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On the difficulty of defining disease: A Darwinian perspective

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Abstract. Most attempts to craft a definition of disease seem to have tackled two tasks simultaneously: 1) trying to create a series of inclusion and exclusion criteria that correspond to medical usage of the word disease and 2) using this definition to understand the essence of what disease is. The first task has been somewhat accomplished, but cannot reach closure because the concept of "disease" is based on a prototype, not a logical category. The second task cannot be accomplished by deduction, but only by understanding how the body works and what each component is for, in evolutionary detail. An evolutionary view of the origins of the body and its vulnerabilities that result in disease provides an objective foundation for recognizing pathology. Our social definition of disease will remain contentious, however, because values vary, and because the label "disease" changes judgments about the moral status of people with various conditions, and their rights to medical and social resources.

Key words: Darwinian perspective, defence mechanisms, disease concept, evolution, genetic traits

The problem of defining disease has occupied so many good minds for so long with so much continuing contention, that it seems foolhardy for a nonspecialist to even venture thoughts on the issue. However, the very lack of consensus suggests that the question may be either miscast or unanswerable. Given this situation, it seems worthwhile to examine the question from the perspective of a secure scientific foundation, that of evolutionary biology (Nesse and Williams, 1995).

As best I can understand it, the quest has generally been for a series of words that define disease in a way that matches conventional use of the word and that provides insight into the essence of disease (Humber and Almeder, 1997). These two aims are actually quite distinct, and may require very different approaches. The first aim attempts to define disease by crafting phrases whose intersections create a Venn space that encircles all that we mean by disease and nothing else. The enterprise has made considerable progress, with most authorities specifying a state of the body that differs in disadvantageous ways from species typical states. All of these definitions, however, fail in some respect or another to fully satisfy the criterion of matching common medical usage. For instance, some include pregnancy as a disease, but exclude upper respiratory infections (Clouser et al., 1997). I suspect this difficulty arises because human concepts like disease refer, not to categories defined by logical inclusion and exclusion criteria, but to prototypes. In the case of disease, this prototype approach makes great sense. The disease concept must have emerged when people tried to communicate to each other that something was wrong with their bodies, whether from pneumonia, cancer, an infected wound, or kidney stones. People with no idea about microbes, genes, or even anatomy, must have used the concept of disease to refer quite generally to any undesirable bodily condition, and perhaps to mental conditions as well. In those days, such conditions could be identified only by suffering, disability, or cues that indicated increased vulnerability to suffering or disability. From this vantage point, the very origins of the disease concept involve a value judgment – suffering and disability are undesirable. Whether this value judgment exists only in our evolved minds is another matter, but our negative judgments of suffering and disability are by no means arbitrary, having been shaped by natural selection. The utility of pain as a motivator of escape and avoidance depends, after all, on its intrinsic aversive character.

The second goal has been to use a definition of disease to gain insight into its nature, often with the implicit assumption that disease exists as an ideal form. In recent writing, this question seems to have been posed as a choice between naturalistic views of disease, such as those of Boorse, versus normative positions, as proposed by Englehardt (Boorse, 1997; Englehardt, 1996, pp. 189–238). I can see the issue, but it is not clear to me that these positions are mutually exclusive alternatives (Kovács, 1998). Disease can refer to specific objective bodily conditions, and yet the interpretation of those conditions, and their valuation, may vary from culture to culture. Furthermore, the social significance of defining a condition

as a disease varies considerably. The separate, and to my mind more fundamental question, is whether there is some objective way of specifying when a body is abnormal and when it is not. This is probably not susceptible to deductive analysis, but requires, instead, a full knowledge of how every aspect of the body works, how it contributes a fitness advantage, and how it was shaped by natural selection. In most instances, our knowledge about the body provides a basis for strong opinion, in many cases a definitive opinion. Nonetheless, we don't understand everything, so we cannot always determine whether a condition is a disease or not. If we did have a full and detailed understanding of every aspect of the body and its origins, this would, I believe, provide an objective basis for determining if any given condition is pathological or not.

Interestingly, debates about the definition of disease often mix these two goals. Actually, three goals could be identified, if one wanted to consider the social significance of the label "disease," separately from the mere designation of a condition as a disease. For instance, Boorse claims that disease can be defined apart from social values, but his definition relies on statistical normality rather than to any biological criterion, and he assesses the quality of a definition by how well it conforms to how doctors use the word disease.

