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EVOLUTION BY NATURAL SELECTION

> Now, as each of the parts of the body, like every other instrument, is for the sake of some purpose, viz. some action, it is evident that the body as a whole must exist for the sake of some complex action.
>
> —Aristotle

The solutions to the mysteries discussed in Chapter 1 are to be found in the workings of natural selection. The process is fundamentally very simple: natural selection occurs whenever genetically influenced variation among individuals affects their survival and reproduction. If a gene codes for characteristics that result in fewer viable offspring in future generations, that gene is gradually eliminated. For instance, genetic mutations that increase vulnerability to infection, or cause foolish risk taking or lack of interest in sex, will never become common. On the other hand, genes that cause resistance to infection, appropriate risk taking, and success in choosing fertile mates are likely to spread in the gene pool, even if they have substantial costs.

A classic example is the spread of a gene for dark wing color in a British moth population living downwind from major sources of air pollution. Pale moths were conspicuous on smoke-darkened trees and easily caught by birds, while a rare mutant form of moth whose color more closely matched that of the bark escaped the predators' beaks. As the tree trunks became darker, the mutant gene spread rapidly and largely displaced the gene for pale wing color. That is all there is to it. Natural selection involves no plan, no goal, and no direction—just genes increasing and decreasing in frequency depending on whether individuals with those genes have, relative to other individuals, greater or lesser reproductive success.

The simplicity of natural selection has been obscured by many misconceptions. For instance, Herbert Spencer's nineteenth-century catch phrase "survival of the fittest" is widely thought to summarize the process, but it actually promotes several misunderstandings. First of all, survival is of no consequence in and of itself. This is why natural selection has created some organisms, such as salmon and annual plants, that reproduce only once, then die. Survival increases fitness only insofar as it increases later reproduction. Genes that increase lifetime reproduction will be selected for even if they result in reduced longevity. Conversely, a gene that decreases total lifetime reproduction will obviously be eliminated by selection even if it increases an individual's survival.

Further confusion arises from the ambiguous meaning of "fittest." The fittest individual, in the biological sense, is not necessarily the healthiest, strongest, or fastest. In today's world, and many of those of the past, individuals of outstanding athletic accomplishment need not be the ones who produce the most grandchildren, a measure that should be roughly correlated with fitness. To someone who understands natural selection, it is no surprise that parents are so concerned about their children's reproduction.

A gene or an individual cannot be called "fit" in isolation but only with reference to a particular species in a particular environment. Even in a single environment, every gene involves compromises. Consider a gene that makes rabbits more fearful and thereby helps to keep them from the jaws of foxes. Imagine that half of the rabbits in a field have this gene. Because they do more hiding and less eating, these timid rabbits might be, on average, a bit less well fed than their bolder companions. If, hunkered down in the March snow waiting for spring, two thirds of them starve to death while this is the fate of only one third of the rabbits who lack the gene for fearfulness, then, come spring, only a third of the rabbits will have the gene for fearfulness. It has been selected against. It might be nearly eliminated by a few harsh winters. Milder winters or an increased number of foxes could have the opposite effect. It all depends on the *current* environment.

NATURAL SELECTION BENEFITS GENES, NOT GROUPS

Many people have seen the nature film in which droves of starving lemmings jump eagerly to a watery death as a resonant voice explains that when food becomes scarce, some lemmings sacrifice themselves so that there will be enough food for at least some of the group to survive. A few decades ago, such "group selection" explanations were taken seriously by professional biologists, but not now. To see why, compare two imaginary lemmings. One is a noble fellow who, upon sensing that the population is about to outrun its food supply, quickly jumps to his death in the nearest stream. The other is a selfish lout who waits for the noble ones to do away with themselves and then eats as much food as he can get, mates as often as possible, and has as many offspring as possible. What would happen to the genes that code for the behavior of sacrificing oneself for the benefit of the group? No matter how beneficial they might be for the species, they would be eliminated.

