Malignants in the Body Politic

Redefining War through Metaphor

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Abstract

In the aftermath of 9/11, President George W. Bush declared the dawn of a new kind of war. He has repeatedly emphasized that means and measures of success in this new war will differ greatly from wars past. However, if this "war on terrorism" is unlike any other war, then what *is* it like? From the public statements of high-ranking US officials, metaphorical answers emerge: terrorism is a metastasizing cancer, a plague, a threat from which we are not immune. This study explores the analogies of immunity, infection, and cancer. In doing so it addresses the classic strategic question: What is the nature of the enemy and of the fight? In the never-ending battle against microbes and a 30-year-old "war on cancer," the enemies are microbes and malignancies—threats from without and threats from within. In the context of the announced war on terrorism, I convert these biological and medical themes for reflective contemplation and conclude that the administration might look further to the language of disease to better communicate the challenges of the war on terrorists.

About the Author

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To my family: Later.

Chapter 1

Emerging Metaphors

This will be a different kind of conflict against a different kind of enemy.

—President George W. Bush

International terrorism also demands that we develop new ways of comprehending seemingly familiar problems. The language of "war"—and the images, metaphors, and memories it conjures up from a previous era—does not capture all of the task ahead. . . . I suggest we view international terrorism as analogous to a terrible, lethal virus.

—Dr. Richard N. Haass

In the aftermath of the 9/11 terrorist attacks, President George W. Bush declared the dawn of a new kind of war, "unlike any other we have ever seen."[1] A month later, the noted historian Sir Michael Howard voiced concern that US officials "made a very natural but terrible and irrevocable error" when they misused the term *war.*[2] Invoking war in the struggle against terrorism, Howard asserts, could have "dangerous consequences. To declare that one is at war is immediately to create a war psychosis that may be totally counterproductive for the objective being sought. It arouses an immediate expectation, and demand, for spectacular military action against some easily identifiable adversary, preferably a hostile state—action leading to decisive results."[3] Howard is right in that the word *war* cannot be withdrawn, and the lenses of America's twentieth-century battlefield victories could distort our vision for this new war.

However, less than a day after the attacks, President Bush "'instinctively knew that we were going to have to think differently' about how to fight terrorists."[4] He quickly set out to educate the public and to reshape the lenses through which many might view the conflict:

> How will we fight and win this war? We will direct every resource at our command—every means of diplomacy, every tool of intelligence, every instrument of law enforcement, every financial influence, and every necessary weapon of war—to the disruption and to the defeat of the global terror network. This war will not be like the war against Iraq a decade ago, with a decisive liberation of territory and a swift conclusion. It will not look like the air war above Kosovo two years ago, where no ground troops were used and not a single American was lost in combat. Our response involves far more than instant retaliation and isolated strikes. Americans should not expect one battle, but a lengthy campaign, unlike any other we have ever seen.[5]

In this message one hears no cry for immediate, decisive military action; one hears no promise of quick victory. However, the president's message is clear: our means and methods of war must differ from recent victories because the adversary differs; we need to alter our preconceptions of war.

If the adversary and the war are unlike any others, then what *are* they like? What images and metaphors more fully "capture all of the task ahead"?[6] Rather than summoning images of military battles and adversaries past, the president and his most senior advisors offer disease-related metaphors: "terrorism is a cancer on the human condition," "a plague on all civilized nations," and a threat to which "we are not immune."[7]

This language of disease transcends rhetorical vilification of an adversary. It suggests, depending on the disease terms one adopts, not only the nature of the adversary but also the nature of the war and some broad-based actions with which it might be fought. The State Department's Richard Haass put forth what is, to my knowledge, the most wide-reaching application of disease language to the current crisis:

> Another way of looking at the challenge is to view international terrorism as analogous to a terrible, lethal virus. Terrorism lives as part of the environment. Sometimes dormant, sometimes virulent, it is always present in some form. Like a virus, international terrorism respects no boundaries—moving from country to country, exploiting globalized commerce and communication to spread. It can be particularly malevolent when it can find a supportive host. We therefore need to take appropriate prophylactic measures at home and abroad to prevent terrorism from multiplying and check it from infecting our societies or damaging our lives. We need, for instance, better border control regimes and improved international counterterrorism cooperation across the board. We also need to make sure that the virus does not mutate into something even more deadly through the acquisition of nuclear, biological, or chemical weapons of mass destruction.
>
> The challenge of terrorism is thus akin to fighting a virus in that we can accomplish a great deal but not eradicate the problem. We can take steps to prevent it, protect ourselves from it, and, when an outbreak occurs, quarantine it, minimize the damage it inflicts, and attack it with all our power. Therefore, the ultimate goal of our campaign is progress through the steady accumulation of individual successes. Patience and persistence will be the watchwords for this campaign.[8]

By borrowing the language and concepts of medicine, Haass recast the conceptual framework of the war on terrorism into something very different from traditional American wars—his is a war without a clearly defined victory ahead.

Others also invoke medical and biological metaphors to explain the task ahead. For instance, National Security Advisor Condoleezza Rice stressed protective measures as she announced, "the United States is actively helping countries to improve their immune systems against terrorism."[9] She likened eradication of deadly terrorist cells to surgical intervention: "It's like cutting out a cancer now in 60-plus countries."[10] Deputy Secretary of Defense Paul Wolfowitz might agree. While he spoke of a "plague of terrorists" and the need to "drain the entire swamp," he also sees malignancy in the evil of terrorism. Wolfowitz insists, "Terrorists and their evil influence have spread throughout the world like a cancer. Our response must be correspondingly broad, sustained, and unrelenting."[11] He further states that it is "sort of like a cancer that's spread throughout

the body. I don't know the right analogy, but you don't just clean it up in one place."[12]

This study explores the analogies of immunity, infection, and cancer. In doing so, it addresses the classic strategic question: What is the nature of the enemy and the nature of the fight? In the never-ending battle against microbes and a 30-year-old "war on cancer," the enemies are microbes and malignancies—threats from without and threats from within. In the context of the announced war on terrorism, this study converts the biological and medical themes for reflective contemplation. What it does not do is advance the correct or sole analogy for our quest to rid the body politic of the terrorist blight. It does not claim that the solution to the war on terrorism provides a perfected or simplified parallel to solutions found in the battle against cancer. This study offers no diagnosis, prognosis, or prescription. This is a search for questions, nothing more. Such a search is the foundation of further analysis, a preliminary evaluation of the terrorist disease that threatens us all, and the framework for what may be a fruitful means to a solution.