Origins of the idea of disease in human experience and desires

We have already noted that the concept of disease undoubtedly arose early in human speech and cognition to describe undesirable bodily conditions. People want their bodies to be healthy instead of sick, and they created words to describe these desirable and undesirable states. As time went on, however, several other questions arose. Even if we know what we mean by disease, what is it? Where does it come from? Why does it exist at all? What can we do about it? Is it necessary? Can it be prevented? Now instead of mere definition, we need a causal analysis. The core simple notion of disease indicates that something is wrong with the body. Some mechanism is not working correctly. This implies, of course, that we know what "working correctly" means. It suggests that we know how to recognize normality. Often, of course, we can. Cancer is abnormal, shivering is normal. But as soon as we inquire deeply, our intuition fails us. Is depression an adaptation or a disease, given that natural selection may have shaped a system to turn off motivation in situations where action is likely to be maladaptive (Nesse, 2000)? Diabetes of pregnancy is a disease for the mother but it seems to exist to benefit the fetus (Haig, 1993).

The difficulty here is understanding what we mean by normal. Reference to statistical norms is helpful, especially if care is taken to adjust these norms for age and sex (Boorse, 1997). Nonetheless, tooth caries and heart disease are statistically normal in many cultures, but still abnormal because they interfere with function. Other conditions, such as manic-depressive illness, may even give a selective advantage, and yet be abnormal. A deep understanding of what is abnormal requires a richly detailed understanding of what is normal. Statistical generalizations will not suffice. Instead, we require nothing less than a complete knowledge of what the body is for, how it works, and, especially, how it came to have its current form. If we had this knowledge in hand, then we could define abnormality with reference to deviations from normality, not needing to resort to either statistical or value laden information. In some cases pathognomonic signs define the presence of a disease (Wulff and Gøtzsche, 2000). The problem is, of course, that not all diseases can be sharply distinguished from normal. Our knowledge is limited. On the other hand, we now know a great deal about he design and function of the body and recently, we have gained a much better understanding of how the body was shaped by natural selection and for what. The rest of this article will attempt to determine how helpful this knowledge can be in deepening our understanding of what disease is.

Some contributions from an evolutionary perspective

The benefits of an evolutionary approach to understanding what disease is emerge largely from a series of distinct principles. These are listed below, with details and their significance expanded in subsequent exposition.

1. The values that humans use to decide what is disease are socially influenced, but they are built on preferences shaped by natural selection.
2. Defenses are not diseases but evolved solutions to challenges. The suffering associated with defenses is a product of natural selection. Failure to express a defense in response to a challenge results in disease.
3. Individual health is not the expected outcome of natural selection except insofar as it contributes to reproductive success. When health and reproductive success conflict, natural section will benefit reproduction at the expense of health.

4. Bodies are not shaped to maximize individual reproductive success, but the inclusive fitness of genes, that is, the net benefit to genes including those in an individual and genes identical by descent in kin.
5. Interference with mechanisms that maximize inclusive fitness in the natural environment offers an objective foundation for distinguishing pathology from normality if we understand enough about the mechanisms and the environment.
6. Because we define health in terms of individual functioning and well-being, we often call a condition a disease even if it maximizes fitness.
7. What is beneficial and harmful depends on whose perspective, gene, individual, society.
8. Bodies are not machines.
9. There is no one normal genome.
10. From an evolutionary point of view, there are only a few reasons why diseases exist at all.

Values

While many of our values are strongly socially influenced, they arise from evolved preferences designed to maximize reproductive success (Nesse, 1990). The very preference for living instead of dying is the most basic. People lacking this preference have been selected against. Likewise, the wish for health and good function, and the wish to get back to normal when an illness strikes, are primal wishes. Yes, a student facing an exam may welcome a minor infection, but this is merely a matter of tradeoffs. Fundamentally, people have a basic desire for health and longevity. Thus, while some definitions of disease are strongly socially influenced, there is a solid underpinning to these values. Even apparent perturbations can make sense in this context. People who believe that their desire to masturbate is pathological, for instance (Engelhardt, 1996, pp. 273–285), are responding to the strong human tendency to wish to conform to social norms, even if that is in conflict with their sexual desires.

Defenses

The origins of the concept of disease are not in pathology, but in suffering. Pain is the exemplar, but nausea, fever, cough, malaise and all the other forms of human suffering give rise to searches for relief. These forms of suffering are products of natural selection. They are not diseases; they are defenses that help to protect us (Williams and Nesse, 1991). The *presence* of pain indicates tissue damage and motivates us to escape it and prevent recurrence. The *capacity* for pain, by contrast, is a defense (Melzack, 1973). People born without the capacity for pain are dead by early adulthood. The same logic applies to the discomfort associated with rhinorhea, cough, vomiting and diarrhea. These traits are latent until aroused by some cue that expresses the defense.

