNA code. The widespread occurrence of these minor differences between humans has become evident from various sequencing projects. They are the most common type of polymorphism in the genome; the National Institutes of Health estimates that the human genome contains between 6 and 30 million SNPs, spaced relatively regularly at 100-1,000 base intervals. In addition to the obvious importance that SNPs may have in changing the biological activity of a gene product, SNPs are currently considered the most promising genetic marker for mapping studies for human traits, especially complex diseases such as cancer, diabetes, heart disease, or arthritis. The SNP Consortium has estimated that as many as 300,000 SNPs may be needed to fuel these studies, and has committed to mapping a minimum of 100,000 SNPs by 2003. SNPs are largely biallelic (that is, they have two forms) in nature, thereby lending themselves well to automated, high through-put genotyping methods.

The human SNP patterns we see today are the culmination of the genetic history of those genomes and individuals. They are shaped by evolutionary forces that act over time, including mutation, drift, selection, mating structures, and migration. To make effective use of SNPs as tools to unravel current phenotypes, it is necessary to understand this evolutionary context of human variation. Studies to determine nucleotide diversity in different portions of the genome and the geographic distribution of genomic diversity are the next step.

We can point to several examples of the exciting and intriguing findings that have emerged from projects that use SNPs as genetic markers. First, SNPs linked to the Y chromosome have been used to trace the ancient origins of modern peoples, and to contribute information to more recent historical questions such as the controversies surrounding the relationship between Thomas Jefferson and Sally Hemming. Second, we can identify the surprising results of SNP mapping on one gene believed to be associated with heart disease. Finally, glancing into the crystal ball, we must consider prospects for genome-wide “genotyping” and “personalized molecular medicine.”

Macroevolution: Evolution on a big scale

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The study of macroevolution, or evolution above the species level, involves a change in scale and a change in approach from that of microevolution. Macroevolution is concerned with origins, diversifications and extinctions over the sweep of geologic time: what the embryologist C.H. Waddington called "The whole real guts of evolution, how we get horses and tigers and things." The invasion of land by plants and animals, the derivation of wings in bats, pterosaurs, and birds from the forelimbs of their respective ancestors, and the evolutionary explosion of mammals after 120 million years of life in the nooks and crannies of the dinosaurs' world, are just a few of the dramatic events that fall under this heading. This means that much of macroevolution, like astronomy, is an historical science, a matter of reconstructing history and testing hypotheses of ancient cause-and-effect using evidence from the fossil record, embryology, molecular biology, and other geological and biological sciences. What is sometimes not appreciated is that these different lines of evidence tend to converge on a single picture; their disagreements are almost always in the details, and even the larger remaining points of contention make sense in terms of the weaknesses and biases of one style of research or another. I'm going to review a few major points in order to clarify the outlines of an emerging macroevolutionary consensus (while acknowledging that this a very active field and that consensus does not imply unanimity).

1. Speciation is too slow to be easily observed by the biologist, but from the perspective of the fossil record, speciation is often too fast!

The fossil record contains many beautiful examples of the evolutionary transformation of one -- morphologically defined -- species to another, but these mainly occur in a few environments that are particularly good at recording the fine details of a time sequence: in lakes that accumulate annual beds of silt, for example, or in deep-sea deposits that record the steady rain of plankton from the surface waters. In contrast, the land-surface is more continuously subject to erosion than the seafloor, with catchbasins like lakes and swamps tending to be geologically short-lived, so the terrestrial record will be patchier and less complete than the marine record. The operation of plate tectonics, consuming the Earth's crust in subduction zones and smashing continental edges into mountain ranges during collisions, creates a record that becomes more patchy with age: the vast Precambrian interval is the first 80% of earth history, but it now provides only 10% of the rock record. This is a basic point about the nature of the fossil record: it's undeniably incomplete and imperfect (as is our knowledge of the living biota, of course), but it's imperfect in ways that make sense from what we know about how sediments accumulate and rocks form. Similarly, the nature of the record is a logical consequence of the biology of the organisms that contribute to it. Hard parts more readily resist physical and chemical destruction, so the record of organisms with shells, teeth, or tough pollen grains is more complete than the record for flimsier creatures. Rare species will be less frequently preserved than abundant ones; localized species will

be less frequently preserved than widespread ones. Common-sense rules like these (which are now being put into quantitative terms) go a long way towards explaining the unevenness of the fossil record: fabulous for shelled, marine microplankton, not very good for dinosaurs or early hominids, and miserable for earthworms and slugs.

2. "Punctuated equilibrium" is a hypothesis about evolutionary change at the species level.

This most famous of macroevolutionary concepts has been wildly overextended and misused, but it simply states that species tend to be morphologically static over most of their histories, and that most changes in form occur in close association with the geologically-rapid splitting of populations into new species. Everyone now agrees that both stasis and splitting are common, but that gradual change and non-branching evolution also occur and may even dominate in some situations; notice these alternatives can be tested even if the fossil record is bunched into packages separated by gaps of missing or fossil-free rocks. We can recognize stasis in species form even using widely spaced samples (one photo per decade can demonstrate that the Statue of Liberty hasn't changed much since it was installed in New York Harbor), and we can detect lineage splitting whenever the ancestral species outlives the first appearance of its descendent. Note that this doesn't require that all new species be morphologically distinct, only that species-level changes in morphology arise at splitting events, and not by continuous change of the kinds of large, widespread populations that can be studied in the fossil record.

The most exciting research in this area now focuses on testing for regular patterns in the distribution of stasis versus gradual change, and in splitting versus unidirectional evolution, among species in different major groups, life-habits, environments, or regions; on testing hypotheses for the mechanisms of stasis (the punctuations are geologically rapid but slow on biological timescales and thus consistent with an array of speciation mechanisms); and on exploring the macroevolutionary implications of stasis and lineage-splitting (some argue, for example, that if species are static through much of their history, then large-scale trends, e.g. from primitive to modern horses, must arise via differences in speciation and extinction rates among different sublineages within a larger group).

3. The topology of evolution is a bush, not a ladder.

As biologists and paleontologists gain a fuller picture of the large-scale outlines of evolutionary history, it has become abundantly clear that our basic view of evolution at this scale should not be a ladder or any other icon of directional, progressive change, but a bush with many branches, stems and twigs. This in no way undermines the role of natural selection and other forces at the population level, but when we take a step back and look at the broader outlines, evolutionary lineages must diversify if they are to withstand even the relatively low levels of "background" extinction that prevail over much of geologic time. Complex evolutionary transitions, e.g. from dinosaur to bird, or from small, multi-toed ancestral horses to their large, hoofed descendents, do not occur

as single mutational steps, or as a simple parade of increasingly more modern forms. Instead, these major shifts generally occur within a swarm of related lineages.