Overview

Immunology, infectious disease, and cancer biology are enormously vast and complex fields.[13] The following chapters thus focus only on some major themes within these disciplines. The material is written to accommodate readers who have little familiarity with the life sciences. Additionally, this study does not follow standard scientific citation practices. For specialized topic coverage, reference to general reviews or news articles is provided rather than to the original publications. Chapter 2 concentrates on the immune system as a model protection system and outlines general principles underpinning its successes and failures. In so doing, aspects of the microbial threat are introduced and a few major prevention and intervention themes in the battle against infectious disease are explored. Chapter 3 explores the nature of the adversary and of the individual battles in the war on cancer. Chapter 4 considers how one might approach the war on terror in the light of disease-related themes.

Some Notes on Methodology

This is a work of metaphor. There is no mention of terrorism—save in the epigraphs—until the concluding chapter. The intervening chapters are, on the surface, works about biology and medicine. If one reads them literally, one will get a science lesson and nothing more. To proceed beyond the science you must accept, or at least not reject, the assumption that conflict and competition in one area of life—particularly when it involves life and death—*might* reveal strategic concepts relevant to war.

It is also assumed—strictly for purposes of generating ideas—that terrorists *are* infectious agents (chap. 2) or cancer cells (chap. 3). This study views the battle against disease/terror as having a threefold strategic framework: immune system as protection, public health programs as prevention, and medicine as intervention. Within this construct a discussion regarding the nature of cancer cells is also presented as a discussion about the *possible* nature of terrorist cells. A passage about the body's immune system warding off microbial invaders is also a passage about how a state's protective systems *might* ward off terrorist invaders. Talk about medical measures to combat malignancies is also talk about a state's (or the global community's) *potential* intervention strategies against domestic (or international) terrorism.

This study is successful if it achieves any of the following goals: (1) provides useful images—along the lines of those already used by Rice, Wolfowitz, and Haass—to help enrich understanding about the war on terror; (2) induces others to look at seemingly familiar problems and presumed solutions from a slightly different angle; or (3) discovers specific terms with transfer value to the war on terror.[14] The analogies herein breakdown, as do all others. Therefore, this study does not ask that the readers accept a framework by analogy for the entire war on terror.[15] It simply asks readers to consider whether any of the larger concepts resonate and inform.

Notes

1. George W. Bush, address to a joint session of Congress and the American people, 20 September 2001, n.p., on-line, Internet, 20 June 2002, available from http://www.whitehouse.gov/news/releases/2001/09/20010920-8.html.

2. Michael Howard, "What's in a Name? How to Fight Terrorism," *Foreign Affairs* 81, no. 1 (January/February 2002): 8.

3. Ibid., 9.

4. Bob Woodward and Dan Balz, "10 Days in September: Inside the War Cabinet," *Washington Post,* 28 January 2002.

5. Bush; Dr. Condoleezza Rice, national security advisor, press briefing, 19 September 2001, n.p., on-line, Internet, 20 June 2002, available from http://usinfo.state.gov/topical/pol/terror/01091921.htm; and Donald H. Rumsfeld, secretary of defense, "Rumsfeld Says Anti-Terrorism Efforts Are Broad-Based," 25 September 2001, n.p., on-line, Internet, 20 June 2002, available from http://usinfo.state.gov/topical/pol/terror/01092511.htm. While the president discourages comparisons to the Persian Gulf War and the Kosovo operation, Dr. Rice has discouraged comparisons to Pearl Harbor, and Rumsfeld notes how we will not see victory celebrations as in World War II.

6. Richard Haass, "The Bush Administration's Response to Globalization," 21 September 2001, n.p., on-line, Internet, 20 June 2002, available from http://www.state.gov/s/p/rem/5508.htm.

7. The three statements were made by Defense Secretary Rumsfeld, Secretary of State Powell, and President Bush, respectively. Donald H. Rumsfeld, statement, 7 October 2001, No. 491-01, on-line, Internet, 20 June 2002, available from http://www.defenselink.mil/news/Oct2001/b10072001_bt491-01.html; Colin L. Powell, secretary of state, interviewed by Noah Adams, National Public Radio, "All Things Considered," 27 September 2001, n.p.,

on-line, Internet, 20 June 2002, available from http://www.state.gov/secretary/rm/2001/5091.htm; and Bush.

8. Richard Haass, "The Bush Administration's Response to September 11th—and Beyond," 15 October 2001, n.p., on-line, Internet, 20 June 2002, available from http://www.state.gov/s/p/rem/5505.htm.

9. Dr. Condoleezza Rice, remarks to the Conservative Political Action Conference, 1 February 2002, n.p., on-line, Internet, 20 June 2002, available from http://www.whitehouse.gov/news/releases/2002/02/.

10. Dr. Condoleezza Rice, press briefing on the Asia-Pacific Economic Cooperation Meeting, 15 October 2001, n.p., on-line, Internet, 20 June 2002, available from http://www.whitehouse.gov/news/releases/2001/10/20011015-6.html.

11. Dr. Paul Wolfowitz, deputy secretary of defense, interviewed by Indonesian television, 28 November 2001, n.p., on-line, Internet, 20 June 2002, available from http://www.defenselink.mil/news/Dec2001/t12012001_t1128wol.html; and Dr. Paul Wolfowitz, remarks to the American Jewish Congress, 22 October 2001, n.p., on-line, Internet, 20 June 2002, available from http://www.defenselink.mil/speeches/2001/s20011022-depsecdef.html.

12. Dr. Paul Wolfowitz, interviewed by the *Atlanta Journal–Constitution,* 14 January 2002, n.p., on-line, Internet, 20 June 2002, available from http://www.defenselink.mil/news/Jan2002/t01212002_t0114cox.html.