Failure to recognize this distinction has caused much confusion in medicine. General practice is, to a considerable degree, the task of responding to people's wishes to be relieved of the discomfort that is associated with the normal operation of defenses. The tools now available to help are truly wonderful. Drugs that block pain, fever, nausea, cough and malaise make life better. Given that these aversive experiences are useful capacities shaped by natural selection however, one has to wonder if we are harming people by blocking their defenses. Sometimes we are. Blocking diarrhea caused by shigellosis causes increased complications and slower recovery (Dupont, 1973). What about taking aspirin for fever? Incredibly, we do not know if it slows recovery from colds or influenza despite abundant evidence for fever's utility (Kluger, 1979). The illusion that fever is unnecessary is prevalent because the body has multiple mechanisms for opposing infection; if one is blocked, the others are usually sufficient.

A related point is of great importance to philosophical approaches to human suffering, and has practical applications as well. Natural selection should shape mechanisms that regulate defenses to give optimal benefit. Yet it appears, from the generally beneficial effects of blocking defenses, that these mechanisms are released too early, too often, too much, and for too long. Consideration of the optimum regulation requires, however, consideration of the probabilities of different outcomes and the costs and benefits of different situations. If the cost of vomiting is 500 calories, then vomiting will pay off whenever this is less than the cost of a threat, times the probability that the threat is present. If the threat is an illness that would eliminate five days of food gathering at 2000 calories per day, then the response should optimally be expressed if the risk of the threat being present exceeds 5% (500/10,000). This means that 19 times out of 20, the vomiting will be unnecessary, but completely normal. This simple calculation gives great hope that we can safely relieve much suffering, even as it calls attention to the risks of blocking a defense that 20th time. The most important point here, however, is that we must carefully distinguish defenses from diseases. Furthermore, the capacities for suffering are not abnormal, but sophisticated evolved capacities. In

short, suffering usually indicates some pathology or challenge, but is, it, useful.

Natural selection shaped maximal reproductive success, not health

Consideration of the expected products of natural selection is even more sobering. It seems natural to expect that selection will shape a body for maximum health and longevity. This is, unfortunately, incorrect. Genes become more frequent in the gene pool if they make bodies that yield greater than average net reproductive success. If a mutation causes a disease, but yields a net increased reproductive success, it will be selected for. If a gene causes life to be shorter, but more fecund, it will be selected for (Williams, 1957). Instances of each effect are known, and many more are likely to be found.

In general, health and longevity contribute to reproductive success. It is only when they conflict that things get interesting. The best example is the early death of half the human population, the feeble sex, males. Males have immune systems weakened by testosterone, and brains, similarly influenced, that induce them to dangerous displays of their machismo. They fight and kill each other and compete to no apparent purpose except to gain relative status and to impress women. These purposes turn out, of course, to strongly influence reproductive success. They influence both access to resources and desirability to females. Variation in female reproductive success is smaller than that of males. In species where there is strong competition for females, especially polygynous species, males whose life energies are concentrated into an intense burst early will out-reproduce those who live quieter, longer, healthier lives. Health is not the outcome of natural selection, maximal reproduction is.

A related argument shows why aging is inevitable. It is theoretically possible for an organism to have the capacity to repair all of its tissues and to live forever. The difficulty is that those repair mechanisms are expensive and the resources could also be put into current reproduction. Natural selection shapes lifespan as a life history trait to maximize reproduction. The genes that cause senescence persist for one of two reasons (Nesse, 1987). First, some are never exposed to selection, because they have no deleterious effects during the lifetimes of animals in the wild. Other forces kill all individuals before the effects of aging genes have any effect, so there is no selection against the aging genes unless, that is, the species passes several generations in a new more benign environment, such as a zoo or laboratory, where long-lived individuals will have a reproductive advantage. The second reason genes that cause senescence persist is because they also offer benefits early in life that are greater than their costs later in life. Such pleiotropic effects can increase the frequency of a gene even if it causes substantial effects on life span in the wild. The hypothetical example used by George Williams in developing this idea was a gene that changed calcium metabolism in a way that sped bone healing in youth, but that steadily calcified the coronary arteries in adulthood (Williams, 1957). Because there are more individuals alive early in life, selection is stronger then, thus magnifying the effect. Menopause is sometimes seen as a problem for this point of view, however most species do not show any cessation of reproduction with age, and the very existence of menopause in humans may be a life history trait that maximizes fitness, perhaps by ensuring care for existing children instead of risking more reproduction.