4. At higher levels, the fossil record is rich in " missing links."

We can hardly expect the fossil record to capture every single species within those swarms of transitional lineages, but we have a spectacular sample of intermediate forms between the many of the major groups of plants and animals. For example, an exquisite sample of intermediate forms are now known for the transitions from "fish" to tetrapods, from "reptiles" to mammals, dinosaurs to birds (or, strictly speaking, non-avian dinosaurs to birds). Intermediate fossils for many other lineages within these groups, for example whales, horses, and for that matter humans, are also being increasingly well documented as exploration and analysis continues. Mosaic evolution is clearly the rule, that is different anatomical features (and presumably behavioral, physiological...) evolve at different rates and different times. Thus, the earliest known bird, Archaeopteryx, has features typical of modern birds like feathers and a wishbone but retains the dinosaurian tail, clawed forelimbs pelvis and teeth of its ancestors; slightly younger forms evolved a more birdlike, perching hindlimb and pelvis, but still retain those teeth and forelimb claws, and so on. Human evolution operated in same way, with upright posture evolving before the short face and large cranial capacity of modern humans.

5. Major changes in morphology don't always require major genetic changes

Remarkable advances in developmental biology are beginning to merge with the study of macroevolution. We now understand that striking differences in morphology and behavior need not be correspond to massive genetic differences, but instead may arise by relatively modest changes in the timing, duration, or location of gene expression. A complex hierarchy of genes orchestrates development of fertilized egg into complex, multicelluar adult, which is now being probed by molecular developmental biologists. Many of the major control genes, such as those that establish the body axes of the embryo or that, like the Hox genes, that provide positional assignments along the anterior-posterior axis, are conserved throughout all animals. Changes in the expression of those control genes must have been involved in some of the major evolution transitions during the initial radiation of animals. Such changes have also been implicated in more modest changes as well, such as changes in limb morphology in arthropod evolution. These control genes result in an embryo that develops in modular fashion, with semi-independent regions, so that limb development, for example, can proceed even if jaw development has changed. This helps to explain the mosaic evolution pattern mentioned above. The role of gene regulation in shaping major evolutionary changes also helps to explain how apes and humans can be genetically so similar (differing by only 50 genes out of ca 80,000 by a recent estimate): our differences with our closest living relatives must reside almost entirely in changes in the expression pattern of genes.

Despite this modularity and the existence of major regulatory genes, development is not

infinitely flexible: an embryo must retain viability at every step and must give rise to an integrated adult body. This constrains the direction of feasible evolutionary changes. Further, because some aspects of development can become deeply entrenched as precursors to later developmental steps, the traces of past evolutionary history are almost always retained. Thus, when reptiles went back to the sea and evolved into ichthyosaurs, and when mammals evolved into dolphins, they converged on a shark-like morphology owing to the stringent adaptive requirements of their predatory marine lifestyles, but they retained many tell-tale reptilian and mammalian characters. Developmental programs are too complex, and evolutionary history too long and peculiar for each lineage, to permit true evolutionary irreversibility at this scale.

6. Major evolutionary events are pulses in geologic time

One of the triumphs of evolutionary paleobiology has been the clear documentation that the history of life has not been a steady increase in numbers or a simple linear trajectory towards the modern world. Instead, the story is one of rapid radiations, long plateaus in biodiversity, and mass extinctions. The Cambrian Explosion marks the appearance of most multicellular animal designs (all but one of the living phyla having preservable skeletons plus a number of problematic forms) within a 10-million-year window starting about 530 million years ago (Ma). This event, which lasted less than 0.5% of the history of the Earth to that point, and less than 2% of the time from the base of the Cambrian period to the present day, certainly represents a geologically explosive appearance of animal body plans, recognizable not only in tallies of phylum-level taxa but in analyses that directly quantify morphological variety. The relation of those first appearances to their actual time of evolutionary origination is a hot topic, but the simultaneous increase in the number, size and complexity of tracks and burrows in and on the sediment is strong evidence that a major part of the evolutionary action was in fact within the Cambrian explosion interval; the trigger mechanism is a focus of intensive research. We have an increasingly good picture of the run-up to the explosion, with evidence of early metazoans in the form of minute trails from rocks as old at 600 Ma in the late Precambrian (Neoproterozoic), astonishingly well-preserved eggs and embryos exhibiting well-defined cleavage stages at around 570 Ma, more elaborate trails and burrows at the re-defined base of the Cambrian Period at 543 Ma, and a steadily expanding diversity of small shelly forms from 543 to the explosion proper at 530 Ma. One minor lineage recorded within the great range of new body forms were the primitive chordates, which eventually gave rise to the major vertebrate diversifications.

Additional pulses of diversification -- though none so dramatic at the Cambrian explosion -- represent events that opened major ecological opportunities to evolutionary lineages. The invasion of land by plants, invertebrates, and finally vertebrates, is followed by waves of evolutionary experimentation and diversification. We are increasingly coming to realize that mass extinctions play an important role in evolution, by removing dominant forms and providing opportunities for the survivors to diversify in their place. The exuberant radiation of mammals after the demise of the dinosaurs and related forms at the end of the Mesozoic Era (at the end of the Cretaceous Period) is the most famous example, but similar patterns are seen after each of the "Big Five"

mass extinctions. The marine fauna familiar to today's beachcomber and skin diver was profoundly shaped by the great end-Paleozoic mass extinction (at the end of the Permian Period), which removed roughly 95% of marine species and permanently altered the balance of life in the seas. This is not to say that the accelerating extinctions of the present-day faunas and floras under pressure from human activities can be seen in a natural or positive light: recoveries from mass extinctions are painfully slow on human timescales (5-10 million years for reef systems for example), and the most persistent survivors need have no relation to human needs.

Why Evolution Matters

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There are abundant popular views about evolution. It isn't that most people wake up and stumble towards the coffee maker thinking, "Oh, man, what am I going to do about evolution today?" It is instead that evolution, as a subject has become enough of a cultural common currency that most people feel comfortable having an opinion.

Among biological sciences, this is actually a somewhat enviable position--herpetologists (who study reptiles and amphibians) would give a year's supply of snake skins for the popular attention given evolution. But such attention has its bad points as well as good and does as much to complicate the understanding of evolution as it does to raise interest in the subject. Although many people have a deep understanding of evolution, several major misconceptions about evolution are so common as to seem like dogma. These misconceptions simultaneously raise a storm of controversy about evolution and prevent understanding of an increasingly important biological crisis riding the crest of a human-made evolutionary wave.

Evolution and the Origin of Species

A critical misconception is that "evolution" and "the origin of species" are exactly the same thing. Most discussions (or law suits) on the " theory of evolution" are really about the "theory of the origin of species due to evolution by natural selection." In fact, evolution by natural selection is a biological process that is abundantly documented by observations and experimental evidence. It is as much a scientific reality as nuclear fusion (and is easier and safer for the average person to observe).