So how can we explain the observations of apparently suicidal lemmings? When food becomes scarce in late winter, lemmings migrate, rushing along in large groups that do not always stop when they encounter waters created by early snowmelt. Drownings are, however, rather uncommon. To get the footage they wanted, the makers of the film apparently had to use brooms to surreptitiously herd the lemmings into the water, a dramatic example of the human preference for altering reality rather than theory when the two conflict! There are special circumstances in which selection at the group level can outweigh the usually stronger force of selection at the level of the individual, but they do not apply very often.

As British biologist Richard Dawkins, author of *The Selfish Gene*, has emphasized, individuals may be viewed as vessels created by genes for the replication of genes, to be discarded when the genes are through with them. This perspective mightily shakes the common view that evolution tends toward a world of health, harmony, and stability. It does not create such a world. We would like to imagine that life is naturally happy and healthy, but natural selection cares not a whit for our happiness, and it promotes health only when it is in the interests of our genes. If tendencies to anxiety, heart failure, nearsightedness, gout, and cancer are somehow associated with increased reproductive success, they will be selected for and we will suffer even as we "succeed," in the purely evolutionary sense.

KIN SELECTION

We have implied that reproduction is the essence of the fitness maximized by natural selection, and in our discussion of lemmings we indicated that evolution does not favor individuals who act to help others at their own expense. These generalizations tell only part of the story. Ultimately, it is the genetic representation in future generations that counts, whether that is accomplished by having children or by doing things that increase the reproduction of your close relatives, many of whose genes are identical to yours.

Half of the genes in a child are identical to those in the mother, and half are identical to those in the father. Full siblings, on average, also share half of each other's genes. One fourth of the genes in a grandparent are identical to those in the grandchild. Cousins share one eighth of their genes. This means that, from the perspective of your genes, your sister's survival and reproduction are half as important as your own and your cousin's one eighth as important. For this reason, selection favors extending help to relatives if, all else being equal (e.g., age and health), the cost to oneself of extending the help is less than the benefit to the relative times the degree of relationship. In a classic anecdote, British biologist J. B. S. Haldane was asked if he would sacrifice his life for his brother. "No," he said, "not for one brother. But I would for two brothers. Or eight cousins." Formal recognition of this principle and its importance in explaining cooperation awaited the landmark 1964 paper by British biologist William Hamilton, winner of the 1993 Crafoord Prize, created to honor scientists whose work is in fields not covered by the Nobel Prize. Another great British biologist, John Maynard Smith, christened the phenomenon *kin selection*.

Another apparent exception to the nice-guys-finish-last principle in evolution is the result of reciprocal exchanges of favors between individuals who need not be relatives. If Elsa is an expert maker of shoes and Fritz is a skillful hunter of animals that supply excellent leather, trading resources will benefit them both. It pays me to be nice to you, and vice versa. Ever since Robert Trivers's classic 1971 paper on reciprocity theory, biologists have routinely interpreted cooperative relations among organisms in nature as resulting from either reciprocal exchanges or kin selection. The biology of social life has grown thanks to the efforts of pioneers such as E. O. Wilson, author of *Sociobiology*, and Richard Alexander, author of *Darwinism and Human Affairs*. Early controversies and misunderstandings have been largely supplanted by growing work in this new field of science.

HOW DOES NATURAL SELECTION OPERATE?

There is a widespread misconception that evolution proceeds according to some plan or direction, but it has neither, and the role of chance ensures that its future course will be unpredictable. Random variations in individual organisms create tiny differences in their Darwinian fitness. Some individuals have more offspring than others, and the characteristics that increased their fitness thereby become more prevalent in future generations. Once upon a time (at least) a mutation occurred in a human population in tropical Africa that changed the hemoglobin molecule in a way that provided resistance to malaria. This enormous advantage caused the new gene to spread, with the unfortunate consequence that sickle-cell anemia came to exist, as will be discussed in later chapters.