It is tempting to say that some diseases of old age are normal because they are statistically prevalent. I believe this is a mistake. The body's capacity to resist disease of all types declines with age; consequently, the frequency of nearly every disease increases. They may be common, but they still are disruptions of normal functioning.

Natural selection benefits genes, not individuals

So, natural selection makes organisms that maximize their reproductive success, even at the expense of individual happiness, health and longevity. There is still one more factor to consider – whose reproductive success is maximized? Two points are important here, kin selection and "outlaw" genes. We have already referred to kin selection by references to "net inclusive reproductive success." The word "net" reminds us that the number of births is of relevance only as it relates to the number of offspring that reach adulthood and reproduce. Actually, what really matters is the number of surviving grandchildren and great grandchildren. The word "inclusive" refers to the discovery that individuals can advance their gene's interests by helping other individuals who have genes that are identical by descent. This is derived from Hamilton's principle of kin selection and it explains much otherwise unaccountable self-sacrifice (Hamilton, 1964). Examples such as a parent protecting its baby from wolves are so expected as to be unremarkable. A better, albeit subtle example, is when a mother allows an offspring to continue to nurse beyond the time when the mother's direct reproductive interests would be served by having another baby, because giving more to the current offspring will eventually contribute to its

ability to bear grandchildren. Later, nursing becomes more conflicted. At some point, even taking inclusive fitness effects into account, the mother's interests are served best by weaning but the infant tries to improve its own reproductive success by continuing to nurse (Trivers, 1974). The global conclusion is that natural selection tends to shape mechanisms that benefit genes in kin, even if that results in a cost to the self, including vulnerability to disease.

A dramatic example illustrates the more fundamental point that phenotypes, that is individuals, are devices constructed by genes to transmit themselves to the next generation. In general, genes cannot do anything to benefit themselves except by contributing to the welfare of the individual and his or her kin. There are, however, exceptions. So-called "outlaw" genes advance their interests at the expense of the individual. In general this is because they distort segregation during the formation of gametes and thus increase their chances of being transmitted above the expected 50% (Haig, 1992). The means by which they accomplish this feat are more complex than the plot of a 4-hour spy movie, but in outline they seem to involve pairs of genes, one of which disables or destroys any zygote that lacks the partner gene that protects against such effects. The T locus in mice is the best-studied example (Franks and Lenington, 1986). No examples are known in humans yet, but we may well come upon them. The DNA in mitochondria, transmitted in the ova from the mother, is not subject to the recombination that may help to limit the effects of such rouge genes in the nuclear DNA. While outlaw genes are so far not known to cause human health problems, their very existence is a potent reminder that selection maximizes benefits for genes, not individuals. We are fortunate that the DNA in all of our cells is effectively the same, and that the germ cells are sequestered in a special cell line, thus ensuring the correspondence of interests of genes and the individuals they make. I have taken a bit of care in refraining from overly attributing motives to genes, but it is always worth a reminder that no planning or motives are in play here. Genes have no interests, but their effects tend to increase or decrease their representation in future generations, so it is hard for human minds to avoid thinking of them as acting in their own interests.

Normality

One way or another, most attempts to provide objective criteria for disease depend on comparing normal to a state defined as "abnormal." This very slippery concept has given rise to much difficulty. First off, in everyday parlance it refers simultaneously to the presence of bodily defects, and to the social acceptability or unacceptability of a condition. Attempts to separate these two uses are opposed by powerful social forces that insist on using the language of medical pathology to label those people and conditions they disapprove of, and yet hold unaccountable and in need of treatment. Those same social forces systematically deny the label "disease" to conditions they believe people should be morally accountable for. For instance, in the USA radio talk show hosts are currently gaining much notoriety by claiming that homosexuality is a choice, a position that is harder for liberals to oppose now that homosexuality has been demedicalized. As noted already, it is most difficult to define normality without a comprehensive and detailed knowledge of physiology and evolutionary history. From an evolutionary point of view, if lack of sexual interest in members of the opposite sex is shown to result from autoimmune damage to a particular part of the brain, then it is abnormal. If, however, it is shown to be a facultative adaptation that is aroused only in certain circumstances where it contributes to kin survival and reproduction, then it would be an adaptation. Although Wilson suggested this second possibility (Wilson, 1975), I know of no evidence for it, and the whole question is unresolved despite much speculation. Is a suntan normal or pathological. It depends on whether the color results from mere cell damage or an organized special process, and whether the capacity for tanning gives a net advantage or not. In this case it is assuredly normal.