Evolution by natural selection can be seen in many experimental situations. For example, larger predatory fish that tend to consume more brightly colored males than duller males eats fresh water guppies. When predators are abundant, the result is an evolutionary shift, in just a generation or two, towards males with drab colors. But females prefer to mate with bright males (in terms of hue), so in the race for mates, colorful males dominate. These two types of selection, driven by predators and choosy mates, result in evolutionary shifts in color when ecological conditions change. When predators are common, dull colors predominate. In the absence of predators, gaudy males dance the streambeds to attract discerning mates.

Another example is the beak size of seed-eating finches living on dry islands in the Galapagos archipelago. During particularly dry years, plants do not produce many seeds. Finches live mainly on a diet of seeds and tend to consume smaller, softer seeds first. As the small seed supply is consumed, finches are left with the chore of cracking into harder, larger seeds. Birds with the smallest beaks can not do this well. As a result, during drought years birds with small beaks may well starve, leaving populations dominated by larger members of a species. Years with unusual weather thus lead to populations of unusual finches.

To such examples of natural selection can be added many examples of artificial selection, conducted in laboratory settings or by selection for particular characteristics by plant and

animal breeders. In virtually every experiment in which a sufficiently large and variable population is culled by artificial selection, an evolutionary response is observed. This response has been used countless times in the domestication of animals and plants. Long before Darwin recognized this as an evolutionary response, it had been used to shape the nature of agriculture. To be fair, there are limits to this response and sometimes there are unforeseen consequences. One fruit fly biologist tried to select for resistance to high temperatures by eliminating flies that passed out and fell off a heated cylinder. Instead, he ended up selecting for flies that passed out but hung tenaciously and unconsciously onto the cylinder wall. Nevertheless, evolution by natural or artificial selection is a biological phenomenon that's easily and rigorously demonstrated.

One area of active research is how evolution by natural selection leads to the formation of new species. Darwin envisioned that evolutionary "adaptation" in changing environments could lead to divergence of new species from their ancestors. Other mechanisms of species formation have also been envisioned (Mayr, etc.), and processes by which particular species form are often hotly debated. This is because speciation is not as easily observable or experimentally demonstrable as is simple evolutionary change.

This is not to say that speciation is an inexplicable process. Indeed, the dominant view of species evolution, the gradual divergence of populations in separate geographic locales, has been observed experimentally. However, successful experiments in species formation are rather rare. They take a long time and result in small shifts in morphology or behavior compared to species observable in the wild.

In a few cases, mechanisms of species formation have been observed. Abrupt shifts in behavior can result in species boundaries. Tephridid fruit flies lay their eggs on ripening fruit, and often females have highly discriminating tastes about which fruits are the best for their larvae. In the late 1800's, flies that lived on Hawthorn fruit in North America developed an egg-laying preference for apples introduced for agriculture. The shift in preference is heritable - daughters of apple-loving flies also lay eggs on apples - and so a new race or species became established. How different are these species? It takes an expert to tell them apart. But the potential now exists for these two types of flies to evolve separately, gradually diverging in defining characteristics, some important, some not, some visible, some depending on deep physiological or biochemical differences.

Because speciation is so difficult to study, understanding it has long been a primary evolutionary quest. It is a subject rich in experimental possibilities and theoretical convolutions, and it draws heavily on what we know about evolution by natural selection. But "evolution" and "speciation" are not the same, and uncertainties about the how the latter occurs do not mar our increasing understanding of the former. In addition, the impact of humans on the biological world around us does not hinge on species formation. Instead it hinges on evolutionary shifts in diseases and insect pests and the plants we raise for food. So we must move on to consider the second common misconception about evolution - the one that matters most - the speed of evolutionary change.

The Speed of Evolution

The dinosaurs evolved and ruled the earth for over 100 million years, succumbing finally in the aftermath of an asteroid strike 65 million years ago. Over tens of millions of years, different forms arose and went extinct. The plastic stable of species familiar in toy chests of most 5 year-olds (Triceratops, Stegosaurus, Apatosaurus, Tyrannosaurus) slowly came and went on the evolutionary stage. And so evolution seems a majestic and slow process, minutely ticking away during vast stretches of time. Infinitesimally - different generations are strung together long enough so that, while the mountains wear away and the very continents plow the seas, species evolve new forms.

Darwin thought this way too. Evolution by natural selection was born as an idea in the early decades of the 19th century, when the age of the earth was considered to be immense--so large that tiny, random variations could slowly be selected for during the struggle for survival. In fact, a debilitating challenge to the theory of evolution by natural selection came from calculations of physicists who concluded in the late 1800's that the Earth was cooling so fast that life could be no older than 20-40 million years. Darwin was dismayed by this time frame - too short for his view of slow evolution to play out - and died before the discovery of heat-producing radioactive decay could over-turn these objections.

To find examples of evolution, Darwin and his predecessors tended to scan large tracts of time. They saw in the stately change of the fossil record or in the fine-tuned adaptation of precise biological machinery the signature of evolution over the millennia.

So, too, modern accounts of evolution often emphasize missing-link fossils from long ago and the happenings (especially for the Hollywood fossils--the dinosaurs) of tens of millions of years in the past. Yet biologists have long noticed rapid evolutionary change, both within the fossil record and in modern plants and animals. Sometimes studied for their value as exceptions to the slow evolutionary rule, sometimes studied for purely practical reasons, rapid evolution is increasingly well known. We no longer need to dig into Earth's rocky past to uncover evolutionary events, but we can turn to the modern world around us. And once we begin to look for active evolution, we can find it all around us. In the signature of every harsh winter, every drought summer, every invasion of a new pest, and every dose of antibiotics, there is an evolutionary twist, a shift toward a new way of living. Perhaps the shift will be short-lived like this year’s rain hydrating last year’s drought, as one evolutionary shift cancels out the previous. But also perhaps the chance evolution of a resistant bacterial strain could create a plague or require a billion-dollar search for a novel antibiotic.

To understand this speed requires an understanding of evolution’s engine - the interlocking gears and power train that drives change across the generations. We need to understand what connects the engine’s parts and why they work together. We need to understand why sometimes the engine runs quickly and sometimes slowly - why it races and why it stalls. And once we do understand its function we can apply that intuition to the world around us and to the evolutionary events that transpire every day. The power of evolutionary science to explain and the power to predict will then let us organize our effect on the biological world to take inevitable evolutionary change into account. This change is all around us already, but we cast

it as an adversary - a facet of the biological world to tame. Tame it we can, but not without understanding, and not all the time.