Chance can influence the outcome at each stage: first in the creation of a genetic mutation; second in whether the bearer lives long enough to show its effects; third in chance events that influence the individual's actual reproductive success; fourth in whether a gene, even if favored in one generation, is, by happenstance, eliminated in the next; and finally in the many unpredictable environmental changes that will undoubtedly occur in the history of any group of organisms. As Harvard biologist Stephen Jay Gould has so vividly expressed it, if one could rewind the tape of biological history and start the process over again, the outcome would surely be different. Not only might there not be humans, there might not even be anything like mammals.

We will often emphasize the elegance of traits shaped by natural selection, but the common idea that nature creates perfection needs to be analyzed carefully. The extent to which evolution achieves perfection depends on exactly what you mean. If you mean "Does natural selection always take the best path for the long-term welfare of a species?" the answer is no. That would require adaptation by group selection, and this is, as noted above, unlikely. If you mean "Does natural selection create every adaptation that would be valuable?" the answer again is no. For instance, some kinds of South American monkeys can grasp branches with their tails. This trick would surely also be useful to some African species, but, simply because of bad luck, none have it. Some combination of circumstances started some ancestral South American monkeys using their tails in ways that ultimately led to an ability to grab onto branches, while no such development took place in Africa. Mere usefulness of a trait does not necessarily mean that it will evolve.

There is a sense, however, in which natural selection does regularly come close to perfection, and that is in optimizing some quantitative features. If a trait serves a specific function, selection among minor modifications over many generations tends to make its quantitative aspects closely approach the functional ideal. For instance, a bird's wings must be long enough to give good lift but short enough to allow the bird to maintain control. Measurements on birds found killed after a major storm showed more than expected numbers of unusually long or unusually short wings. The survivors showed a bias toward intermediate (more nearly optimal) wing lengths.

In human physiology, there are hundreds of similar examples in which traits have been shaped to nearly optimal values: the sizes and shapes of bones, blood pressure, glucose level, pulse rate, age at onset of puberty, stomach acidity—the list could go on and on. The observed values may never be exactly perfect, but they usually come close. When we think that natural selection has erred, it is more likely that we have missed some important consideration. For instance, stomach acid aggravates ulcers, yet people who take antacids can still digest their food. So is there too much acid? Probably not, given the importance of stomach acid in digestion and in killing bacteria, including those that cause tuberculosis. To identify the imperfections of the body, one must first understand its perfections and the compromises on which many of them are based.

Like any engineer, evolution must constantly compromise. An auto designer could increase the thickness of the fuel tank in order to decrease the risk of fire, but at some point increased cost and decreased mileage and acceleration require a compromise. Thus, fuel tanks do rupture in some collisions, and this compromise costs some lives each year. While natural selection cannot achieve perfection in every character simultaneously, its compromises are not random but are accurately shaped to give the greatest net benefit.

An apocryphal story tells of Henry Ford looking at a junkyard filled with Model Ts. "Is there anything that never goes wrong with any of these cars?" he asked. Yes, he was told, the steering column never fails. "Well then," he said, turning to his chief engineer, "redesign it. If it never breaks, we must be spending too much on it." Natural selection similarly avoids overdesign. If something works well enough that its deficiencies do not constitute a selective force, there is no way natural selection can improve it. Thus, while every part of the body has some reserve capacity to deal with occasionally encountered extreme circumstances, every part is also vulnerable when its reserve capacity is exceeded. There is nothing in the body that never goes wrong.

Moderate increments of a resource often have enormous value, while higher amounts may have less benefit. If you are making a stew, two onions may be better than one, but ten onions would be much more expensive yet offer little, if any, extra benefit. Such cost-benefit analyses are routine procedures in economics, but they are useful in biology and medicine as well. Consider the use of an antibiotic for pneumonia. A tiny dose will probably have no detectable benefit, a moderate dose will cost more but offer much greater benefits, while a high dose will have still higher costs with no additional benefits and perhaps significant danger.