It is here that an evolutionary approach has the most to contribute to the definition of disease. Our knowledge of how natural selection has shaped the body and how it works allows us to be quite confident about what is normal and what is not in many instances that are otherwise hard to assess. The key notion is that disease is present when a bodily mechanism is defective, damaged, or inadequate to the current challenge. Thus, Huntington's chorea results from a defective gene, and congestive heart failure can result from a defect in the mitral valve. Damage to the brain after a stroke is clearly an abnormal state, as is inability to walk whether because of a twisted ankle or an infected joint. Influenza results when the body's defense mechanisms are inadequate to repel the virus, heat stroke when the ability to regulate temperature is inadequate. In every such case, however, the recognition of pathology depends on a comparison of the current body's mechanisms to those of another body that is healthy. I can see no way around this. Disease is a disadvantageous difference from normal; this requires a way to recognize what is normal, a difficult task, as already noted.

Our knowledge that the body is shaped to maximize

the reproductive success of its genes is helpful. The strong implication is that any deviation from the usual state of the mechanisms will lower reproductive success, and we can assess whether a state is pathological or not by determining its deviation from the usual and its effects on reproductive success. There is no need to be distracted here by individuals who use birth control. Such a novel environmental factor distorts the reproductive outcome, but there is no reason to think that people in the natural environment would be shaped to seek to have children. Seeking to have sex was fully sufficient except in rare circumstances. Whether these rare circumstances were frequent enough to shape a desire for children independent of a desire for sex is an interesting question. Perhaps couples that fail to have children lose interest in the relationship. Also, the huge medical investments made by infertile couples seem so suggest a primary desire for offspring, but it may be simply that they perceive the pleasures of having children, and want to partake.

A few examples of potentially difficult cases will illustrate this approach. Pregnancy certainly can be a malady (Clouser et al., 1997), but it nonetheless is perfectly normal. It is associated with increased risks of pathology, but this does not justify calling pregnancy abnormal or a disease. Likewise, senescence involves the gradual decrease in reserve capacity in all tissues, with resulting increased risks of nearly every disease. Senescence itself is normal, not just because it happens to everyone, but because we can see how it results from a combination of selection for pleiotropic genes that give a benefit in youth despite their later costs, and genetic mutations that accumulate despite causing damage late in life because natural selection is too weak at that time in life to eliminate them. The diseases associated with old age remain diseases, even if nearly everyone gets them, and even if the genes that cause them offer other benefits. Cataracts and Alzheimer's disease interfere with normal mechanisms and function. One might be tempted to say that such conditions at such ages do not much influence reproductive success, and so are not diseases, but they do disrupt normal function. Besides, individuals at any age can help their kin, and they can do this better if they can see, walk, hear, and remember.

What about the farsightedness that affects everyone in middle life? It results from the universal stiffening of the lens, probably a result of tissue oxidation. This case is a bit more ambiguous because it happens to everyone. Nonetheless, it decreases function by disrupting a normal mechanism, so I would call it a universal disease resulting from a tradeoff that makes repair of such damage impossible.

Nausea and vomiting during pregnancy is another challenging example. It happens to most, but not all pregnant women, starting a few weeks after conception and stopping at the end of the first trimester. It is certainly a malady, but is it a disease? That depends on whether it is an abnormality or a defense. Marjorie Profet has suggested that it is a defense that prevents pregnant women from eating food that have toxins that might interfere with tissue differentiation (Profet, 1992). If this is true, then it is a defense. If not, then it might be a disease. If protection against toxins could be accomplished equally well without the nausea and vomiting, then it is a defense, but one that is constrained to a suboptimal design that results in a disadvantageous syndrome. Instead of trying to figure out if this is a disease or not, it may be more productive to use it as an example of a condition that challenges the notion that diseases are essences distinctly separate from normal conditions.

Hypothetical conditions

Next, I would like to consider some hypothetical conditions that should prove illuminating. The first is an actual condition, manic-depressive illness. Individual differences in susceptibility to this condition depend mainly on genetic differences (Goodwin and Jamison, 1990). Yet manic-depressive illness is associated with a high suicide rate and considerable additional dysfunction secondary to alcohol and drug use and the social complications of manic and depressive behavior. The question is, of course, how genes that cause such a condition can persist. I suspect, as others have, that these same genes, in other combinations, provide advantages. There is considerable evidence for increased creativity in manics and a bit of evidence that their relatives are also especially creative (Jamison, 1993). No one has, insofar as I know, looked to see if people with manic depression or their relatives are especially sought after sexual partners or whether they have more children than other people.

