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Signs and Symptoms of Infectious Disease

Suppose you are on the side of the mice in cat-mouse conflicts. The mice say they hate the smell of a cat. It makes them jittery and unable to concentrate on important matters, such as food and courtship and babies. You know of a drug that will dull the sense of smell so that the mice will no longer be bothered by the odor of cats. Do you prescribe the drug? Probably not. The ability to detect cat odor, however unpleasant it may be, is a valuable asset for mice. The presence of the cat's smell may signal the imminent arrival of its claws and teeth, and avoiding these is far more important than the stress of an unpleasant odor.

More realistically, suppose you are a pediatrician treating children with colds. Colds bring many symptoms that children dislike—runny nose, headache, fever, and malaise. Acetaminophen (e.g., Tylenol) can reduce or eliminate some of these symptoms. Do you tell the parents of cold-stricken children to give them acetaminophen? If you are a traditional physician or are in the habit of using acetaminophen yourself to relieve similar symptoms, you probably do. Is this wise? Consider the analogy between acetaminophen and the drug we were considering for the mice. Like the smell of a cat, fever is unpleasant but useful. It is an adaptation shaped by natural selection specifically to fight infection.

Fever as Defense Against Infection

Matt Kluger, a physiologist at the Lovelace Institute, believes that "there is overwhelming evidence in favor of fever being an adaptive host response to infection that has persisted throughout the animal kingdom for hundreds of millions of years." He believes that using drugs to suppress fever may sometimes make people sicker—and even kill them. Some of the best evidence comes from his laboratory. In one experiment, he showed that even cold-blooded lizards benefit from fever. When infected, they seek out a place warm enough to raise their body temperature about two degrees Celsius. If they cannot move to a warm place, they are more likely to die. Baby rabbits also cannot generate a fever, so when they are sick they too seek out a warm place to raise their body temperature. Adult rabbits do get fever when infected, but if the fever is blocked with a fever-lowering drug, they are more likely to die.

Fever results not from any mistake in temperature regulation but from the activation of a sophisticated evolved mechanism. If you put a rat with a two-degree fever into a very hot room, the rat activates its cooling mechanisms to keep its body temperature two degrees above normal. If you put it into a cooler room, it activates heat-conservation mechanisms to maintain that two-degree fever. Body temperature is carefully regulated even during fever; the thermostat is just set a bit higher.

Perhaps the most dramatic human evidence for the value of fever comes from studies by Julius Wagner-Jauregg in the early decades of this century. After noting that some syphilis patients improved after getting malaria and that syphilis was rare in areas where malaria was common, he intentionally infected thousands of syphilis patients with malaria. In an era when fewer than one in a hundred syphilis patients recovered, this treatment achieved remission rates of 30 percent, an advance that made Wagner-Jauregg worthy of his 1927 Nobel Prize in Physiology or Medicine. At that time, the value of fever was much more widely recognized than it is now.

Doctors still say, as the joke goes, "Take two aspirin and call me in the morning." This isn't so surprising, given that only a few human studies have tried to evaluate fever as an adaptation to combat infection. In one study, children with chicken pox who were given aceta-

minophen took on average about a day longer to recover than those who took a placebo (sugar pill). In another study, fifty-six volunteers got colds on purpose, from an infectious nasal spray. Some then took aspirin or acetaminophen, others a placebo. The placebo group had a significantly higher antibody response and less nasal stuffiness. They also had a slightly shorter period of infectious dispersal of viruses. The paucity of detailed studies of this sort, given that so many drugs are used to relieve the symptoms of so many infectious diseases in so many patients, shows the reluctance to study the adaptive aspects of unpleasant symptoms.

This may be about to change. Dr. Dennis Stevens, professor of medicine at the University of Washington, cites "evidence that treating a fever in certain circumstances actually may make it more likely the patient will develop septic shock." Medications that block fever apparently interfere with the normal mechanisms that regulate the body's response to infection, with results that may be fatal.

Before going on to other defenses, we should emphasize that a given expression of a defense need not be adaptive, and that even when it is, it may not be essential. We would not dream of recommending that people never take drugs to reduce fever. Even if many studies were to establish decisively that fever is usually important for combating infection, that would not justify an unbending policy of encouraging fever or even of routinely letting it rise to its natural level. An evolutionary perspective draws attention to the costs as well as the benefits of an adaptation like fever. If there were no compensating disadvantage in having the human body operate at 40° C. (103° F.), it ought to stay at that temperature all the time, so as to prevent infections from ever getting started. But even this moderate fever has costs; it depletes nutrient reserves 20 percent faster and causes temporary male sterility. Still higher fevers can cause delirium and perhaps seizures and lasting tissue damage. It should also be realized that no regulation mechanism can perfectly anticipate all situations. We would expect temperature to rise, on average, to a level close to an optimum to fight infection, but because regulatory precision is limited, fever will sometimes rise too much and at other times not enough.

Even if we knew that it would prolong an infection, we would still sometimes want to block fever. Maintaining and improving health are, after all, not the only goals of medicine. If she is about to sing Nanetta in a Metropolitan Opera performance of *Falstaff*, soprano

Barbara Bonney might well decide to take a medication to relieve a touch of laryngitis, even if she knew it might delay her complete recovery. The rest of us may choose to take drugs just to feel better during a cold, even though our recovery might be slower.