13. The National Library of Medicine's PubMed database, for instance, contains more than 1.1 million cancer-related professional articles.

14. The images and terms will only transfer if readily understood; this study thus uses language suitable for those without a scientific background. Examples of medical terms previously adopted for military use include *surgical* air strikes, the naval *quarantine* of the Cuban missile crisis, and the generally pejorative *antiseptic warfare.*

15. Even if some of the images resonate, readers should avoid any "because cancer cells, thus terrorist cells" type of conclusions. If the nature of terrorists, for instance, seems to share much with the nature of cancer cells, then perhaps the methods for fighting the former can benefit from general principles used in fighting the latter. The images simply suggest areas for more detailed study.

Chapter 2

Threats from Without

September 11th, 2001 . . . set another dividing line in our lives and in the life of our nation. An illusion of immunity was shattered.

—President George W. Bush

Immunity does not prevent attack; it protects one when attacked, but protection is conditional. The mind falls captive to the illusion of immunity when it believes that demonstrated protection against some guarantees protection against all. Writings from as early as the fifth century B.C. inform us of these principles, at least in rudimentary form. When a devastating plague descended upon Athens in the second year of war with its Spartan foes, Thucydides recounts of the survivors, "These knew what it was from experience, and had now no fear for themselves; for the same man was never attacked twice—never at least fatally. And such persons not only received the congratulations of others, but themselves also, in the elation of the moment, half entertained the vain hope that they were for the future safe from any disease whatsoever."[1]

While the Athenian public could trust its vaunted wall to protect it from Spartan invaders, the body must rely on "two lines of strategic defence against foreign invaders."[2] Whether bacteria, viruses, or parasites, invaders first confront the body's innate immune system—the ever-ready, first responders to any attack. If innate immunity proves insufficient, then adaptive immunity engages. For instance, adaptive immune responses countered Athens' plague and endowed survivors with what we now call "protective immunity": the resistance to a specific infection after having once survived and remembered an earlier attack by the same infectious agent. However, this protection demands a price: "Raising an immune response can cost the host significantly because, to some extent, a degree of collateral damage to the host's own cells and tissues is an inevitable side effect and outcome of immunity."[3] Therein lies the central challenge on the path to protective immunity: to distinguish self from nonself—host from invader—and to limit damage to the former and eradicate the latter.

Innate Immunity

As porous as US physical borders are in an age of burgeoning trade and travel, its "cyber borders" are even more porous—and the critical infrastructure upon which so much of the US economy depends can now be targeted by nonstate and state actors alike. America's present global predominance does not render it immune from these dangers.

—Report of US Commission on National Security/Twenty-First Century

We need to give our nation's first responders—the firefighters, the police, the medical professionals and other emergency officials—the tools to do their jobs even better. Before September 11, many in our country never thought of these men and women as first responders. Nobody really ever thought of these individuals as the first line of a homeland defense. Now today, after September 11, I believe every American understands their mission.

—Homeland Security Director Tom Ridge

Our contact with the world exposes us to danger. Our adversaries exploit the ways we derive sustenance. We touch, breathe, eat, drink, and procreate—each necessary port of entry a possible path of infection. Thus, the body must protect itself so it may prosper. These unseen and often unrecognized protective efforts start with the body's "first line of defence against infectious disease," the innate immune response.[4] "Present and ready to resist an invader at any time," generally within minutes, the innate system can control or eradicate many infections before the slower developing adaptive response mobilizes.[5] Still, some microbes may overwhelm the initial response. Nevertheless, the innate system proves vital for an effective immune response even in such circumstances: components of innate immunity first signal the more powerful adaptive system as to the nature of the threat and then assist it in the necessary response.

The innate "line of defense" consists of both passive and active defenses: (1) a set of barriers and (2) immune cells that recognize and respond to the threat should the barriers be breached. For instance, the body's borders form formidable barriers to potential pathogens, microorganisms that can cause disease. The skin is a physical barrier through which few pathogens can penetrate. The mucosal linings of the respiratory and gastrointestinal tracts form a similar yet more penetrable barrier. Other surface defenses include nasal hair and mucous to trap particles and cough and sneeze reflexes to expel them.[6] Chemical barriers complement the physical. Stomach acid kills most microbes. Sweat and oil glands, tear ducts, and the mucosal lining release antimicrobial chemicals, or peptides. Similar to antibiotics yet differing in chemical action, "the peptides are less subtle killers: they punch holes in an invader's membranes or disrupt its internal signaling."[7] Such compounds, reactive against a broad range of microorganisms, not only spare the host but may even boost its subsequent immune response. Finally, the hundreds of species of normally harmless bacteria that inhabit the skin, mouth, and colon suppress growth of invading microbes.[8]

Microbes breach these barriers (i.e., through wounds), but the cells of innate immunity cannot react unless they first recognize that a breach has occurred. Recognition in the cellular community occurs through cell surface receptors that bind particles on other cell or microbe surfaces—a lock-and-key type of fit. Chemical features on microbial surfaces form the key, and innate cell surface receptors form the lock. Because the innate system's receptors recognize shared structures peculiar to broad classes of microorganisms, the receptors are called pattern-recognition receptors.

The recognized patterns, estimated to be less than 1,000, are often those essential for microbe survival and infectivity. The innate cells, for example, might recognize the chemical components of a bacterium's cell wall, without which the bacterium could not live any more than a human can live without skin and skeleton.

Pattern recognition produces three notable benefits. First, it ensures that the innate response only targets invading microbes instead of host cells, since host cells do not possess the recognized patterns. Second, it facilitates a rapid, consistent immune response. Since all innate immunity cells of a given type express the same set of receptors, many immune cells can recognize and then respond to the same microbe type. Moreover, because these receptors recognize patterns shared by broad classes of microorganisms, each immune cell can also respond to many microbe types. The net effect is that of many responders rapidly countering many types of threats. Third, because pattern recognition often focuses on vital microbe components, the microbes are less able to evade immune detection—mutational changes or concealment of the target key might render the microbe unable to infiltrate and infect. The would-be attacker might have to alter its form and methods so much that it loses any significant power of attack.