For the sake of argument, however, let us imagine that the presence of genes for manic depression give a slight but definite reproductive advantage. If this were the case, they would gradually increase in frequency until they became universal. One can imagine a species in which almost every individual is subject to wild highs and lows of mood; only a few deviants would have steady mood. In such a condition, would manic depression still be a disease? According to my definition based on deviation from some normal state of the species, it would not be. But compared to the behavior regulation of our current species, it certainly would be abnormal. Compared to objective criteria of longevity and ability to function, it would be disadvantageous, but if reproductive success is the only criterion, one

would have to call it normal. Actually, if the above scenario were true, there would be selection for modifier genes that allowed the benefits of the condition to continue, while ameliorating the costs. Thus, its evolutionary status would be the same a gout, a disease that results from genes that generally give a selective advantage.

A related cause of disease is male behavior. It is hard to comprehend the magnitude of testosterone effects on health behaviors. The mortality of males is a bit above that of females throughout childhood, but at puberty the mortality ratio skyrockets. According to calculations I have recently conducted on 1996 data from the USA National Center for Health Statistics, at early sexual maturity the mortality rate for males is three times as high as for females. It gradually decreases, but does not reach equity until age 100. The difference results largely from accidents, violence, and the complications of drugs, alcohol and risky sex, but of the 15 leading causes of disease, 14 are higher overall for men. A mutation that decreased the effects of testosterone would markedly improve human health. By a crude calculation I made, just over 25% of all years lost to premature death could be eliminated if male death rates matched females. But the effects on any intervention on Darwinian fitness might be substantial and negative. Being male harms health by increasing vulnerability to many causes of disease and injury, but is not abnormal, it is just a tradeoff. It is the results that are abnormal. If it specifically disrupted the operation of some normal physiological mechanism, I would be inclined to call it an abnormality that arises as a result of a tradeoff. All of this illustrates how a detailed approach reveals the lack of specificity of common terms.

Another example involves the different effects of a trait at different ages. We have already examined senescence and seen how genes that cause such deficits can nonetheless be selected for. Consider, however, a gene that makes a sperm swim faster than others, but that causes a serious disease later in life, a possibility made more likely for humans by the recent finding that genes that code for sperm proteins evolve very rapidly (Wyckoff et al., 2000). Or, alternatively, a gene that increased the implantation rate of fertilized ova above the usual 25% but that has major health costs late, as has been suggested for the DR4 allele (Rotter and Diamond, 1987). In each case, the huge reproductive advantage would give the gene a net selective advantage despite the cost to health. Then there would be selection for any modifier gene that ameliorated the effects of the gene that made sperm swim faster or the zygote implant more readily. Such complexities suggest that unraveling the functional significance of each gene will be a convoluted task, likely much more challenging that merely finding the sequence of the genome.

Three perspectives

A theme recurs in these examples – at which level of selection should we define abnormality? A condition can benefit the gene, but harm the individual. Should we call this disease? Usually we do, because it is the individual who seeks help for suffering and disability, not the gene or the group. The values so often cited as necessary for defining a condition as a disease generally refer to the benefits or costs to the individual, irrespective of the benefits to the genes. But from the gene's point of view, they are not diseases at all, just instances in which the optimal strategy requires some sacrifice of the individual's welfare (Dawkins, 1976). This gene's eye view of disease is a bit preposterous, but it prepares for a parallel and more common perspective on a different level, social groups.

If an individual has a tendency to do things that benefit his or her self but are costly to the group, is that behavior a disease? Usually, of course, individuals benefit by contributing to the group, and the costs of social deviancy or taking advantage of the group are substantial (Frank, 1998). Nonetheless, the sociopath can sometimes make hay, especially in large mobile social groups. From the group's perspective, such behavior would be described as disease. From the individual's perspective, it may or may not be a disease. It has been suggested that sociopathic behavior may be encoded by genes that are frequency dependent, giving an advantage only when they are rare, thus maintaining considerable allelic diversity (Mealey, 1995). I suspect that this hypothesis is not correct, mainly because sociopaths often have other indications of brain pathology, and because many of them do spectacularly badly in life. There is no net reproductive benefit on the average, even in our fluid society; in ancestral groups the selection against such individuals might well have been fierce. Still, the example remains useful to remind us that whether a condition is considered a disease or not depends on whether the benefits are considered from the point of view of the gene, the individual, or the social group.