Just as there are costs as well as benefits involved in every engineering or medical decision, there are costs associated with every beneficial genetic change preserved in evolution. Natural selection isn't weak or capricious; it just selects for genes that give an overall fitness advantage, even if those same genes increase vulnerability to some disease. Is there any way, for instance, for anxiety to be a functionally desirable trait? Consider what would happen to those rabbits we discussed if they had no anxiety in a year when foxes were especially abundant. Even some genes that cause aging are not necessarily maladaptive. They may give benefits during the early years of life, when selection is the strongest, benefits that are more important to fitness than the later costs of aging and inevitable death. To understand disease better, we need to understand the hidden benefits of apparent mistakes in design.

TESTING EVOLUTIONARY HYPOTHESES

This chapter started with a quotation from Aristotle for a serious reason. We can think of him as the originator of the general procedure for functional analysis that has been particularly fruitful in many kinds of biological research and that we expect to be similarly rewarding in medicine. There is, of course, a big difference between Aristotle's outlook and that of modern biologists. He had almost no grasp of the physical and chemical principles that underlie the workings of any organism. He didn't think experiments were necessary. He had no notion of the principle of natural selection and certainly did not realize that organisms were designed entirely to maximize their success in reproduction. Whether applied to the human hand or brain or immune system, Aristotle's powerful question, "What is it for?" now has a very specific scientific meaning: "How has this trait contributed to reproductive success?" His conviction that the body as a whole exists for the sake of some complex action is correct. Only in the past few decades has it become clear that that complex action is reproduction.

Many people have the notion that questions about the function of a trait are not scientific, that they are "teleological" or "speculative" and therefore not appropriate objects of scientific inquiry. This idea is incorrect, as many examples in this book will demonstrate. Questions about the adaptive function of a biological trait are just as amenable to scientific inquiry as are questions about anatomy and physiology. It makes sense to ask about the adaptive significance of biological traits such as eyes, ears, and the cough reflex because they are products of historical processes that have gradually modified them in ways that improve their capacity to serve special functions.

Yet when we ask these "why" questions, we must guard against too readily believing fanciful stories. Why do we have prominent noses? It must be to hold up eyeglasses. Why do babies cry for no apparent reason? It must be to exercise their lungs. Why do we nearly all die by age 100? It must be to make room for new individuals. Almost anything can be the subject of such speculation, but if this is as far as it goes it is not science. The problem is not in the questions but in a lack of adequate investigation and critical thinking about suggested answers.

The above absurd examples demonstrate how easily some explanations can be tested and proven false. Noses could not have evolved to hold up glasses, since we had noses long before we had eyeglasses. Crying cannot be to develop the lungs, since lung health in adulthood does not require crying in infancy. Aging cannot have evolved to make room for new individuals, because natural selection cannot favor such benefits to the group and the details of aging simply do not conform to the expectations for such a function.

Other functional hypotheses are so easily supported that they are of little interest. Anyone thoroughly familiar with the heart's structure and operation can see that it pumps blood. One can also see that coughing expels foreign material from the respiratory tract and that shivering increases body heat. You don't need to be an evolutionary scientist to figure out that teeth allow us to chew food. The interesting hypotheses are those that are plausible and important but not so obviously right or wrong. Such functional hypotheses can lead to new discoveries, including many of medical importance.

THE ADAPTATIONIST PROGRAM

Studies of the functional reasons for human attributes are based on a method of investigation recently named the *adaptationist program*. By suggesting the functional significance of some known aspect of human biology, you may logically be able to predict some other, unknown aspects. An appropriate investigation can then confirm that these characteristics are either there or not. If they are there, they may be of medical significance. If they're not, we can eliminate our hypothesis and go back to the drawing board.

We will give three examples here of interesting discoveries made by considering questions on how various features might contribute to fitness. They relate to beavers and birds but not to medical questions, for which we will give many examples in the chapters to come. To various degrees these examples show that intuitive ideas about fitness, even the intuitions of professional biologists, may not always be adequate. Serious, often mathematical, theorizing is needed to provide the logical answers that can then be tested by investigating real organisms.