If Evolution is Fast

If evolution is fast then humans are the most crucial evolutionary forces ever unleashed on the planet. This is because we change the world rapidly and repeatedly. We create new environments by the way we live, we create new biological hurdles by the way we protect our crops or cure our diseases. We change what the best strategies are for successful reproduction of other species by choosing when to hunt for them or harvest them or when to disturb the environments they live in. We also have created a worldwide transportation web that is virtually instantaneous compared with "natural" means of movement for most species. Like the asteroid strike that spelled doom for the last of the dinosaurs, we have dramatically altered the biological stage. The landscape and seascape have changed more radically in the past fifty years than virtually any time in the past. And it does not take an intelligent species to respond to the new human world - it does not take planning and forethought, committees and blueprints. All it takes is selection of individuals better adapted to these new environments. All it takes is for the progeny of these selected individuals to inherit these new abilities.

Evolution of antibiotic resistance

Remember the pediatrician's stain-resistant office, and the shrill sounds of crying. You have a baby, and this means that bodily secretions are now acceptable dinner conversation. But when a cold strikes in those tiny airways, the clog of all those secretions overwhelms even the most stoic parent. What fate awaits the pediatrician's decision? What antibiotic will she give baby for the cold? The increasingly likely answer - none.

In small children, a large fraction of chest and head colds are viral. A good pediatrician will not always prescribe antibiotics for colds - but often waits for them to clear naturally. The reason is an evolutionary one - too frequent use of antibiotics selects for resistance. And when a bacterial infection does strike, it would be better if the bacteria hadn't already evolved to eat antibiotics. This ushers in the new medicine, a set of procedures that assumes that evolution will happen, and will happen fast. Part of the current strategy requires withholding medications when not needed, and part of the current problem remains incorrect patient use of the medications that cure.

It hasn't always been this way. The first antibiotics were hailed as the wonder drugs of the 20th century (despite having been described in the Bible - then discovered and forgotten by Pasteur and Belgian scientists). Finally rediscovered by Alexander Flemming in 1928 and used extensively in World War II, penicillin was crystalline death to most infections. But by 1947 the first strong resistance emerged. Since then, the arms race has been fierce, expensive, continuous, and usually won by bacteria. A zodiac of different drugs has been invented by humans and Houdini'ed by bacterial escape artists. Some of the best ones are now reserved as the drugs of last resort - withheld from all but the worst infections. The evolutionary engine dictates this strategy, as well as the emergence of evolutionary medicine as a clever treatment method. Thus, medicine can no longer afford to ignore the fact of evolution and instead has begun to define treatment protocols that 1) assume evolution will occur, and 2) limit the opportunity for evolution as much as possible.

Other examples

There are many other examples of rapid evolution in the biological world around us: HIV viruses evolving within a single person during the course of AIDS, evolution of small body size and new reproductive tactics in over-fished salmon, the evolution of insects to insecticides, including those genetically engineered into crop plants. These examples provide a source of insightful information about the evolutionary process, and show how important evolution has become to our modern society. These examples can be very personal, may deal with our daily lives, and thus may be a powerful tool in teaching evolution at many levels.

Applied Evolution: Technology for the 21st Century

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Evolutionary biology has an image problem. Some people are threatened by it and thus oppose it. Many people - even many of its defenders - view evolutionary biology as irrelevant outside of academia. And in the few places where evolution is perceived as relevant, it is responsible for death and misfortune - drug-resistance in medicine and pesticide-resistance in agriculture.

Most people are unaware of uses of evolutionary biology. Public non-appreciation of evolutionary biology may depend as much on its perceived irrelevance as anything else. Yet, evolution, especially microevolution, has been fundamental to some social improvements this century, and it promises to be profoundly important to biomedical technology in the next generation. For example, evolution underlies many improvements in agriculture (e.g., the artificial selection of crop strains and livestock breeds). A less well known fact is that evolutionary principles were used to produce many of our best vaccines and that evolution also causes problems with the use of some of those vaccines. Some of the most promising areas for the future use of evolutionary biology lie in drug development and the biotechnology industry; patents worth vast amounts of money are based on ways of creating evolution (or avoiding evolution) in test tubes.

Polio vaccine -- an old example. The vaccine now used to immunize against the disease poliomyelitis is a live poliovirus that we eat. This live virus does not give us the disease (except to about 1-2 in a million people vaccinated) because it is genetically weakened so that our body can defeat it. This process of weakening is called attenuation, and it is an evolutionary process. The attenuated vaccine strains came from wild, virulent strains of poliovirus, but they were evolved by Albert Sabin to become attenuated. Essentially, he grew the viruses outside of humans, and as the viruses became adapted to those non-human conditions, they lost their ability to cause disease in people. This method of attenuation has been used to create many live vaccines. Evolution was the good guy here because it helped us make the vaccine.

But the role of evolution and evolutionary biology does not end here -- evolution becomes the bad guy too. When a person eats the attenuated virus, it infects his/her gut cells and starts doing what viruses do -- making copies of itself. These viral progeny infect other cells in your gut, those in turn make other viral progeny, and so on, until you have a population of poliovirus growing inside your gut. Some of these viruses carry mutations, and some of those mutations (one or two in particular) restore most of the virulence to the virus. In your gut, these restored viruses may have a selective advantage over the weakened viruses, and in the course of a week or so after eating the

vaccine, you begin shedding virus with restored virulence. In short, an evolutionary process inside your gut undoes Albert Sabin's attenuation of the virus.

These restored viruses does not hurt the person taking the vaccine because by the time restored viruses get to be abundant in the gut, the immune system has enough of a head start to keep the virus from getting into the central nervous system. Disease is caused only if the virus gets into the central nervous system. However, if we were to vaccinate just one person in a population of non-immunized people, the restored viruses shed from this one person would infect other people and could start an epidemic of nasty poliovirus. In fact, people have gotten the disease from people who were recently vaccinated. Fortunately, this problem caused by evolution has an easy solution. When polio vaccine is first introduced to a community, we try to vaccinate everyone in the community at once. This is what happened in the U.S. when the Sabin vaccine was first introduced in the U.S. in the 1950's (vaccine "Sundays"), and it was done in other countries as well. The WHO did all of China in 3 days, and vaccinated 90,000,000 people in India in one day. Thus, understanding the evolution of poliovirus virulence allows us to use the vaccine without causing unnecessary disease.