Normal function of bodies and machines

Consideration of pathology depends, as already noted several times, on comparison with some normal state, and the normality of a state depends on being able to see how it serves a function, in this case contributing to reproductive success. We have already said enough

about reproductive success as a criterion for normal function, but it is worthwhile noting how this related to machines. Most of us use a tacit metaphor of a machine when we think of the body. We think of the engineer's planning, blueprints, and the construction of components with specific functions that contribute to the overall functions of the machine. But the body is not a machine, it is a body, and that is very different. It is different because it was not designed, because its function is not to serve any human or divine purpose but only to maximize the reproduction of its genes, and because it can be changed only in increments, not by any major leaps. Furthermore, while there is one master blueprint for a machine, there is no one normal genome for the body. Likewise, there is no one perfect phenotype. There are just phenotypes that emerge from the products of genes interacting with environments. Thus, there is no ideal type to use as a benchmark for comparison to determine what is normal and what is not. It does not make sense to ask if sickle cell allele is normal or not; it is just an allele that give an advantage in certain circumstances, namely, when paired with a normal hemoglobin allele in an environment where malaria is prevalent. Sickle cell disease is a disease even if the sickle cell allele is selected for.

Does this kind of individual genetic variation give the deathblow to definitions of pathology that rely on comparison with a purported normal phenotype? Not at all. While there is some genetic variation, and some phenotypic variation, the vast majority of traits are the same in all normal people. We all have a thyroid gland, we all have ureters that empty into the bladder, we all have salivary glands that make secretions as we anticipate or eat food. Deviations that negatively influence the ability of these mechanisms to carry out their usual tasks are pathological. This is objective and depends on no social input. This said, it is worth repeating that there is no one normal genome, no one normal phenotype that compare to a master blueprint and perfect production model. Organisms are not machines.

Evolutionary causes of disease

The usual medical approach to explaining disease is to look for the factors that explain individual differences – why one individual has a disease and another does not. These factors are drilled into every medical student: genes, developmental abnormalities, infection, inflammation, degenerative processes, nutritional abnormalities, trauma, toxins, neoplasm, radiation, and reproductive, psychogenic, and factitious disorders. The list is not elegant, but it is serviceable.

An evolutionary approach asks an entirely different question – why are all individuals in a species susceptible to a disease (Nesse and Williams, 1994)? In other words, why didn't natural selection shape a body that is better protected from that kind of disease? This question is not about how people differ but about why we are all have the same sub-optimal body. The old, easy answer to the question was that natural selection depends on chance, and is not all that powerful, so you can't expect the resulting product to be perfect. Indeed, the stochastic nature and limited power of natural selection do account for some our susceptibility to disease, but several other reasons are even more likely explanations. I will review each with an example or two because our understanding of what disease is will likely be illuminated by understanding where disease comes from.

First, for orientation, a list of possible evolutionary explanations for why the body is not better:

1. Defenses can be costly and dangerous even though giving a net benefit.
2. Competition between different organisms.
3. Novel environmental factors the body is not evolved to cope with.
4. Tradeoffs in design parameters.
5. Constraints on the process of natural selection.
6. The body is shaped for reproductive success not health.
7. The body is shaped for genes, not individuals.
8. Chance factors.

Defenses we have already covered. They are not diseases or causes of diseases, but latent mechanisms that are aroused by cues that a problem is present. They are usually aversive, and sometimes they lead to pathology or become pathological by dysregulation. Thus, diarrhea clears toxins from the large bowel, but can also cause fatal dehydration, and the symptoms can continue when the threat is past.

Competition between organisms causes disease because natural selection for our defenses cannot keep ahead of natural selection acting on other organisms. The paradigmatic case is, of course, infection. Bacteria and viruses evolve faster than we do. The wonder is that metazoans exist at all! A whole world of complexity exists here, with selection for increased and decreased virulence, and arms races between defenses and counter-defenses that lead to expensive and elaborate and fragile mechanisms that are dangerous in themselves (Ewald, 1994). Our immune system, for instance, causes tissue damage in all of us, and autoimmune diseases in some of us. Selection could change the parameters to decrease these costs, but only at the larger cost of making us more vulnerable to infection.