Beavers harvest trees in or near their ponds for their food and shelter. They use their teeth to chop through the trunks near the ground, drag the trees to the water if they are not already in it, and tow them to their lodges. How do beavers decide which trees to chop down? They do so *adaptively*, was the hypothesis considered by Michigan biologist Gary Belovsky. This implies an economically rational decision based on a tree's likely value to a beaver, the difficulty expected in chopping it down and moving it, and how far it is from home. Belovsky's calculations showed that an efficient beaver ought to be increasingly discriminating as the distance from the pond increases. Small trees may be rejected for not being worth the time to transport them, large ones for not being worth the labor of felling and transporting them, especially dragging them or pieces of them through the woods to where they can be floated in the pond. Belovsky predicted that the range of sizes of trees harvested by beavers would steadily decrease as the distance from the pond increased. At some point, only trees of an ideal size would be harvested; beyond that, none at all. Observation of stumps of beaver-felled trees near their ponds confirmed the prediction. The next time you see a beaver pond, admire not only the beaver's legendary industry but also its cleverness at setting priorities.

Now imagine a woodland songbird about to lay a clutch of eggs that she and her mate will incubate. Her reproductive success for this breeding season will depend entirely on those eggs. How many should she lay? Remember, she is not trying to assure the survival of the species, she is trying to maximize her own lifetime reproductive success. Laying too few eggs would obviously be foolish, but laying too many can also decrease her total lifetime reproduction if there is not enough food and some of the chicks die, or if she exhausts her energy reserves in caring for her brood and thus jeopardizes her chances of living until the next breeding season. These considerations apply equally to every individual in the woodland, but different birds reach different decisions on how many eggs to lay. If the average for a species is four eggs per pair, some pairs may have five and some only three. Do we conclude that all are trying for four but some can't count? Or do we perhaps conclude that egg numbers are not subject to optimization by natural selection?

An adaptationist forgoes such explanations until after considering the possibility that the birds deserve more credit. Could it be that, as a general rule, three eggs is best for those that lay only three, four for those that lay four, and so on? A simple sort of experiment provides the answer. If there are thirty nests with four eggs, leave ten randomly selected nests alone. From ten other nests remove an egg (the owners are now down to three) and add them to the ten remaining nests (four-egg birds now have five eggs). Now measure the average success of the three groups of birds: those allowed to choose their own egg number and those with one more or one less than they originally laid.

If all relevant factors are carefully considered, the results of such studies usually vindicate the conclusion reached fifty years ago by Oxford ornithologist David Lack: birds adjust the number of eggs they lay to maximize their individual reproductive success. To do this requires an accurate assessment of their own individual health and capabilities and experience. Having to provide food for four nestlings is more difficult and hazardous than providing for only three. Nestlings in more crowded nests may weigh less at fledging and be less likely to survive the following winter. Conditions vary unpredictably from year to year, and worse-than-normal years are especially dangerous for the more crowded broods. Surely such knowledge enhances a naturalist's pleasure in watching a pair of wild birds feed their young. Those birds are doing it right—not just right in general or on average, but right for them as unique individuals.

In this discussion of clutch size we considered the optimal number of offspring. We ignored the fact that there are two kinds of offspring, male and female. Should our birds ideally produce one or the other or both in some ideal proportion? In the natural selection of sex ratio one overwhelmingly important strategy maximizes fitness: producing offspring of whichever sex is in short supply. Any frequenter of singles bars knows that the minority sex has a mating advantage. In nature, individuals that produce male offspring when females are scarce will be selected against because many of those males will never have offspring. If males are scarce, individuals that produce females will not have as many grand-offspring as individuals who produce males. The operation of this process of selection explains why there are equal numbers of males and females. This simple, elegant evolutionary explanation was first recognized by the great evolutionary geneticist

R. A. Fisher in 1930. If you are thinking that an equal sex ratio arises because an individual has an equal chance of getting an X or a Y chromosome from its father, you are right, but this is a proximate explanation. The insufficiency of a proximate explanation is demonstrated by the many special cases such as ants and fig wasps, which are too complex to describe here but in which grossly unequal sex ratios turn out to match the more complex predictions.