After the prerequisite recognition, the real strength of the innate system rests in its ability to coordinate a complex, immediate, and concerted immune response. Macrophages mediate this "cellular defense of the borders."[9] Upon recognizing pathogens, the macrophages issue a flood of chemicals, the messages by which cells communicate. This chemical communication cascade initiates the familiar inflammation response—heat, redness, swelling, pain—by inducing changes in local blood vessels, part of the body's vast transportation network. As your blood vessels expand and increase their permeability, you may experience heat, redness, and swelling. Other chemical signals released by macrophages summon assistance to the infected area. Reinforcement cells move in, taking advantage of the increased mobility allowed by the blood vessel changes. The influx of these immune cells and their resultant action may cause painful inflammation—part of the inevitable collateral damage of effective immune responses. While the reinforcements rush in, other signals coordinate the clotting of small blood vessels downstream from the infection; these vascular roadblocks help contain and block the spread of the pathogen. Still other signals put reinforcements, the aptly named complement proteins, on alert in the bloodstream, a hedge should the containment strategy fail.[10] Finally, further chemical communications initiate wound healing to close the port of entry to further pathogens.

Innate immunity at its most effective may thwart attacking pathogens so rapidly that noticeable or disagreeable symptoms do not appear.[11] The combination of persistent border barriers; consistent and reliable recognition of known microbial patterns, or profiles; numerous, dispersed defenders with on-call reinforcements; and extensively coordinated response is formidable. Nevertheless, pathogens arise that can breach the body's border. Others

appear that do not resemble the predetermined patterns and thus evade recognition. Still more may be too powerful in either number or action for the innate system to contain. Therefore, while macrophages orchestrate the innate response, other innate immunity cells in the infected area also detect a threat, and they alert the adaptive immune system that a more potent defense might prove necessary.[12]

Adaptive Immunity

> *A great writer has said that the struggle of humanity against tyranny is the struggle of memory against forgetting. . . . This republic is young, but its memory is long. Now, we have inscribed a new memory alongside those others.*
>
> —President George W. Bush
> 11 December 2001

In experiencing a pathogenic species for the first time, the adaptive immune system progresses through five general phases: (1) recognizing the pathogen, (2) activating armed effector cells, (3) eliminating the pathogen, (4) scaling back the response, and (5) remembering the encounter.[13] Mobilizing this response takes time, perhaps four to seven days, and the pathogen may cause much illness during that delay. Immune memory is irrelevant to that first encounter; it may prove vital for the next. To understand why this is so, one must follow the phases of that first encounter, one initiated by innate immunity.

Recognition forms the first step on the path to memory and protective immunity, but how can the immune system recognize an invader before forming a memory of that invader? The innate system recognizes microbe patterns. While this can be thought of as a form of institutional memory, it is not memory from direct experience; the innate system of a given individual does not recall that it earlier fought the same pathogen that infects it now. Rather, the human genome encodes the lessons of countless years of evolutionary host-microbe interaction and passes these lessons down from generation to generation. The rapid pace of microbial evolution and adaptation may, however, quickly make some of these lessons obsolete as microbes don biological disguise. There is no time in such cases for the plodding advancement of human generational change and long-term adaptation. The infected body must quickly adapt through the adaptive system, which does not inherit a genetic file of known pathogen profiles. Instead, it creates its own profiles afresh in every individual.

Since the body does not know what threats it will encounter, it prepares with an adaptive immune system that, ideally, can recognize and respond to any threat that it may encounter. To this end, the adaptive system randomly generates myriad recognition receptors before the immune system ever encounters pathogens. Each body produces perhaps a billion or more receptor types, and individual T and B cells each possess one type of receptor; they demonstrate specificity.[14] The process is somewhat akin to building billions

of locks so that any yet unseen key of certain size parameters will work in at least a couple of them. The keys in this case are small biological pieces called antigen, which might belong to a possible pathogen that the body may encounter. However, few cells exist to recognize each antigen; only one in 100,000 to one in 1,000,000 are specific for a given antigen.[15] The scarcity of these adaptive cells precludes dispersal for border defense, hoping for a chance contact between an antigen and the few T and B cells activated by recognition of that antigen. In effect, the antigen must go to the T cells and B cells for the first encounter.

The body solves this dilemma by channeling antigen into immune system checkpoints. Lymphatic fluid that normally drains the body's tissues sweeps antigen into the lymph nodes; the spleen collects antigen from the bloodstream.[16] Additionally, specialized antigen-presenting cells (APC) of the innate immune system also carry antigen to these organs. APCs live in the tissues alongside macrophages; both ingest invading pathogens.[17] The macrophages ingest to destroy, but APCs ingest to present. First, the APC degrades pathogen into deoxyribonucleic acid (DNA) fragments and other antigenic pieces. Second, it prominently displays these pathogen antigens on its own cell surface and migrates to the nearest lymph node.[18] As lymphatic fluid deposits free-floating antigen and APCs arrive with attached antigen, the lymph node becomes an area of heavy antigen concentration. In the meantime, naïve T and B cells, those that have never encountered their matching antigen, circulate through the body's many lymph nodes. If a naïve T-cell receptor does not encounter an APC displaying a matching antigen, then the T cell moves on to a different lymph node. If a B-cell receptor—an antibody—does not encounter free-floating antigen, then it also moves on. In this fashion T and B cells, although few in number for a given antigen, can effectively survey the entire body.

Should a naïve T or B cell recognize antigen—that is, identify a threat—then that cell activates and rapidly proliferates and differentiates into cells capable of eliminating that specific invader. However, this transformation from single surveillance cell to numerous armed effector cells requires a second signal—chemical confirmation that the antigen is of microbial origin and not a closely matching piece of the body's own molecular makeup. APCs provide this second or costimulatory signal to T cells. In a process called linked recognition, a certain class of these activated T cells provides a costimulatory signal to B cells that have recognized antigen.[19] Activated T and B cells then remain in the lymph node and divide repeatedly for days.[20] Now, rather than having only one or several cells capable of binding a given antigen, the body has millions, perhaps billions, of clones all capable of recognizing the invading pathogen.[21] Four or five days into the rapid proliferation cycle, the T and B cell clones differentiate into armed effector cells—killer T cells, helper T cells, and antibody-secreting B cells.