The important point, with respect to the adaptive significance of fever, is that we need to know what we are doing before we interfere with it. At present we don't. If discomfort were the whole story, we could always choose to reduce or eliminate it. But if reducing fever will often delay recovery or increase the likelihood of secondary infection, we should interfere only when the expected gain is worth the risk. We hope that medical research will soon produce the evidence to help doctors and patients decide when fever is and is not useful.

Iron Withholding

Our bodies have a related defense mechanism, of which most people are unaware and which physicians sometimes unwittingly attempt to frustrate. Here are some clues about how it works. A patient with chronic tuberculosis is found to have a low level of iron in his blood. A physician concludes that correcting the anemia may increase the patient's resistance, so she gives him an iron supplement. The patient's infection gets worse. Another clue: Zulu men often drink beer made in iron pots and often get serious liver infections caused by an amoeba. In contrast, less than 10 percent of Masai tribesmen have amoebic infections. They are herdsmen and drink large amounts of milk. When a group of Masai were given iron supplements, 88 percent soon got an amoebic infection. In another study, well-meaning investigators gave iron to supplement the low levels found in Somali nomads. At the end of one month, 38 percent had infections versus 8 percent of those who had not taken the supplements.

Yet another clue: eggs are a rich source of nutrients, but their porous shells can be readily penetrated by bacteria. So how can eggs stay fresh so long? They contain lots of iron, but it is all in the yolk, none in the surrounding white. Egg white protein is 12 percent conalbumin, a molecule whose structure tightly binds iron and thereby withholds it from any bacteria that might get in. Prior to the antibiotic era, egg whites were used to treat infections.

The protein in human milk is 20 percent lactoferrin, another molecule designed to bind iron. Cow's milk has only about 2 percent lactoferrin, and breast-fed babies consequently have fewer infections than those fed from bottles. Lactoferrin is also concentrated in tears and saliva and especially at wounds, where an elevated acidity makes it especially efficient in binding iron. The researchers who discovered conalbumin predicted that there should be a similar molecule to bind iron within the body. This led to the discovery of transferrin, another protein that binds iron tightly. Transferrin releases iron only to cells that carry special recognition markers. Bacteria lack the needed code and can't get the iron. People suffering from protein deprivation may have levels of transferrin less than 10 percent of normal. If they receive iron supplements before the body has time to rebuild its supply of transferrin, free iron in the blood makes fatal infections likely—as has been a tragic outcome of some attempts to relieve victims of famine.

By now the nature of this defense is surely obvious. Iron is a crucial and scarce resource for bacteria, and their hosts have evolved a wide variety of mechanisms to keep them from getting it. In the presence of infection, the body releases a chemical called *leukocyte endogenous mediator* (LEM), which both raises body temperature and greatly decreases the availability of iron in the blood. Iron absorption by the gut is also decreased during infection. Even our food preferences change. In the midst of a bout of influenza, such iron-rich foods as ham and eggs suddenly seem disgusting; we prefer tea and toast. This is just the ticket for keeping iron away from pathogens. We tend now to think of bloodletting as an example of early medical ignorance, but perhaps, as Kluger has suggested, it did help some patients by lowering their iron levels.

It became clear in the 1970s that low iron levels associated with disease could be helpful, not harmful, but even now, Kluger and his associates find that only 11 percent of physicians and 6 percent of pharmacists know that iron supplementation may harm patients who have infections. Although the sample was small, the study illustrates the difficulty of making clinicians aware of some established scientific findings. Even top researchers may neglect to mention this adaptive mechanism. A recent study in *The New England Journal of Medicine* showed that children with cerebral malaria were more likely to recover if they were treated with a chemical that

binds iron, but the article did not describe the body's natural system for binding iron during infection. The evolved mechanism that regulates iron binding is but one specific illustration of the broader principle that we should be careful to distinguish defenses from other manifestations of infection, slow to conclude that a bodily response is maladaptive, and cautious about overriding defensive responses. In short, we should respect the evolved wisdom of the body.

STRATEGIES AND COUNTERSTRATEGIES

Medical researchers are not the only ones who deal with conflicts between organisms. Ecologists and animal-behavior specialists routinely deal with predator–prey relationships, struggles between males for mating opportunities, and many other sorts of conflict. They recognize the evolutionary significance of the phenomena they observe and use such terms as *strategy* and *tactic*, *winner* and *loser*, and other indications of commitment to the adaptationist program. This approach has been richly rewarding for ecologists and others who are steeped in Darwinism. A similar approach to phenomena such as fever ought to be similarly rewarding in a field of such vital interest to all of us.

The contest between parasites and their hosts is a war, and every sign and symptom of infection can be understood in relation to the underlying strategies of one or the other belligerent. Some, like fever and iron withholding, benefit the host (defenses); others benefit the pathogen; and a few are incidental effects of the war between them. The strategies are not, of course, products of conscious thought, but they are strategies nonetheless. Bacteria that sneak into the body by pretending to be harmless are rather like Greek soldiers hiding in a wooden horse. When the manifestations of infection are related to conflicting interests, they fit neatly into categories based on their functional importance. Table 3-1 gives an overview of these categories and a guide to the organization of this chapter.