Does natural selection in fact produce populations with exactly the same number of males and females? No, it does not, as would be expected by detailed reflection on factors such as the two sexes reaching maturity at different ages, differing death rates, differing costs to male and female parents, and other factors. Careful calculations support the conclusion that, for organisms with sex-determination and reproductive processes like ours, the sex ratio will stabilize when the parents collectively spend equal resources on rearing sons and rearing daughters. The demography of human and many other populations conforms closely to these expectations.

We hope to convince you in the coming chapters that the modern theory of natural selection can be just as helpful in making medically important discoveries as it is for predicting the foraging patterns of beavers, the effects of altered clutch sizes of birds, and the sex ratios of mammals. The reasoning will always start with some prior information about health or disease and a question about evolved adaptation: Is this feature of the human body a part of some adaptive machinery? If so, what must the rest of the machinery be like? How can we test our predictions for unknown aspects of the machinery? If any feature of human biology seems functionally undesirable, how can natural selection have permitted it to arise? Is an undesirable trait the price of a positive feature? Could it be a trait that was adaptive in the Stone Age but that now causes disease? What are the medical consequences of natural selection acting to improve adaptation in our pathogens and parasites? These are just a few of the sorts of questions now routinely asked by evolutionary biologists, and efforts at answering them have been enormously fruitful.

We must temper our enthusiasm with a note of caution. A question about function can have more than one right answer. For instance, the tongue is important both for chewing and for speech; the eyebrows, both for keeping the sweat out of the eyes and for communication. Second, the evolutionary history of a species or a disease is like any other kind of history. There is no experiment, in the usual sense, that we can do now to decide how long ago our ancestors first started to use fires for cooking or other purposes and what subsequent evolutionary effects that change may have had. History can be investigated only by examining the records it has left. Charred bones or even carbon deposits from an ancient campfire can be informative documents to people who know how to read them. Likewise, the chemical structure of proteins and DNA may be read to reveal relationships among now strikingly different organisms. Until a time machine is invented, we will not be able to go back and watch the evolution of major traits, but we can nonetheless reconstruct prehistoric events by the records they left in fossils, carbon traces, structures, and behavioral tendencies, as well as protein and DNA structures. Even when we cannot reconstruct the history of a trait, we can often still be confident that it was shaped by natural selection. This can be supported by evidence for its function in other species and by the match between the trait's characteristics and its functions.

So hypotheses about the evolutionary origins and functions of a trait, just like hypotheses about proximate aspects of a trait, need testing and are often testable. Special difficulties attend the testing of evolutionary hypotheses, but these are no reason to give up—they just make the work more challenging and interesting. Do we claim to test evolutionary hypotheses in this book? Not really. While we will try to separate speculation from fact, and will cite evidence for most of our examples, hardly any of them can be considered proven by the evidence we present. Some of the examples are based on many studies, each with different data bearing on a different aspect of the problem, but even this is often insufficient.

Our goal is not to prove any specific hypothesis but to show that evolutionary questions are interesting, important, and testable. We want people to start asking new questions. So, without apology, we ask questions about the possible evolutionary significance of diverse aspects of disease and offer answers that are often speculative. Some people will, despite our warnings, insist on taking these speculations as facts. Perhaps in a few years Darwinian medicine will have enough confirmed findings to fill a book. For now, our goal is not to exhaustively test a few hypotheses but to encourage patients, doctors, and researchers to ask new questions about why disease exists. As Gertrude Stein said on her deathbed, "The answer, the answer, the answer. What is the answer? . . . In that case, what is the question?"