Modern applications of evolutionary biology

Drug resistance and chemical resistance in microbes, plants, and animals. In the latter half of this century, industry has been exceptionally good at providing compounds to kill viruses, bacteria, insects that eat crops and weeds that grow in crop fields. We even have an abundance of chemotherapy drugs to kill rogue cancer cells. Yet virtually without exception, our attempts to kill these organisms cause them to evolve resistance against the chemicals used to kill them. Thus, isolates of the AIDS virus with up to 15 different drug-resistance mutations are known, and the latest drugs are becoming ineffective. Some strains of bacteria are resistant to all available antibiotics. For multi-drug resistant tuberculosis, surgery is the only cure because antibiotics don't work and only 50% of those infected survive. Chemotherapy for cancer often fails because drug-resistant cells evolve during treatment. Pesticide resistance and herbicide resistance is so common now that the financial incentive to make new pesticides and herbicides is break-even or worse.

Evolutionary biology suggests how best to use the drugs/chemicals to prolong their useful lives. The amounts of chemicals used, what combinations of chemicals to use, and when to apply them are all questions that can be assessed from the perspective of preventing or slowing the evolution of resistance. In some cases now, the companies marketing the compounds have a financial interest in maintaining the longevity of their product, and they are funding studies by evolutionary biologists to develop wise use protocols. In other cases, however, economic and emotional forces dictate policies that speed up the evolution of resistance (e.g., patients demand and physicians write prescriptions for antibiotics for viral infections; antibiotics are used in animal feed).

The harm in misunderstanding evolution. The evolution of drug resistance in bacteria is one of the simplest examples of evolution that we have. It is extremely

relevant to medicine. And since it is a case of microevolution, it is an example that should be widely embraced. Yet many people profoundly misunderstand drug resistance. Even news reports from the BBC have gotten it wrong. Bacterial resistance to antibiotics is an evolutionary phenomenon -- heavy use of antibiotics selects bacteria that are genetically resistant to the drug. With continued use of antibiotics, those resistant forms of the bacteria multiply and spread to other hosts, so that resistant bacteria replace the population of once-sensitive bacteria.

In the minds of some people, however, the problem with misuse of antibiotics is that it can lead to a physiological tolerance in the person taking the drugs, so that antibiotics are no longer effective in that person. That is, they think that drugs become ineffective because of the *person*, not the bacterium. This erroneous, non-evolutionary view has serious ramifications, because it can lead to an unwarranted complacency about antibiotic misuse. Because drug resistance is evolutionary, your neighbor's misuse of antibiotics can injure or kill you. The unregulated use of antibiotics in Europe can bring strains for which we have no defense to the U.S. and our hospitals. It is not simply a matter of the proper use of antibiotics in each of us individually; it is a matter of everyone's proper use of antibiotics.

It is tempting to speculate that the common, though not universal, public failure to understand the evolutionary basis of drug resistance reflects a widespread ignorance of evolutionary principles, even principles professed to be uncontroversial. The fact that this misunderstanding is not confined to the western side of the Atlantic suggests that political opposition to the teaching of evolution is not the only cause.

Evolutionary trees. Perhaps the core of evolutionary theory is that all life forms are connected with each other through common ancestry. Molecular biology has reinforced this view to a far greater level than was deemed possible even 50 years ago. On a short time scale, of course, we observe that this is true - everything alive comes from something else that is both alive and similar. One of the big developments in evolutionary biology over the last 2 decades is a methodology to estimate the underlying patterns of ancestry among living things. These reconstructions of evolutionary history are known as phylogenies, or phylogenetic trees, because they are branched somewhat like trees when drawn from bottom to top. We can use molecular data to estimate the common ancestries of life as far back as we like -- for example, between bacteria and our mitochondria (the energy-producing organelles in our cells). But we can also use these methods to estimate much more recent ancestries. And these methods have found many worthy uses in tracking infectious diseases.

Molecular epidemiology -- pathogen tracking. To an epidemiologist studying infectious diseases, it is very useful to know how or where a person became infected with the disease. This information is perhaps the most basic fact we can use in preventing the further spread of a disease. For over a decade now, epidemiologists have been using DNA sequences of viruses to make phylogenetic trees and thereby track the sources of infections. Some of these examples are spectacular.

1) *Law: A case of intentional HIV injection*? In a highly publicized case in Lafayette, Louisiana in 1998, a woman claimed that her ex-lover (a physician) deliberately injected her with HIV-tainted blood (HIV is the virus that causes AIDS). She did not know whose tainted blood it was nor did she realize she had been injected with blood until she became sick with viral infections months later. Records showed that the physician had indeed drawn blood from an HIV+ patient on the day she was injected. There were no records of her injection and no witnesses. So how could her story be tested?

Evolutionary trees provide the best scientific evidence in a case like this. HIV picks up mutations very fast – even within a single individual. If one person gives the virus to another, there are few differences between the virus in the donor and the virus in the recipient. As the virus goes from person to person, it keeps changing and gets more and more different over time. Thus, the HIV sequences in two individuals who got the virus from two different people will be very different. Thus, if the woman's story were true, her virus should be very similar to the virus in the person whose blood was drawn but should be very different from viruses taken from other people in Lafayette. That was exactly what the evolutionary trees showed; her virus appeared to have come from the patient's virus but was unlike the virus taken from other people in town. Since there was no way to explain how she would have gotten THAT patient's virus on her own, the evolutionary analysis supported her story. (Incidentally, this case was the first use of phylogenetics in U.S. criminal court.)

2) *Did a Florida dentist with AIDS transmit the virus to his patients?* Kimberly Bergalis made national headlines and testified in congressional hearings as a heterosexual young woman who got AIDS. The only known potential source of her virus was her dentist, and over half a dozen of his other patients also had the disease. In this case, the initial evidence implicating the dentist was merely the statistical association of several people with AIDS whose only known exposure was the dentist. Again, evolutionary trees were created to see if the patients' viruses appeared to have descended from the dentist virus. The dentist virus did appear to be closely related to many of the patient viruses, as if it was the source. However, two patients appeared to have gotten their virus elsewhere, and those two patients were the only two infected patients with other risk factors. So again, the evolutionary analysis provided a critical means of understanding HIV transmission.

3) *Other cases.* Evolutionary trees have been used in many other cases of infectious disease transmission. They were used to identify deermice as the source of hantavirus infections in the Four-Corners area in the early 1990s. They are routinely used to determine the source of rabies viruses in human cases, and they led to the discovery of a case in which rabies virus took at least 7 years to kill a person (a length of time far in excess of anything known previously). And trees have been used to determine whether recent cases of polio in North America were relict strains from the New World, were vaccine strains, or were introduced from Asia.