TABLE 3-1 A CLASSIFICATION OF PHENOMENA ASSOCIATED WITH INFECTIOUS DISEASE

OBSERVATION	EXAMPLES	BENEFICIARY
Hygienic measures taken by host	Killing mosquitoes, avoiding sick neighbors, avoiding excrement	Host
Host defenses	Fever, iron withholding, sneezing, vomiting, immune response	Host
Repair of damage by host	Regeneration of tissues	Host
Compensation for damage by host	Chewing on other side to avoid tooth pain	Host
Damage to host tissues by pathogen	Tooth decay, harm to liver in hepatitis	Neither
Impairment of host by pathogen	Ineffective chewing, decreased detoxification	Neither
Evasion of host defenses by pathogen	Molecular mimicry, change in antigens	Pathogen
Attack on host defenses by pathogen	Destruction of white blood cells	Pathogen
Uptake and use of nutrients by pathogen	Growth and proliferation of trypanosomes	Pathogen
Dispersal of pathogen	Transfer of blood parasite to new host by mosquito	Pathogen
Manipulation of host by pathogen	Exaggerated sneezing or diarrhea, behavioral changes	Pathogen

How can a host guard against infection? First, it can avoid exposure to pathogens. Second, it can erect barriers to keep them out of the body and act quickly to defend and repair any breaches in the defenses. If pathogens do get beyond the outer ramparts, it can flag any cells that lack proof of identity and expel them from their entry portal. If they have breached this defense line, it can poke holes in them, poison them, starve them, do whatever is necessary to kill them. And if all this does not work, it can wall them off so that they cannot reproduce and spread. If they have done damage, it can repair it. If the damage can't be repaired immediately, it can compensate for

it in some way. Some of this damage and the resulting impairment benefit neither the host nor the pathogen. They are, like the aging bomb craters on the coast of France, just incidental relics of an old battle.

The pathogens will not, of course, give up readily. Our bodies are, after all, their homes and dinners. We understandably tend to see bacteria and viruses as evils, but how anthropocentric this is! Our defenses attempt to prevent the poor streptococcus from getting even a microgram of our body tissues, but if it cannot find a way around our defenses, it will die. So, for each of our defenses, pathogens have evolved counterdefenses. They find ways to get transmitted to us and ways to breach our walls. Once inside, they hide from our sentries, attack our defenses, use our nutrients to make copies of themselves, and find ways to get those copies out of the body and to new victims, often by turning our own defenses to their own advantage. Before describing the clever stratagems used by pathogens to elude our defenses, we will discuss the defenses in more detail.

HYGIENE

The best defense is avoidance of danger; proper hygiene can prevent a pathogen from gaining that first toehold. Instinctively slapping at a mosquito is not just an attempt to spare oneself the minor annoyance of a mosquito bite. It may also prevent a long list of serious insect-borne diseases, of which malaria is the best known. Is the itch of a mosquito bite just part of the insect's nastiness? It may be merely an accidental result of the chemicals the mosquito uses to ensure that our blood flows freely, but it may also be our adaptation for avoiding future bites. Imagine what would happen to a person who did not mind being bitten by mosquitoes. And imagine how successful a mosquito could be if its biting were not noticeable!

Our tendencies to avoid contact with people who may be infectious may have the same significance. Likewise, an instinctive disgust motivates us to avoid feces, vomit, and other sources of contagion. Our tendency to defecate away from others may prevent the infection of close associates, and social pressures to conform to such practices may protect us from infection by others. The best defense

against infection is avoidance of pathogens, and natural selection has shaped many mechanisms to help us keep our distance.

THE SKIN

Our skin is like the wall around an ancient city, a formidable protective barrier. It not only prevents the entry of parasites but also protects against injury by mechanical, thermal, and chemical forces. Unlike induced defenses such as fever, which are aroused only when a particular danger threatens, the skin is constantly present, always on guard. It is tough and much more resistant to puncture and abrasion than the internal tissues it protects. Minor infections here and there are harmless because the skin is constantly being sloughed off the top and renewed from below. An ink stain on the fingers will be gone in a few days, not because the ink has been absorbed or chemically altered but because the stained cells are replaced by others rising from below. Fungal growths or other potential pathogens in surface cells are constantly cast off by this rapid replacement of the epidermis. Sycamores and shagbark hickory trees seem to use the same strategy.

Not only is the skin a good defensive armor in general, it is also good in particular. Those parts of the body that are most in need of armor, such as the soles of the feet, have thicker and tougher skin right from birth. Any particular patch of skin that is subjected to repeated friction, like that at the top edge of a shoe or the tip of a cellist's finger, grows the thicker skin we call a callus. This adaptive growth, an induced defense, not only minimizes mechanical injury, it also prevents breaks in the skin that could provide entrances for pathogens.

Some of our most useful hygienic behaviors help maintain the skin's barrier. The most obvious are behaviors that keep nasty things off the skin. Scratching and other grooming maneuvers remove external parasites, important sources of discomfort and disease transmission for most people during most of human history and still problems in less fortunate societies. Benjamin Hart, a veterinarian from the University of California at Davis, has shown just how crucial grooming is to preventing illness in animals. An animal that cannot groom is quickly infested with fleas, ticks, lice and mites, and will

lose weight and fall ill. The mutual grooming of monkeys is not just a ritual, it is preventive health care.