From the development of naïve cells through the rapid expansion to armed effectors, the adaptive system must overcome a serious challenge as it prepares for emerging threats: not all antigen represent a threat. In addition to antigen from pathogens, the immune cells will also encounter antigen from self—countless pieces of the body's own population of cells. Since the randomly generated T and B cell receptors exist in such large numbers, it is not surprising that many nascent cell receptors match small biological pieces native to the body. The potential thus exists for the adaptive system to mistake host cells for pathogens and unleash its killing power on the very body that it otherwise protects. The requirement for a costimulatory signal is just one safeguard against this self-destruction or autoimmunity. Other extraordinarily complex control mechanisms also exist to eliminate or suppress those immune cells that react against self. Many immature T and B cells that react against self will die. Others, in the case of some B cells, will undergo receptor editing: a form of reprogramming that eliminates self-reactivity. Still others, upon maturation, will bind to self and learn not to react, a phenomenon known as immunologic tolerance.[22] Should the body's immune system utterly fail to tightly regulate itself and develop this tolerance to its own cells, then microbes would be of slight concern—the body would destroy itself.

The immune system generally keeps its potential self-destructive power in check and turns its newly generated effector cells against invading pathogens. While the new effector cells recognize the same pathogen, they perform different eradication roles. Antibody-secreting B cells remain in the lymph nodes and secrete large quantities of antibodies into the blood. During the immune response, these "antibody molecules are altered so they can bind to intruders more strongly."[23] The intruders are microbes that live outside cells, either in the blood or in the tissue spaces between cells. The antibodies optimize their ability to bind and recognize, but they do not kill. Rather, they mark pathogens for destruction by others. In doing so, they also prevent immediate damage by neutralizing bacterial toxins, blocking bacteria from adhering to cells, and preventing viruses from entering cells. Moreover, antibody-marked pathogens are increasingly vulnerable to macrophage ingestion.[24] In turn, the macrophages' killing power is increased when activated by helper T cells. In such cases, neither antibodies nor macrophages nor helper T cells alone can eliminate the infection; it takes the concerted efforts of all to do so.

Immune cells are not the only cooperators in the protective effort; the protected also coordinate with the protectors. This cooperation is strikingly revealed between killer T cells and their targets—pathogen-infiltrated body cells.[25] Killer T cells deploy from the lymph nodes to the infected area. However, they cannot identify the infected cells unless those cells cooperate. The infected cells alert the T cells much as APCs activated the T cells; they display viral particles on their cell surfaces. Now, however, the T cells do not need costimulatory signals. Having only recognized the displayed pathogen antigen, they will "kill infected targets with great precision,

sparing adjacent normal cells. This precision is critical in minimizing tissue damage while allowing the eradication of infected cells."[26]

Infected cells actively participate in their own deaths; a killer T cell does not kill in a conventional sense. Rather, it activates within the target cell a genetic program that signals the cell to kill itself.[27] Calling this "sacrifice" for the good of the cellular community is too anthropomorphic, yet sacrifice illustrates the effect. The cell would, in most cases, fall victim to the virus anyway. The virus and its offspring would then infect and kill many more. Thus, the precise, coordinated, and highly regulated immune response may cause relatively few cell deaths early in the infection but preserve the lives and functions of not only many more cells but also the body itself.

After the effector cells clear the infection, the body clears the effector cells. "The actions of effector cells remove the specific stimulus that originally recruited them. In the absence of this stimulus, they then undergo 'death by neglect.' "[28] Perhaps the energy expenditure to maintain these cells is too great, or maybe having an enormous population of highly lethal cells patrolling the body constantly presents an unacceptable risk. For whatever reason, the body drastically scales back its response force. For instance, it destroys more than 90 percent of the effector T cells.[29] How does the body stand ready for another attack by that same pathogen? It remembers. Some of the effector cells do not die; they differentiate into memory cells.

A memory cell does not remember disease, illness, or even a specific set of symptoms. It remembers an antigen associated with a pathogen, which caused some set of symptoms that the afflicted call "disease."[30] Memory allows the adaptive system, should it again encounter that antigen, to bypass the time-consuming recognition and activation of naïve cells. Thus, any subsequent or secondary exposure to a given antigen produces a much more rapid and pronounced immune response than the primary exposure did.

A case of simultaneous antigen exposure best illustrates the specificity of this enhanced response. For instance, if a person simultaneously experiences secondary exposure to antigen A and primary exposure to antigen B, then the body will respond quickly and strongly to A and much more slowly and weakly to B. The person will not likely get ill from the pathogen that carries antigen A but very well may from a different pathogen that carries B. The differential response times and magnitudes—and the illness that may or may not result—reflect the specificity of immune memory. This memory effect is simply a convenience if the attacking pathogen, at its worst, can induce only cold-like symptoms. Should the pathogen prove lethal, survivors of that first attack benefit greatly from enhanced protection against a second attack.

The adaptive system must both identify and react while under attack. However, it neither knows what threats it will face nor the timing of future attacks. Moreover, it lacks the luxury to initiate attack—it must al-

ways react. Success thus depends on its extraordinary array of recognition receptor capabilities; rapid expansion once one of these recognition capabilities identifies a threat; lethal effectors, tailored to target that specific threat; and memory, tasked to remember the now-eliminated threat. Should disease again strike, has immune memory failed? Many "half entertained the vain hope that they were for the future safe from any disease whatsoever."[31] Should the same symptoms again appear, has memory faltered? Many distinct pathogens produce like symptoms. Should the same pathogen again successfully strike, now may memory be blamed? Same pathogen in name, but is the antigen still the same? There is only memory of what has been seen. To expect otherwise is to fall captive to an illusion of immunity.

When Immunity Fails

Now, many nations are trying hard to do the right thing, to improve their border security, to enforce their laws, to improve their ability to track terrorists in their movements and finances. And the United States is actively helping countries to improve their immune systems against terrorism.