Industrial production of biochemicals and other agents. "Directed evolution" has become part of the jargon in biotechnology. Artificially evolved enzymes and other proteins are soon to become part of household and medical technologies. We will have protein-based drugs that, unlike the proteins inside our bodies, degrade slowly so that we don't need to take so much of them. Enzymes are being evolved to work in detergents (which they don't normally do). And as the stuff of futuristic novels, molecules are being developed to bind anthrax spores, ricin molecules, and other potential bioterrorism agents. All of these developments take advantage of one or more forms of test-tube evolution. Armed with a knowledge of how natural selection works and combined with the right kinds of laboratory technology, people can create molecules to perform seemingly any kind of function. In some of the more spectacular cases, these test tube evolution methods have created enzymes from purely random pools of DNA (or RNA) sequences. Even 10 years ago, it was thought that a DNA enzyme was impossible, yet armed with only an understanding of how to apply test tube evolution, a DNA enzyme can now be created in days.

Closing. The pace of evolutionary biology and its ramifications has outstripped public awareness as well as expanded beyond the knowledge base of most classical evolutionary biologists. Even the textbooks have not kept up. It is thus difficult but important to recognize that evolutionary biology has implications to a new century of medicine, agriculture, biotechnology, and even law. Students educated with this knowledge will have an edge in the competitive job markets of the future, but at least in some areas of medicine, a basic public understanding of evolutionary principles may be essential in successfully waging the ongoing war with infectious diseases.

DNA and Early Human HistoryNeandertals and Early Humans: But Did They Mate?

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Studies in Molecular Evolution, especially those with forensic, ancient DNA or human history implications, provide a compelling framework for teaching. Since such research topics tend to capture the attention and imaginations of students, they provide excellent opportunities for instruction in basic biological disciplines such as evolutionary biology, genetics, molecular biology, physiology and anatomy, biochemistry and cell biology. In addition, they illustrate the capacity of biological studies to reinforce and contribute to knowledge in history, archaeology and anthropology, geography and geology, linguistics, law, and social studies. We are also provided with the opportunity to emphasize critical and recurrent themes in scientific research such as the importance of sample sizes and experimental design, the linkage between methodology and conclusions, and the differences between results, interpretation, and extrapolation. In this example we consider the nature of the relationship between Neandertals and the ancestors of modern humans.

Neandertals, named after the German valley (Neander Tal) where their fossil remains were first discovered in 1856, are extinct hominids that lived in Europe and Western Asia. Living from approximately 30,000 to 300,000 years ago, they were the prototype for the "robust" classic "caveman", in contrast to the "gracile" modern human. Neandertal skeletons suggest they were a larger and more muscular version of modern man with low foreheads, protruding brows, poorly defined chins, and large noses with broad nostrils. Portrayed at various times in modern history as brutish, clumsy, ape-like creatures, the Neandertals were, in fact, large-brained hominids who survived for hundreds of thousands of years with distinctive culture (including burial of their dead) and techniques for making tools, spears, and objects of art.

Archaeological evidence reveals that the Neandertals disappeared somewhat abruptly 25,000 to 30,000 years ago. Their demise was preceded by the arrival in their geography of our direct ancestor, the anatomically modern Cro-Magnons. There is ample rchaeological evidence that the two groups likely co-existed and even sequentially inhabited the same sites over perhaps thousands of years. Were the two groups completely unaware of each other, and thus could not interact at all? Were the two aware of each other only through distant observation? Or as some scientists believe, did they
directly interact with each other, leading to stimulations in cultural achievements for both groups? Or, in the intriguing question that inquiring minds want to know,: "Did they mate?" Of course, this is the way the question is posed to capture our attention. What the scientist really wishes to know is "Did Neandertals contribute DNA to modern humans?" Whether or not our ancestors had sex with Neandertals, if there were no fertile offspring, there cannot be any historical record in DNA.

Another way of stating this is if there were widespread, successful matings among Neandertals and the ancestors of modern humans, then there would be contribution of Neandertal genetic sequences to the genomes of modern humans.

Three hypotheses about the nature of the genetic relationship between Neandertals and modern humans have been offered. At one extreme is a replacement hypothesis, proposing that the Neandertals were a fundamentally different type of human (perhaps even a different species) that represent an evolutionary dead-end, with no genetic contributions to present-day humans. At the other extreme is a linear evolution hypothesis that modern humans in Europe evolved directly from Neandertals, providing major genetic contributions to present-day humans. In an intermediate model, it is possible that Neandertals made limited genetic contributions of some genes to modern humans.

Testing these hypotheses requires a comparison of DNA from Neandertal and modern human samples - a formidable task at best. Technical challenges abound in the analysis of ancient DNA. Accurately dated, well-preserved fossils are rare and extremely valuable. Even when such exist, the DNA will be subjected to normal degradative processes that occur over time, resulting in both very short segments of DNA and alterations in chemical structure. The extremely sensitive polymerase chain reaction (PCR) that is instrumental in retrieving DNA segments from ancient DNA is particularly prone to problems with damaged DNA. Further complicating the problem is the likelihood that handling of the fossils by modern humans may have resulted in contamination. For these reasons, a number of criteria for acceptance of ancient DNA sequences have been widely adopted, including sequencing from multiple, cloned segments and reproduction of results in independent laboratories.

Nuclear genes occur in two copies per cell. The combination of their low abundance and the aforementioned technical problems make it highly unlikely that nuclear DNA sequences will be amenable to analysis in ancient samples. Scientists have concentrated instead on the use of mitochondrial DNA (mt DNA). The mitochondrial genome is present in hundreds to thousands of copies in each cell, providing an important technical advantage. The control region of the mitochondrial genome does not encode proteins, and contains hypervariable regions that are known to reveal differences between populations of humans. MtDNA has an additional unique feature in that it traces maternal lines of inheritance only.

In what has been widely hailed as a milestone in genetic studies of early human history, Svante Paabo and his collaborators (Krings et al., 1997) successfully isolated and analyzed a segment of Neandertal DNA. They used PCR to amplify sequences from the control region in mitochondrial DNA from samples isolated from a piece of right humerus from the Neandertal type specimen. They obtained the Neandertal sequence of one of the hypervariable regions and compared it to the reference sequence for modern humans. The Neandertal sequence was closer to that of humans than to chimpanzees, although there were dramatic differences from modern humans. Within the

small region analyzed, there were 24 transition mutations, 2 transversion mutations, and one single nucleotide insertion when compared to modern humans. By comparison, modern humans differ, on average, by 8 substitutions in this same region; interestingly, the sites that vary between modern humans are not identical to those that vary between them and the Neandertal DNA. Krings et al. (1997) find that the Neandertal sequences lie outside of the variation present in modern humans, and suggest that Neandertals became extinct without contributing to the mtDNA pool present in extant human populations.