Pain and Malaise

Just as an itch can motivate defensive scratching, pain is an adaptation that can lead to escape and avoidance. The skin, sensibly enough, is highly sensitive to pain. If it is being damaged, something is clearly wrong, and all other activities should be dropped until the damage is stopped and repair can begin. Other kinds of pain can also be helpful. While an abstract realization that chewing is impaired because of an abscessed tooth might possibly lead to more chewing with other, unimpaired teeth, the tormenting pain of a toothache far more effectively prevents the pressure on the tooth that would delay healing and spread bacteria. Continued pain from infection or injury is adaptive because continued use of damaged tissue may compromise the effectiveness of other adaptations, such as tissue reconstruction and antibody attacks on bacteria. Pain motivates us to escape quickly when our bodies are being damaged, and the memory of the pain teaches us to avoid the same situation in the future.

The simplest way to determine the function of an organ like the thyroid gland is to take it out and then see how the organism malfunctions. The capacity for pain cannot be removed, but very occasionally someone is born without it. Such a pain-free life might seem fortunate, but it is not. People who cannot feel pain don't experience discomfort from staying in the same position for long periods, and the resulting lack of fidgeting impairs the blood supply to the joints, which then deteriorate by adolescence. People who cannot feel pain are nearly all dead by age thirty.

Generalized aches and pains, or merely feeling out of sorts (malaise, in medical terminology), are also adaptive. They encourage a general inactivity, not just disuse of damaged parts. That this is adaptive is widely recognized in the belief that it is wise to stay in bed when you are sick. Inactivity also likely favors the effectiveness of immunological defenses, repair of damaged tissues, and other host adaptations. Medication that merely makes a sick person feel less sick will interfere with these benefits. This is fine when patients are

well informed about the risks and realize that they are sicker than they feel and should make a special effort to take it easy. Otherwise, a drug-induced feeling of well-being may lead to activity levels that interfere with defensive adaptations or repairs.

Defenses Based on Expulsion

The body must have openings for breathing, for the intake of nutrients and expulsion of wastes, and for reproduction. Each of these openings offers pathogens an invasion route, and each is endowed with special defense mechanisms. The constant washing of the mouth with saliva kills some pathogens and dislodges others so they can be destroyed by the acid and enzymes in the stomach. The eyes are washed by tears laden with defensive chemicals and the respiratory system by antibody and enzyme-rich secretions that are steadily propelled up to the throat, where they can be swallowed so the invaders can be killed and the protein in the mucus recycled. The ears secrete an antibacterial wax. Projections inside the nose, called turbinates, provide a large surface that warms, moistens, and filters pathogens from the incoming air. Mouth-breathers don't get the full benefit of this defense and are more subject to infection. The nose and ears have hairs strategically arrayed to keep out insects.

The defenses at each body opening can be quickly increased if danger threatens. Irritation of the nose by a viral infection provokes the discharge of such copious mucus that one can go through a whole box of tissues in a day. Millions of people use nasal sprays each year to block this useful response, but there are remarkably few studies that have investigated whether the use of such devices delays recovery from a cold. If they do not demonstrably delay recovery, as seems to be the case from the limited data, it would be evidence that a runny nose is not a defense but an example of a pathogen manipulating the host's physiology in order to spread itself. Sneezing is obviously a defensive adaptation, but not every sneeze need be adaptive for the sneezer. Some sneezing may possibly be an adaptation that viruses use to disperse themselves.

Irritation deeper in the respiratory tract induces coughing. Coughing is made possible by an elaborate mechanism that involves detect-

ing foreign matter, processing this information in the brain, stimulating a cough center at the base of the brain, and then coordinating muscle contractions in the chest, the diaphragm, and the tubes in the respiratory tract. All along the lining of these tubes tiny hairs called cilia beat in a steady rhythm, sweeping pathogen-trapping mucus upward. In the urinary tract, periodic flushing washes pathogens away along with the cells on the surface of the urethral lining, which are systematically shed like those on the skin. When the bladder or urethra becomes infected, urination understandably becomes more frequent.

The digestive system has its own special defenses. Bacterial decomposition and fungal growths produce repulsive odors, the repulsiveness being our adaptation to be disinclined to put bad-smelling things into our mouths. If something already in the mouth tastes bad, we spit it out. Taste receptors detect bitter substances that are likely to be poisonous. After we swallow something, there are receptors in the stomach to detect poisons, especially those made by bacteria that multiply in the gastrointestinal tract. When absorbed toxins enter the circulation, they pass by a special group of cells in the brain, the only brain cells directly exposed to the blood. When these cells detect toxins, they stimulate the brain's chemoreceptor trigger zone to respond first with nausea and then with vomiting. This is why so many drugs are so nauseating, especially the toxic ones used for cancer chemotherapy.

Circulating toxins almost always originate in the stomach, so it is easy to see how vomiting is useful: it ejects the toxin before more is absorbed. What about nausea? The distress of nausea discourages us from eating more of the noxious substance, and its memory discourages future sampling of whatever food seemed to cause it. Just a single experience of nausea and vomiting after eating a novel food will cause rats to avoid it for months; people may avoid it for years. This remarkably strong onetime learning was named the "sauce béarnaise syndrome" by Martin Seligman, a psychologist who recognized its significance after contemplating the untimely loss of his gourmet dinner. Why is the body capable of such a strong association after a single exposure to a food that produces illness? Imagine, for a moment, what would happen to the person who ate poisonous foods repeatedly.