—National Security Advisor Condoleezza Rice

Immunity arises from a system in "delicate balance."[32] We may wish for improved vigilance, increased lethality, or more immediate response, but we should remember, "beneficial immune protection has had to develop in equilibrium with the potentially lethal damage that immune responses can cause."[33] While "constant bidirectional cross talk" between innate and adaptive immunity help maintain the equilibrium, some damage arises unavoidably as a side effect of a robust and normal immune response.[34] Infected tissue becomes inflamed. Some destructive mechanisms target less precisely than others. Even the precise killer T cell attacks may kill so many infected cells as to impair organ function.

However, not all immune-mediated destruction falls under this "collateral damage" rubric. Sometimes the finely balanced system goes awry and turns its destructive powers against healthy cells and invaders alike.[35] Infections predispose a person to these adverse reactions; one leading idea suggests that these are cases of mistaken identity. Certain microbe antigens might so closely resemble self-antigens that the immune system cannot distinguish between the two.[36] Once the immune system responds to the microbe, the persisting memory cells will encounter look-alike self-antigen and mistakenly interpret its presence as a sign of another microbe attack—and thus attack the presumed threat.

While reaction against self is somewhat rare, the immune system frequently overreacts to normally harmless, foreign substances—with potentially fatal results. We know this hypersensitivity as allergies. Generally, those without allergies produce low-grade immune responses to common allergens, such as cat dander, dust mites, and pollen. However, the allergic in-

dividual generates a vastly exaggerated response. This immune response and not the otherwise innocuous foreign invader produces the symptoms.[37]

Finally, while some immune systems respond inappropriately, others respond insufficiently. The problem most commonly stems from immune system immaturity; it is not fully formed at birth.[38] The developing human body thus needs help; it obtains aid through passive transfer of some protective measures from the mother. For instance, the child obtains antibodies from the mother's developed immune system both through the placenta and from milk. The effect is the same—a temporary boost in the ability to ward off infection until the immune system can protect on its own.

However, some systems never fully develop or maintain this ability; they lack proper resources. In rare cases, genetic conditions may leave the system without key immune responders, such as B or T cells. More often, ineffective immune responses result from inadequate nutrition—protein malnutrition is the leading form of immunodeficiency.[39] This malnutrition-induced immunodeficiency sets up a vicious cycle: malnutrition increases susceptibility to infection. Infection may further depress the immune response. Some infections can increase loss of nutrients. Immunity becomes further depressed. Treating the patient for the specific infection may help in the short term but will do little for the long term. The problem must ultimately be treated at its root—genetic deficiency, malnutrition, chronic infection, or another cause. Otherwise, only a continuing battle against a cycle of infections awaits.[40]

Emerging Disease

A generation ago, some policy makers suggested that the time had come to "close the book" on infectious diseases. With the availability of a growing arsenal of antibiotics and vaccines and the eradication or near-eradication in developed countries of diseases such as smallpox, polio, and diphtheria, it was argued that biomedical research resources should be diverted from infectious diseases to other concerns. . . . the folly of this position has become clear.

—Anthony S. Fauci, MD Director
National Institute of Allergy
and Infectious Diseases
January 1998

My hope is that all nations will heed our call and eliminate the terrorist parasites who threaten their countries and our own.

—President George W. Bush
State of the Union Address
January 2002

We often associate this cycle of infection with poverty, an observation that others made long ago. While we know now that malnutrition, lack of clean water, and lack of proper sanitation account for much disease among the impoverished, many once attributed disease to miasma—the foul smell and filthy environment—that often accompanied poor people,

particularly in early industrial cities. Consequently, activists pushed to remove the filth. They cleaned. Infectious disease declined. Their methods worked—but for reasons scientists would only later discover.[41]

While the sanitarians cleaned and the industrial nations became wealthier, numerous factors contributed to healthier and longer lives: improved nutrition and housing, less-contaminated food and water, and improved sanitation and personal hygiene.[42] Nonetheless, infections exacted a monstrous toll. Even within the wealthy United States as late as 1900, tuberculosis, pneumonia, and diarrheal diseases were the top three killers and accounted for 30 percent of all deaths.[43] In spite of that, infectious disease by that point was already on the decline.

The scientific, technological, and social advances of the late nineteenth to midtwentieth centuries essentially allowed industrialized societies to vanquish many illnesses. Vaccination, which mimics an infection so as to induce immune memory, eradicated smallpox worldwide. The United States witnessed nearly a 100 percent decline in polio; 99 percent in measles, mumps, and rubella; and 97 percent in whooping cough.[44] In an age of antibiotics and advanced medical care, few in the industrialized countries fear, as did earlier generations, that their children may die of diarrhea. These advances were sufficiently along in the developed countries by the late 1960s that the US surgeon general declared it time to close the book on infectious disease and concentrate on ailments such as heart disease and cancer. He spoke too soon; the microbes forced the book back open.

New diseases emerged, and once-controlled diseases again raged. Ebola virus, hantavirus, Lyme disease, and mad cow disease appeared. The human immunodeficiency virus (HIV) ravages entire villages in sub-Saharan Africa. Cholera, yellow fever, dengue fever, malaria, and tuberculosis resurge around the globe.[45] The World Health Organization reported that three diseases alone—malaria, tuberculosis, and HIV—killed 5.7 million people in 2001.[46] Even in the United States, infectious disease deaths climbed 58 percent between 1980 and 1992.[47] So much for vanquished foes.

What went wrong? We changed; the microbes changed. Consider first the human side. The US Institute of Medicine (IOM) identified human demographics and behavior, technology and industry, economic development and land use, and international travel and commerce as partially responsible.[48] Increased population density and urbanization returned unsanitary conditions to many cities. Medical care in the developed nations increased the number of people living with immunosuppression (the elderly, cancer patients, sufferers of various chronic diseases, and organ transplant patients) who are more susceptible to acquire and pass infections. Medical care in hospital settings further contributes: nearly two million US patients acquire infections while being treated for other conditions; and nearly 88,000 of them die each year.[49] The sexual revolution brought increases in sexually transmitted diseases, most notably HIV. Air conditioners led to Legionnaires' disease, and tampons led to toxic shock

syndrome. Reforestation of vast segments of the United States supported increasing deer populations and Lyme disease.