While acknowledging this research as a pioneering study in Neandertal scholarship, the scientific community (including the authors) raised the problems inherent in generalizing from a single sample. What if this individual were at an extreme in the genetic variation present in the Neandertal population? Could there be other, more prevalent, Neandertal
mtDNA types that would be represented in the mtDNA spectrum of modern man? The critical corroboration of Neandertal mtDNA sequences came shortly after the Krings' study with the publication of two additional Neandertal sequences: one from an individual from Mezmaiskaya Cave in Russia (Ovchinnikov et al., 2000) and the other from Vindija Cave in Croatia (Krings et al., 2000). The three Neandertal sequences form a clade distinct from modern humans. Knowledge of mtDNA types from three different individuals who are geographically and temporally isolated reinforces the fact that
Neandertals are genetically distinct from modern humans. It also strongly corroborates the interpretation that Neandertal mtDNA types are not present in extant human pools.

For the conclusion that Neandertals do not contribute to modern gene pools to be correct, it is necessary for the known human sequences to be an accurate representation of the event in question. The unique inheritance patterns and evolutionary pressures on mtDNA make it reasonable to question whether it accurately represents all possible genetic athways. Since we do not yet have (and may never get) other DNA sequences from ancient DNA, this is something of a moot objection. Assuming that mtDNA is the only option, it is important to note that the current human database includes over one thousand
individuals representing a variety of different populations. While there may be additional variants not yet discovered, it is unlikely that the current view of existing mtDNA types is fundamentally unrepresentative of existing humans.

A more thorny issue is whether the mtDNA variation present in modern people is an accurate representation of our full genetic history. What if the existing variation is but a subset of that which has occurred in the direct lineage of modern man? Is it possible that Neandertals mated extensively with our ancestors and that the Neandertal type mtDNA contribution has been lost? In other words, could an absence of Neandertal mtDNA types in modern humans be due to forces of evolution other than reproductive isolation? The
fact that much evidence points to modern humans as arising from a small number of progenitors in a bottle neck event makes this an important consideration.

Recently, Adcock et al. (2001) provided evidence that mtDNA sequences can "go extinct". Among the remains of ten ancient Australian individuals typed for mtDNA sequences was an anatomically modern man from Lake Mongo. The remains of the Lake Mongo man had been dated by three separate methods to be older than 60,000 years. The Lake Mongo man mtDNA contains a sequence that is different from the other fossil remains and different from all modern humans, meaning that he must have possessed a now extinct lineage of mtDNA. Interestingly, a remnant of this particular mtDNA sequence does survive in modern people as an inserted segment on chromosome 11 in the nucleus! If a mtDNA sequence found in an early modern human can so easily "go extinct", the possibility exists that the same thing could have happened with a mtDNA from Neandertals.

While it remains to be seen whether the interactions between Neandertals and our ancestors were G, R, or X-rated, it is certain that the Neandertals and Cro-Magnons did not interact as portrayed in "B" movies. Neandertals were hardly the simple-minded, big and bumbling brutes who fell prey to the invading, intelligent and gracile Cro-Magnons. Both types of "humans" walked the earth together for thousands of years in and around Europe. Like many of the most interesting evolutionary questions, the issues surrounding the co-existence of Neandertal (and other ancient hominids) with our early ancestors will be investigated for years to come as new specimens and new approaches come to light. The final chapter in the relationship between Neandertal and modern man remains to be written…..

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Patterns and Processes of Macroevolution – Examples from the Evolutionary History of Dinosaurs

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Introduction: Macroevolution describes the pattern of evolutionary history as it has played out over the grand scale of geological time. The origins of the major living lineages, the emergence of key adaptations, and the exploitation of novel adaptive niches are among the issues considered under the umbrella of macroevolution.

One of the major problems in understanding macroevolution involves mapping historical patterns. Although a lot is known about biological processes operating today, such as genetic mutation and speciation, only after the historical pattern of evolution has been mapped can we begin to determine what processes have occurred historically. Most debate about evolutionary process is a result of underlying uncertainty. So, how can we know the pattern of evolutionary events that occurred millions of years ago?

Historical Background: One of the oldest and most persistent problems of macroevolution involves the origin of birds and the evolution of flight. This was one of the first challenges thrown at the theory of evolution when Darwin published his revolutionary book On the Origin of Species in 1859. At that time it seemed an intractable problem because no transitional forms were known between birds and other vertebrates. Critics challenged that Darwin's mechanistic theory of natural selection couldn't explain how complex new organs like feathers or complex new functions like flight could have evolved gradually and via transitional stages. The thought of a transitional, partly flying bird, was like the thought of being partly pregnant. How could flight have evolved from non-flying ancestors without the force of gravity killing all the transitional species? The origin of birds and the evolution of flight provided one of the first great battlegrounds for the theory of evolution by natural selection.

Dinosaurs provided the first key insights into understanding of how birds and avian flight might have evolved. When Darwin's book hit the newsstands, the scientific image of dinosaurs was that they were all "fearfully great" saurians, that they were all gigantic extinct behemoths. Then, in 1860, a tiny dinosaur named *Compsognathus* was discovered in the famous Solnhofen limestones of Bavaria. A developmental biologist and early evolutionist named Carl Gegenbaur had been studying the development of the skeleton in modern birds. When he learned about the structure of the ankle in *Compsognathus*, he saw features that are present in embryonic stages of modern birds and was he first to make the connection that birds are descendants of dinosaurs. That same year, the discovery of the primitive toothed bird *Archaeopteryx* showed a transitional stage between *Compsognathus* and flying birds. *Archaeopteryx* preserved

feathers like modern birds, along with a bony tail and other skeletal features more characteristic of reptiles. By 1870, scientists had discovered many transitional features between birds and dinosaurs.

The Problem in Mapping Macroevolutionary Pattern: So, if scientists in 1870 found evidence linking living birds to extinct dinosaurs, why does a controversy still persist? Newspapers are full of accounts of disagreement on the ancestry of birds. The answer to this question is the idea of convergent evolution or *homoplasy*. Different, unrelated species can independently evolve similar solutions to common environmental challenges. For example, both birds and bats have wings, but no one today believes that they inherited wings from a common ancestor that could fly. Although similarities are generally indications of relationship, we can be fooled by homoplasy.

At this point it is instructive to ask, "How do we know that the wing in birds and bats evolved convergently?" To answer, we believe that bats are mammals and unrelated to birds because bats have hair, mammary glands, a placenta, and many, many other features that indicate their relationship to other mammals. Birds, on the other hand, have molecular and anatomical structures that indicate they are related to reptiles. There are also many transitional fossils that indicate bats to be branches of the mammalian family tree whereas birds are branches on the reptilian family tree. When all the evidence is considered, it is far simpler to believe that wings evolved convergently than to believe that birds and bats belong to the same flying lineage. We tend to prefer explanations that take into account all of the evidence to explanations that account for only some o the evidence.