The other end of the intestinal tract has its own defense, diarrhea. People understandably want to stop diarrhea, but if relief comes from merely blocking the defense, there is likely to be some

penalty. Indeed, H. L. DuPont and Richard Hornick, infectious disease experts at the University of Texas, found just this. They infected twenty-five volunteers with *Shigella*, a bacterium that induces severe diarrhea. Those who were treated with drugs to stop the diarrhea stayed feverish and toxic twice as long as those who did not. Five out of six who received the antidiarrheal drug Lomotil continued to have *Shigella* in their stools, compared to two out of six who did not receive the drug. The researchers concluded, "Lomotil may be contraindicated in shigellosis. Diarrhea may represent a defense mechanism." Consumers will no doubt want to know when they should and should not take such medications for more commonplace diarrhea, but the needed research has not been done. There are dozens of studies of side effects, of safety, and of the effectiveness of medications that block diarrhea, but few consider the consequences of the main effect of blocking a normal defense.

Our reproductive machinery requires yet another opening, which in males is the same as that of the urinary tract, whose defenses thereby do double duty. Women have a separate opening that poses a special problem for defense against infection. While the female reproductive tract uses many defenses, such as cervical mucus and its antibacterial properties, one largely unappreciated defense is the normal outward movement of secretions that makes it difficult for bacteria and viruses to gain access. These secretions move steadily from the abdominal cavity through the fallopian tubes, uterus, cervix, and vagina to the outside. There is one noteworthy exception to this constant downstream movement. Sperm cells swim upstream, from the vagina through the uterus into the fallopian tubes and the pelvic cavity. Unusually small for human cells, sperm are still large compared to bacteria. Potential pathogens can stick to sperm cells and be transported from the outside to deep within a woman's reproductive system.

Only recently has the threat of sperm-borne pathogens been recognized. Biologist Margie Profet notes that menstruation has substantial costs and argues that it must therefore give some compensating benefit. After a consideration of the evidence, she concluded that many aspects of menstruation seem designed as an effective defense against uterine infection. The same anti-infection benefits that come from sloughing off skin cells are achieved by the periodic extrusion of the lining of the uterus. This is supported by evidence that menstrual blood differs from circulating blood in ways

that make it more effective in destroying pathogens while minimizing losses of nutrients. Studies of menstruation in other mammals suggest that each species menstruates to just the extent appropriate for its vulnerability to sperm-borne pathogens. The threat is small for species that restrict their sexual behavior to widely separated fertile periods, but women's continuous sexual attractiveness and receptivity are largely unrelated to the ovulatory cycle. This extraordinary amount of human sexual activity may have its benefits, as we will discuss in Chapter 13, but it substantially increases the risk of infection. This risk may be responsible for the unusually profuse human menstrual discharge, as compared to other mammals'.

We have mentioned several times that evolutionary hypotheses need to be and can be tested. Beverly Strassmann has mounted a challenge to the hypothesis that menstruation protects against infection. She maintains that the pathogen load in the reproductive tract is the same before and after menstruation, that menstruation does not increase when there is infection, and that there is no consistent relationship between the amount of sperm females in a particular species are exposed to and the amount of menstrual flow. As an alternative explanation, Strassmann proposes that the degree of shedding or reabsorption of the uterine lining depends on the metabolic costs of maintaining it or shedding it, a hypothesis that she supports with comparisons between species and the relationship between menstruation and the body weight of the female and her neonate. Obviously, we have not heard the last word on this issue.

Mechanisms to Attack Invaders

Vertebrates in general, and mammals in particular, have amazingly effective immunological defenses that are in essence a system of carefully targeted chemical warfare. Cells called macrophages constantly wander the body searching for any foreign protein, whether from a bacterium, a bit of dirt in the skin, or a cancer cell. When they find such an intruder, the macrophages transfer it to a helper T cell, which then finds and stimulates whichever white blood cells can make a protein (called an *antibody*) that binds specifically to that particular foreign protein (an *antigen*). Antibodies bind to antigens on the surfaces of bacteria,

thereby impairing the bacteria and also labeling them for attack by specialized larger cells. If the antigens persist, say during a continuing bacterial infection, they stimulate the production of ever more of the cells that make that specific antibody, so that the bacteria are destroyed at an ever-increasing rate. Whatever is recognized as a properly functioning part of the body is permitted to remain. All else—disease organisms, cancerous tissue, organs transplanted from other individuals—is attacked.

How does the body recognize cells as its own? Each cell has a molecular pattern on its surface, called the *major histocompatibility complex* (MHC), which is like a photo ID card. Cells that have a valid MHC are left alone, but those that have a foreign or missing MHC are attacked. Interestingly, when cells are infected, they transport protein from the invader to the MHC, where it is bound. Like individuals with obviously fake ID cards, such cells are priority targets for the killer cells of the immune system. The adenovirus, a common cause of sore throats, has found a way to get around this defense. It makes a protein that blocks the ability of the cell to move foreign proteins to the MHC. In essence, it prevents the infected cell from signaling that it has been invaded.