Americans long enjoyed relative isolation from foreign disease threats—no longer. International travel and commerce allow global disease transmission. For example, wide-scale importation of fresh fruits and vegetables brings the bacteria of the exporting land. Moreover, the one-half billion people who enter our borders every year are potential disease incubators—as we are when we cross theirs.[50] Many more examples exist, but the message is clear: societal and technological progress pushed diseases into decline and helped them reemerge in unexpected ways.

Microbes play active roles in the emerging change. They evade immune detection by changing their antigenic appearance.[51] They mutate and resist antibiotic action: "Once an antibiotic is proven effective and enters widespread human therapeutic use, its days are numbered. . . . Development of resistance is not a matter of if but only a matter of when."[52] Moreover, antibiotic resistant bacteria can pass their resistance genes to bacteria of other species, with many becoming resistant to multiple antibiotics.[53]

Unintended consequences of progress and the ever-adapting microbes explain much of the emerging threat. Nevertheless, humans share culpability. For example, overuse of antibiotic weapons, particularly when used in subtherapeutic doses, breeds microbial resistance.[54] More pointed is the observation of the IOM study: "There can be a delicate balance between maintaining control of a disease and the initiation of an epidemic. It is one thing to have this balance disrupted by essentially uncontrollable elements; it is quite another to have it go awry as a result of individual or organizational complacency."[55] Complacency set in after our early successes with antibiotics and vaccines. Public health and medical officials began losing interest in the 1950s and 1960s. Vaccination rates dropped.[56] Our public health infrastructure eroded. Some might argue that we practically invited the microbes back into the fight.

While the emerging threats capture our attention and channel our efforts now, they may not hold our focus for long. The history of American public health shows three broad trends extending back to colonial years:

> Among the themes that seem to run through American public health history, possibly the most striking one is the constant alteration between apathy and sharp reaction to public health crises. . . . The fight to replace ineffective traditional ways of maintaining health with more effective ones is another constant in public health history. . . . Another recurrent theme in American public health is the clash between individual liberty and the public welfare, as government attempts to regulate human conduct in accordance with the prevailing principles of community health.[57]

Segments of society vigorously opposed, and still do in some cases, many of today's commonplace protective and preventive measures—sewers; mandatory vaccines; clean water, food, and air standards; food service regulations; and pasteurization. Most take these measures for granted, seldom aware of the extent to which they permeate our daily lives. If only much of the world could do the same. For several generations of Americans, the specter of wide-

spread death from infectious disease is something new. However, for many people outside these borders, it is an old and never-ending fight.

Notes

1. The term *plague* in this context has no relation to bubonic plague, the Black Death of medieval Europe. Medical experts disagree as to what disease afflicted the Athenians. Thucydides, "History of the Peloponnesian War," in *The Landmark Thucydides: A Comprehensive Guide to the Peloponnesian War,* ed. Robert B. Strassler (New York: Free Press, 1996), 2.51.6.

2. Kathryn Calame, "End Game for B Cells," *Nature,* 19 July 2001, 289.

3. Rolf M. Zinkernagel and Hans Hengartner, "Regulation of the Immune Response by Antigen," *Science*, 13 July 2001, 251.

4. Alan Aderem and Richard J. Ulevitch, "Toll-like Receptors in the Induction of the Innate Immune Response," *Nature*, 17 August 2000, 782.

5. Charles A. Janeway et al., *Immunobiology: The Immune System in Health and Disease*, 5th ed. (New York: Garland Publishing, 2001), 43. This text, written for graduate and medical students, is available on-line at the National Center for Biotechnology Information Web site: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books. Much is drawn from the very readable, undergraduate-level introduction to immunology presented in Abul K. Abbas and Andrew H. Lichtman, *Basic Immunology: Functions and Disorders of the Immune System* (New York: W. B. Saunders, 2001).

6. Arthur J. Vander, James H. Sherman, and Dorothy S. Luciano, *Human Physiology: The Mechanisms of Body Function*, 6th ed. (New York: McGraw Hill, 1994), 703.

7. Trisha Gura, "Innate Immunity: Ancient System Gets New Respect," *Science*, 16 March 2001, 2068.

8. The human body contains more normal microbial flora, both on and in it, than the body has cells of its own (10^{14} bacteria as compared to 10^{13} cells). These organisms may cause disease—dental caries, or abdominal infections after an internal injury—but they are often harmless. Some may even provide the body a source of vitamin K and other essential nutrients. Most notably, they suppress potential pathogens by competing successfully for space and nutrients and by secreting harmful antimicrobials and waste products. Charles Patrick Davis, "Normal Flora," in *Medical Microbiology,* ed. Samuel Baron, 4th ed. (Galveston, Tex.: University of Texas Medical Branch, 1996), 113–19.

9. Janeway et al., 87. Macrophage means large eater. As the name indicates, these amoeba-like cells capture and ingest microbial prey, a process aptly named phagocytosis or cell eating. They are also the body's scavengers by cleaning up debris from dead or damaged cells.

10. Complement proteins are not restricted to the bloodstream; they may also operate in the infected tissue. This limited example is not justice to the role and importance of complement proteins in immunity, but the mechanisms by which they act are complex and beyond the scope of this study. The important point is that the immune system has several different types of first responders.

11. Scientists do not know how often this occurs because it is difficult to devise measures to assess the effectiveness of the innate system. If no symptoms appear, for instance, is it because a microbe never attacked or because the innate system cleared it so quickly as to negate any appearance of attack?

12. Our more advanced system is not the universal protective model. Many multicellular organisms fare quite well with more primitive protective systems. Insects, as only one example, lack an adaptive system yet are very resistant to microbial infection. See Gura for an overview.

13. This five-phase construct comes from Abbas and Lichtman, 8–9. The "armed cells" reference comes from Janeway et al., which uses it frequently in discussions of adaptive immunity.