Competition with larger organisms, predators, is a problem our species has largely conquered by extermi-

nating or controlling them. Another class of organismic competitors remains a grave threat to health, however, and that is conspecfics – members of our own species. The whole issue of war is too complex to get into here, but everyday competition saps our energy and causes stress and its complications, to say nothing of anxiety anger and general dissatisfaction with life. The irony is that this competition seems to be unending. Even in communities where everyone is well-fed, financially secure and has a healthy mate and children, social competition is often brutal and a cause for much pathology

Novel environmental factors cause much, perhaps most, disease now (Eaton, et al., 1988). Our bodies were shaped for optimal function on a much more limited diet in an environment where everyone needed to spend 3–4000 calories a day just to get food. The current epidemics of arteriosclerosis, stroke, hypertension, diabetes, obesity, alcoholism, drug addition and eating disorders result from the mismatch between our bodies and the environments in which we now live. This is not to say that health was better back then, absolutely not! But the majority of health problems today arise from exposure to novel environments.

Even our impulses are poorly suited to our environment. In the Paleolithic, a craving for sugar, salt, fat and leisure gave a net benefit. Now it leads us to create social structures like grocery stores that satisfy our evolved needs, and simultaneously cause most disease. The genes that contribute to these diseases, such as most genes associated with high cholesterol, are not defects, but "quirks" that posed no selective disadvantage in our normal environment.

Tradeoffs restrict the durability and performance of machines and bodies alike. You can't have a car that gets 50 miles to the gallon and goes from 0 to 60 mph in 6 seconds. Tradeoffs are inherent in any design. Thicker bones would break less readily, but would make us clumsy. Our eyes could be reshaped, like those of an eagle, to detect small motions from hundreds of meters away, but our color and peripheral vision would suffer proportionately. Uric acid levels could be lower to prevent gout, but then our tissues would be more quickly damaged by oxidation.

Constraints of various sorts limit the perfection that natural selection can achieve. The most severe constraints arise from the design of the information system itself, the genome. Errors creep in, and some of them become more frequent by drift. The fact that the genome is essentially digital, with alleles present or absent, results in pleiotropic costs from some genes tha have costs as well as benefits. Diploidity gives advantages, but having two copies of each gene makes room for heterozygote advantage, with resulting diseases like sickle-cell anemia. And while DNA repair is excellent, it is not perfect, so problems arise. Then there is the matter of sex itself, apparently essential for most organisms, but giving rise to vulnerable extravagances shaped by sexual selection, that increase mortality. As if these constraints were not enough, the whole system is path dependent – it can go forward by tiny increments, but can never start fresh. Finally, chance factors result in the loss of potentially beneficial genes, the absence of mutations that simply have never occurred, and the incorporation of deleterious bits of DNA.

What is the significance of these evolutionary principles for understanding what disease is? First, they emphasize that disease is not something that can be avoided completely. Some disease results from competition with other organisms. Defenses that would more completely prevent infection are not possible because pathogens evolve faster than we do and because better defenses would cause more damage our tissues than the benefit they offer. Diseases that arise from our novel environment can be prevented, but only by huge efforts to control our innate predispositions and preferences for fatty foods and leisure. Others arise from tradeoffs in design, or from the limits of natural selection. There are not just a dozen diseases, there are thousands. This is the result of natural selection. It can shape protection only from problems that occur, so almost any problem that can occur, does occur. Problems that are common should, until evidence shows otherwise, be considered to be results of organismic competition or a mismatch between the body and the environment,

Another implication is that most diseases have objective status independent of our values. Conditions that involve defects, damage or deficiencies of evolved mechanisms are abnormalities. We may not want to call them diseases unless our (partly evolved) values indicate a wish to change them, but they are abnormal just the same. Tiny deviations from normality do not influence fitness, but in the vast majority of instances we can identify exactly what bodily mechanism has failed and how. Soon, we will pay more attention also to why.

So, what is disease? It seems to me that philosophers have answered the question relatively well, given the constraints of trying to provide a definition in words. Yes, there is disagreement, but for the reasons mentioned, no single definition will serve all the functions demanded of it. An individual has a disease when a bodily mechanism is defective, damaged, or incapable of performing its function. The continuing debates about the definition of disease arise partly from the hope that a logical definition can be found that conforms to common usage based on prototypes, partly from attempts to seek the essence of disease

without reference to all the complexity of the mechanisms of the body and their origins and functions, and partly from the political and moral implications of labeling a condition a disease. We will undoubtedly see if further pursuit of these debates will, or will not, deepen our understanding of what is disease, and what disease is.

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