The operation of the MHC system is a vivid example of altruism in its biological sense. An infected cell "volunteers" for destruction for the good of the rest of the body. This is like a soldier with plague asking his comrades to destroy him before he infects them. The analogy, however, is false in one crucial respect. The cell's comrades are genetically identical, and its only chance for passing on its genes lies in the success of the whole organism. Soldiers, however, seldom share foxholes with identical twins and are understandably less likely to volunteer for elimination.

The weapons of the immune system are truly fearsome. They include general inflammation, several kinds of antibodies—each specialized for a different group of opponents—and a series of chemicals (the complement system), five of which attack the targeted cells, boring holes in their membranes and digesting them. Despite these weapons, some invaders can nonetheless persist. When a clump of bacteria can be neither expelled nor destroyed, it may be walled off by a membrane that keeps it away from vulnerable tissues. The tubercles from which tuberculosis gets its name are the best-known example, but analogous imprisonment of roundworms and other multicellular parasites has also been important throughout most of human evolution.

DAMAGE AND REPAIR

In the contest with their host, pathogens must rob the host to secure their own nourishment. Various bacteria and the protozoa that causes amoebic dysentery secrete enzymes that digest nearby host tissues and then absorb the products of digestion. Others literally eat through host tissues, for example, filaria worms, which live in the anterior part of the eye, or the larvae of another species of worm, *Angiostrongylus cantonensis*, which burrow through the brain. Both of these defend themselves with secretions that inhibit inflammation. Still others, such as the trypanosomes, a group of protozoans that cause diseases such as African sleeping sickness, live in the bloodstream and absorb nutrients directly from the plasma. Whatever the means, parasites secure their resources from the host and then use them for their own maintenance, growth, and reproduction.

These activities of pathogens incidentally damage the host, but this damage is not a pathogen adaptation. It does not do a tapeworm any good to have its host malnourished. It does not do the malarial parasite any good to destroy its host's blood cells (unless, perhaps, this frees up iron for use by the parasite). Most often, the opposite must be true. The survival and well-being of the parasite depend on the host's continued survival and ability to provide it with nourishment and shelter. Such incidental damage must therefore be considered a cost to both host and pathogen.

The cost may be a general reduction in host resources or an obviously localized destruction. Bacteria that attack bone where a tooth is rooted cause structural damage and perhaps the loss of the tooth. The bacteria that cause gonorrhea may erode the connective tissue and cartilage of joints, causing functional impairment. Hepatitis viruses may destroy substantial portions of the liver, so that all liver functions, such as the clearing of toxins from the blood, become less effective. Such functional impairments are simply incidental consequences of pathogen adaptations. It does not do bacteria any good to make the host's chewing less effective or its running less rapid.

It's important to keep damage conceptually separate from any resulting functional impairment. The damage causes the impairment, which can then itself be a cause for another host adaptation, which we call *compensatory adjustment*. There are many examples, some

much more subtle than chewing on the left side of your mouth if it hurts to chew on the right. For instance, when disease-damaged lungs become less effective at oxygenating the blood, this may be partly compensated for by an increase in blood hemoglobin concentration. The body has a mechanism that monitors the oxygen level in the blood. If there is too little, whether from living at a high altitude or from lung damage, the body makes more erythropoietin, a hormone that stimulates the production of more red blood cells.

Another obvious host adaptation is repair of damage. Natural selection has adjusted the ability to regenerate various tissues according to how useful it would normally be to do so. The skin, which is often damaged, is a first line of defense against pathogens and injuries. As might be expected, it quickly regenerates and rapidly recovers its protective capabilities. Other structures that regenerate quickly are the lining of the gut and organs such as the liver, which are in open communication with the gut and therefore with the outside world and its infectious agents. By contrast, the heart and especially the brain are less accessible to most pathogens. If pathogens do gain access and cause serious damage, it is ordinarily fatal, so regenerative capabilities would rarely be of benefit.

Pathogen Evasion of Host Defenses

So far we have mentioned only one kind of pathogen adaptation, the ability to nourish itself in the body of the host. We can also expect it to have evolved ways of shielding itself from the host's efforts to destroy, expel, or sequester it. We will now turn to one such mechanism, *evasion of host defenses.*

The first trick for many parasites, once inside the body, is to gain entrance to cells. Invaders may accomplish this just as door-to-door peddlers do, by appearing to offer something else. The rabies virus binds to acetylcholine receptors as if it were a useful neurotransmitter; the cowpox virus to epidermal growth-factor receptors as if it were a hormone; and the Epstein-Barr virus (which causes mononucleosis) to a C4 receptor. Rhinovirus, a common cause of colds, binds to the intercellular adhesion molecule (ICAM) on the surface of the lymphocytes that line the respiratory tract. This is extremely clever, since attacking lymphocytes releases chemicals that greatly

increase the number of ICAM binding sites, thus providing many more openings by which the virus can enter cells.

Another trick is to evade the immune system. The trypanosome that causes African sleeping sickness does this by rapidly changing its disguises. It takes the body about ten days to make enough antibodies to control the trypanosome, but on about the ninth day, the trypanosome changes its disguise by exposing an entirely new surface layer of proteins, thus escaping attack by the antibodies. The trypanosome has genes for more than a thousand different antigenic coats and so can live on for years in the human host, always one step ahead of the immune system. Two other common bacteria use similar strategies. *Hemophilus influenza*, a common cause of meningitis and ear infections, and *Neisseria gonorrhoeae*, the cause of gonorrhea, both have what seem to be flaws in the genetic mechanisms that make their surface proteins. The seeming errors are useful, however, because the resulting variation makes it hard for our immune systems to keep up with the random changes.