Today's Perspective on the Origin of Birds: Modern computer assisted techniques enable biologists to map historical patterns by comparing huge numbers of anatomical and molecular details. In short, we try to find the simplest hierarchical pattern that explains all of our observations. In the case of the origin of birds, our evidence comes from the anatomy of living species along with the anatomy of fossils. Hundreds of characters have been observed and compared, and there is one overwhelming pattern. Although there are also homoplastic characters in this pattern, the majority of the evidence indicates that birds lie on a branch of the dinosaurian family tree. In a biological sense, birds are dinosaurs and only *some* dinosaurs became extinct.

One reason that this has been controversial is that Mesozoic dinosaurs were highly diversified and many look nothing like birds. Stegosaurs, ceratopsians, the giant sauropods, and many other groups look nothing like birds. But there is one group – the carnivorous theropod dinosaurs – that has detailed resemblance to modern birds. Even the theropods are very diverse and some of their members, like *Tyrannosaurus rex*, are off on their own extinct side branches. However, one lineage of persistently small theropods manifests a hierarchy of unique features that are still present in modern birds.

Since the discovery of *Compsognathus* and *Archaeopteryx* a century and a half ago, many new theropod fossils have been discovered that fill the gap between modern birds

and their extinct dinosaurian relatives. John Ostrom's discovery of *Deinonychus* is the most famous, but there is a great deal of other evidence that points in the same direction. Details of the head, neck, arms, hands, pelvis, hind limb, and tail all point to a dinosaurian ancestry for birds. Some recent discoveries from China preserve soft tissues including proto-feathers. Additional evidence comes from embryology and the development of modern birds.

Based on this pattern of relationships, it now appears that feathers originated before the ability to fly, and that feathers were only secondarily adapted for flight. In a similar fashion, the feathers of birds develop first for insulation and only later in development do flight feathers and the ability to fly emerge. The first dinosaurs to have feathers were fast-running predators who probably used their arms to grab prey items. The bones of the wrist constrain the movements of their hands to the same pattern of movement that we see in the flight stroke of birds. Flight feathers and the ability of powered flight were superimposed upon an anatomical pattern involving predatorial grasping and short proto-feathers.

The Radiation of Living Dinosaurs – the Birds: The macroevolutionary pattern underlying the origin of birds is based on observations from the entire skeleton and integument in living birds and fossils that extend across 230 million years of the fossil record. While the non-avian dinosaurs all became extinct at the end of the Mesozoic, birds speciated in one of the greatest adaptive radiations of all time. Many birds flew out to the islands of Pacifica and thousands of new species emerged in these isolated places. Other fountains of avian species were the circum-Pacific mountains of North and South America.

When the entire macroevolutionary pattern of dinosaurian history is considered, living birds must be considered along with their extinct relatives. From this perspective, it appears that comparatively few dinosaurian species were affected by the great extinction event at the end of the Mesozoic. Far more profound have been the effects of human occupation of the islands of the world. Perhaps as many as 8,000 species of birds became extinct, as humans inhabited these islands. A next wave of extinction is moving onto the continents as the human population soars to unprecedented levels.

Today, scientists studying macroevolution are attempting to measure the complete pattern of speciation for an entire evolving lineage. The pattern that we see today indicates that birds are deeply interested within the hierarchy of dinosaurian relationships, and that humans may be the most severe source of extinction of dinosaurian species.

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Evolution: Variation is the Theme

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When people think about evolution, they often think about natural selection - a major mechanism by which evolution works. However, the fundamental requirement for evolution is not natural selection, but genetic variation. Darwin emphasized how important it was that there were different varieties of a given trait, and that these varieties must be heritable, that is, genetic. From microevolution, *e.g.*, the pepper moths that were selected for dark coloration during the pollution of the industrial revolution, to macroevolution, *e.g.*, the creation of new species, genetic variation is key.

The advent of molecular biology caused a fundamental change in the way researchers think about evolution. Biologists were able to recognize that the heritable variation they were observing was caused by changes to the DNA. More importantly, it was even possible to figure out which changes in the DNA caused the changes in the organism that natural selection appeared to be recognizing. We can look at a collection of DNA sequences and see the footprints of evolution by natural selection. We can use this evidence to suggest which genes were important in evolution, even if the effects of these genes are unknown. And, we can use sequence comparisons to identify which change of many within a given gene is the change that evolution acted on.

In addition to understanding evolution at a level which has never been possible before, the study of evolution at the level of the DNA makes it possible for us to perform amazing feats in medicine, law, and agriculture. By understanding how selection acts on DNA, we can identify genes that cause disease. Recent examples of this include the breast cancer gene, BRCA1. We can also now recognize that multiple changes in a gene cause the same disease, and that the different changes are sometimes more common in some populations than others, because the evolutionary lineages of the populations are different from one another. This is important when we think about genetic testing: the fact that you don't have one particular mutation does not mean you are not a carrier for the disease by virtue of some other mutation in the same gene. And which mutation we are looking for will depend on which population the person is coming from. Thus genetic testing works well only when we keep evolution in mind.

Evolution is also essential for the equitable application of DNA forensics. Because different populations of people have different evolutionary histories, people from different geographic regions or different ethnic groups can have specific DNA characteristics present at different frequencies. It is these frequencies that are used to identify and convict criminals. For example, an expert on DNA forensics will explain that a given combination of DNA characteristics that was found at the scene of the crime is present in the population at large one in a hundred times *vs*. one in a billion

times. If we use the wrong frequency, we could wrongly convict (or wrongly free) a suspect. Understanding evolution is the key to using the correct frequencies, and thus to doing justice.

Finally, we will soon be facing a worldwide food shortage. One approach to this problem is to try to breed plants with higher yields. Populations of plants, like populations of people, have different evolutionary histories. These histories influence how we can detect which genes will confer higher yield. We can also identify genes that cause plants to do better in certain environments, resist certain diseases, and so forth. Any endeavor that involves identifying genes involves understanding evolution.

Genetic variation is the "stuff" of evolution. Further, the ways in which genetic variation is shaped by evolution provide a rich resource that is being used to benefit society in a wide variety of ways. The importance of evolution, particularly its genetic aspects, can hardly be overstated to our students.

Resources

EvoNet.org: A Worldwide Network for Evolutionary Biology

EvoNet.org (www.evonet.org) provides easy access to thousands of websites relating to the growing discipline of evolutionary biology. The science portal, which categorizes web resources ranging from class notes to public outreach, from researchers to software, continues provide a comprehensive one-stop location for educators, scientists and the general public. Among the benefits of the website is the ease with which a user can quickly gain access to educational material for the classroom or for use as a study aid. Users can also link to information about particular scientists and their work, as well as to the scientists' webpages. EvoNet is the only portal developed exclusively for evolutionary biology. The site is funded by the National Science Foundation.

[i] (Roose and Gottlieb 1976; Soltis and Soltis 1989)