Malarial parasites have special surface proteins that allow them to bind to the walls of blood vessels so that they are not swept to the spleen, where they would be filtered out and killed. The genes that code for these binding proteins in malarial parasites mutate at a rate of 2 percent per generation, just enough so that the immune system cannot lock in on the organism. The pneumococcal bacteria that cause pneumonia use a different trick to circumvent the immune system. They have "slippery" polysaccharides on their surface that white blood cells can't get a grip on. The body copes with this by making chemicals called opsonins, which bind to the microbe like handles that the antibodies can grab.

Another common evasion is a chemical analog of a disguise a spy might use behind enemy lines. The external chemistry of some bacteria and some worms is so similar to that of human cells that the host may have difficulty in recognizing them as foreign. (Thus antibodies sometimes attack both invader and host cells.) The streptococcus bacterium, a longtime associate of humans, is especially adept at this trick. The antibodies to some strains cause rheumatic fever, in which a person's antibodies attack his or her own joints and heart. Similar antibody attack on nerve cells in the basal ganglia of the brain can cause Sydenham's chorea, with its characteristic uncontrollable muscle twitches. Interestingly, many patients who have obsessive-compulsive disorder, a psychiatric illness characterized by excessive

hand washing and fear of accidentally harming others, had Sydenham's chorea in childhood. There is now growing evidence that the brain areas involved in obsessive-compulsive disorder are very close to those damaged by Sydenham's chorea. Thus, some cases of obsessive-compulsive disorder may result from the arms race between the streptococcus and the immune system.

Chlamydia, today's most common cause of venereal disease, does the equivalent of hiding in the police station. It enters white blood cells and then builds a wall to prevent itself from being digested. Schistosomes of the *mansoni* type go a step further and essentially steal police uniforms. These parasites, a serious cause of liver disease in Asia, pick up blood-group antigens so that they may look to the immune system like our own normal blood cells.

Attack on Host Defenses

Pathogens not only attempt to shield themselves from the weaponry of the host, they also have destructive weaponry of their own. The bacterium that causes most simple skin infections, *Staphylococcus aureus*, secretes a neuropeptide that blocks the action of Hageman's factor, a crucial first step in useful inflammation. Bacteria that cannot secrete this peptide do not cause infection. Even the common streptococcal bacteria that cause so many sore throats make streptolysin-O, which kills white blood cells. Vaccinia, the virus that causes cowpox, makes a protein that inhibits the complement system, an important host defense, as noted previously. Why doesn't the complement system attack our own cells? In part because our cells have a layer of sialic acid, a chemical that protects them from attack by the complement system. Sure enough, certain bacteria, in this case the K1 strain of the common *E. coli* that live in our guts, are able to cover themselves in sialic acid and thus gain protection from the complement system.

One of the great dangers of serious infection with certain kinds of bacteria is shock, a decrease in blood pressure that can be rapidly fatal. Shock is caused by chemical lipopolysaccharide (LPS) formed by the bacteria. Superficially, it would seem that LPS is a toxin made by bacteria to harm us, but, as researcher Edmund LeGrand has noted, this is unlikely, because LPS is a necessary component of the

cell wall of this whole group of bacteria. Hosts recognize this reliable cue to the presence of dangerous infection and react strongly—sometimes too strongly. Here is an example of a defensive weapon that can turn on its bearer.

The human immunodeficiency virus (HIV), the virus that causes AIDS, hides in the helper T cells that bring antigens to the attention of the immune system. These cells have a protein in their outer membrane called CD-4, to which the HIV binds to gain entrance to cells. This protein on HIV would make it vulnerable to the immune system, except that it is hidden in deep crevices in the viral wall. As HIV kills helper T cells, it incidentally causes the victim to be ever more vulnerable to other infections and cancer, the problems that eventually kill a person who has AIDS.

Other Pathogen Adaptations

There remain two related categories of parasite adaptation. No matter how well a pathogen survives and proliferates in a host, it must have a dispersal mechanism so that it can get itself or its descendants into other hosts. For external parasites this can be rather easy. Lice and the fungus that causes ringworm, for example, are readily spread by personal contact. Internal parasites face greater problems. Those that can regularly get onto the skin have the possibility of contact with other susceptible individuals. Cold viruses and intestinal bacteria may get onto hands or other surfaces and be spread by handshakes or more intimate contact.

Microorganisms in the bloodstream are not likely to be spread in this way. Many can be transmitted only with the help of biting insects or other transport agents (vectors). Malaria is a well-known example. If there are about ten malarial parasites in the dispersal stage (called gametocytes) in each milligram of blood and a mosquito sucks up three milligrams, it will be taking in about thirty gametocytes. The next item on the mosquito's agenda is to convert this rich blood meal into eggs and get them fertilized and laid in an environment suitable for development. Meanwhile, the sexually produced offspring of the malarial plasmodia have migrated to the mosquito's salivary glands, where they transform into an infectious stage in the fluid that will be used to inhibit clotting when the mosquito sucks up its next blood

meal. The mosquito then unwittingly injects the plasmodia into the next victim. An enormous variety of insects and other organisms can serve as vectors of human diseases.

Another kind of parasitic adaptation is technically termed *host manipulation*. By subtle chemical influence a parasite may gain some control over the machinery of the host's body and cause that machinery to serve the interests of parasite rather than host. Many curious examples are known from many groups of organisms. The tobacco mosaic virus causes its host to enlarge the pores between adjacent tobacco cells enough to allow the virus particles to pass through and infect other cells. One kind of parasitic worm alternates its life stages between ants and sheep, just as malarial parasites must alternate between vertebrate hosts and mosquitoes. The worm is effectively transmitted from an ant to a sheep because it enters certain sites in the ant's nervous system where it causes the ant to climb to the top of a blade of grass and hang on, unable to let go. This greatly increases the likelihood that the ant will be eaten by a sheep. Another kind of worm alternates between snails and gulls. It causes the snail, which is ordinarily hard to find in the tangled growths of shallow coastal waters, to crawl up to a high level of bare rock or sand and stay there. It is then easily seen and eaten by a gull.

The rabies virus offers a particularly remarkable and gruesome example of how a pathogen can manipulate a host's behavior. After gaining entrance to the body, usually via the bite of an infected individual, the rabies virus moves along nerve fibers to the brain, where it concentrates in regions that regulate aggression. It can then make the host attack and bite, thereby infecting other individuals. It also paralyzes the victim's swallowing muscles, thus causing virus-laden saliva to build up in the mouth, increasing the likelihood of transmission and incidentally causing the victim to have the terror of choking on fluids that originally gave the disease the name hydrophobia.

Perhaps the most important human examples of manipulation by pathogens are the sneezing, coughing, vomiting, and diarrhea triggered by bacteria and viruses. At some stage in the history of an infection, this expulsion will serve the interests of both host and microbe. The host is benefited by having fewer pathogens attacking its tissues, the microbe by an increased chance of finding other hosts. The losers in this game are currently healthy but vulnerable individuals. A chemical released by cholera bacteria reduces absorption of liquid from the bowel, causing profuse diarrhea that, in a society without

well-developed public hygiene, can effectively spread an epidemic.

Sometimes we are successfully manipulated by our parasites, at other times we successfully resist manipulation, and in still other situations there is some intermediate resolution. Any given example of such a conflict is likely to be at an evolutionary equilibrium and have a consistent outcome. Conflicts are often decided in favor of the antagonist that has the most to gain from winning. If someone is sneezing twice as often as would be ideal for the control of a cold virus, that is not likely to be a great burden of lost time or energy, but it may nearly double the rate at which the virus reaches new hosts. This is just the sort of contest we would expect the virus to win. How frequently are expulsion mechanisms exaggerated by pathogens beyond what would be optimal to a human host? The paucity of evidence on this issue shows the habitual neglect of such evolutionary questions.

A Functional Approach to Disease

We end this chapter by making three remarks about Table 3-1 (page 32), which classifies the signs and symptoms of infectious disease according to their functions. First, a functional classification of the signs and symptoms of disease is important and useful. In order to choose appropriate treatment, we need to know if the cough, or other symptom, benefits the patient or the pathogen. We also need to know if the pathogen is manipulating the host or attacking its defenses. Instead of just relieving symptoms and trying, perhaps ineffectively, to kill the pathogen, we can analyze its strategies, try to oppose each of them, and try to assist the host in its efforts to overcome the pathogen and repair the damage. The second point is that the classification is really rather simple and obvious.

Now for the third point: When and by whom do you think the ideas in this chapter were first proposed? Was it by some nineteenth-century medical researcher building on the ideas of Pasteur and Darwin as well as the rapidly expanding body of knowledge of parasite life histories? No. The classification scheme used in our table and throughout this chapter was first proposed at the University of Michigan in 1980 by Paul Ewald, an ornithologist and evolutionary

biologist now at Amherst College. And when did the ideas in this chapter first become standard elements in the thinking of physicians and medical researchers? The answer to this question is a simple and discouraging *not yet*. We do not mean that physicians never intuitively think in the categories formalized by Ewald. We merely mean that they have not been explicitly taught to use them and that deficiencies of training make it easy to neglect these essential ideas in thinking about infectious disease. There is hope, which is especially evident in the proceedings from several recent conferences that have emphasized the benefits of interchange between evolutionists and infectious disease experts. But it will still be years before this sort of material becomes part of the regular medical curriculum.

Why has the medical profession not taken advantage of the help available from evolutionary biology, a well-developed branch of science with great potential for providing medical insights? One reason is surely the pervasive neglect of this branch of science at all educational levels. Religious and other sorts of opposition have minimized the impact in general education of Darwin's contributions to our understanding of ourselves and the world we live in. There has also been a peculiar neglect of evolution in the training of physicians and medical researchers, a matter discussed further in Chapter 15.

Still another reason is that many of the evolutionary ideas of greatest bearing on medicine have only been formulated in recent years. These ideas are often simple and not very different from common sense—once they are pointed out. Yet their recognition and the appreciation of their importance have come only in the past few years, far behind the development and application of many really complex and subtle branches of physical science and molecular biology. Exactly why the application of evolutionary biology to medicine and other aspects of human life has advanced so slowly after its magnificent inception in 1859 is a question that ought to be getting major attention from historians of science.