14. T and B cells, also called lymphocytes, are types of white blood cells belonging to the adaptive immune system.

15. This differs markedly from the innate system in which all cells of a given type could recognize the same patterns. Essentially, the innate system produces relatively few yet proven capabilities in high quantity. In contrast, the adaptive produces near countless untried capabilities yet each in low quantity.

16. The lymphatic system is more extensive than indicated here. For instance, the mucosal tissues have specialized areas that collect antigen. This study is confined to the processes involving the lymph nodes, which are representative of those occurring in other lymphatic tissues.

17. The antigen-presenting cells (APC) are called dendritic cells. Although they are the most important APCs for the described processes, some other cells, including macrophages, can function as APCs in certain circumstances.

18. This method is how, as referred to earlier, the innate system signals the adaptive that it requires help.

19. In some cases, microbial components can themselves provide the second signal, and the B cell will not require assistance from helper T cells. In either case, the goal is the same: two signals to confirm that the T and B cells are reacting to a legitimate microbial threat.

20. Many people have seen the effects of this proliferation in the form of swollen glands.

21. Each pathogen likely has several antigens that the body recognizes. Thus, several different T and B cells, each with unique antigen receptors, may simultaneously have recognized the pathogen and then proliferated. The different receptors will then recognize different aim points on each microbe target.

22. The lack of a costimulatory signal in the presence of self-antigen can cause functional inactivation of mature T cells—the immunologic tolerance, which may also explain why the body normally does not react against antigens in food.

23. Alberto Martin and Matthew D. Scharff, "Antibody Alterations," *Nature*, 30 August 2001, 870.

24. Some pathogens possess specialized features that allow the pathogens to conceal themselves or otherwise escape earlier destruction by macrophages of the innate system. However, the macrophages can identify antibody-pathogen complexes and eliminate them accordingly.

25. These intracellular pathogens are most often viruses rather than bacteria. Viruses hijack the body's cells and then use the cell's genetic machinery to produce more viruses.

26. Janeway et al., 333. The T cell recognizes antigen only when bound to special receptors on the body's own cells. Therefore, it cannot recognize antigen that is, for instance, floating in the bloodstream. B cells thus perform that role.

27. This process is called apoptosis or programmed cell death; the professional literature often refers to it as "cell suicide." It serves many biological purposes aside from the one mentioned here. The biochemical mechanisms are incredibly complex and beyond the scope of this study.

28. Janeway et al., 401.

29. Jonathan Sprent and David F. Tough, "T Cell Death and Memory," *Science,* 13 July 2001, 246.

30. Think of antigen as a chemical fingerprint, the lymph nodes as a central processing station, and the collection of naïve T and B cell receptors as a database. In this case, the database does not contain prints of known perpetrators; the innate system and the memory T and B cells form those databases. Rather, the adaptive system's naïve database once contained all possible fingerprints. However, the fingerprint of each person who is

verified as a law-abiding citizen (self-antigens and food antigens) is either removed from the database or labeled as not warranting concern. Should those prints subsequently be compared to the database, they would come back as "no match" or "tolerated match" and thus not be considered a threat. Should the forwarded fingerprint match one in the database, then its owner is automatically considered a potential threat. Additional evidence or circumstances (the second or costimulatory signal) would then confirm that the person was an actual threat. The immune system is not the perfect protector. Problems can and do arise. For example, the mechanisms to screen nonthreatening matches from the database can break down and subsequent, erroneous "matches" may falsely indict someone. Some law-abiding citizens can become criminals (normal cell becomes cancerous). Some microbes can change their "fingerprints."

31. Thucydides, 2.51.6.

32. Pamela L. Schwartzberg, "Tampering with the Immune System," *Science*, 13 July 2001, 228.

33. Zinkernagel and Hengartner, 251.

34. Abbas and Lichtman, 23.

35. Ibid., 178. Each is also believed to involve genetic predisposition; we see the damage in conditions such as insulin-dependent diabetes and rheumatoid arthritis.

36. Abbas and Lichtman, 182.

37. A. B. Kay, "Allergy and Allergic Diseases," *New England Journal of Medicine* 344, no. 1 (4 January 2001): 30–37. While the common allergy symptoms are often tolerable, for those with certain drug and food allergies, death may rapidly result after exposure. Some studies indicate that increased exposure to microbes while young may stimulate immune responses that make one less allergy prone, which could explain why allergies are more common in the developed world than the developing and why the incidence of allergies and asthma is rising in Western nations.

38. Some immune processes may take two or more years to develop fully.

39. Protein malnutrition chiefly causes a deficiency in T cell production and function.

40. Armond S. Goldman and Bellur S. Prabhakar, "Immunology," in *Medical Microbiology*, 2–34.

41. For the only comprehensive, single volume history of American public health, see John Duffy, *The Sanitarians: A History of American Public Health* (Urbana, Ill.: University of Illinois Press, 1992). For a comprehensive history of international public health, see the classic volume by George Rosen, *A History of Public Health* (Baltimore, Md.: Johns Hopkins University Press, 1993). Both books are exceptionally readable.

42. Mitchell L. Cohen, "Changing Patterns of Infectious Disease," *Nature*, 17 August 2000, 762–67. Interestingly, the decline for several diseases began before anyone knew of their microbial origins. We know now that the improved living conditions enabled by wealth and government action boosted people's immune systems and decreased their exposure to pathogens. A very clear lesson also emerged: effective prevention does not always demand knowledge of a cause.

43. Cohen, 762.

44. Gordon Ada, "Vaccines and Vaccination," *New England Journal of Medicine* 345, no. 14 (4 October 2001): 1042.

45. For more detailed information about each disease, see the on-line facts sheets at the World Health Organization (WHO) and at the US Centers for Disease Control and Prevention (CDC): http://www.who.int/inf-fs/en/index.html; and http://www.cdc.gov/health/default.htm.

46. See WHO, *Scaling Up the Response to Infectious Diseases* (Geneva: WHO, 2002), n.p., on-line, Internet, 20 June 2002, available from http://www.who.int/infectious-disease-report/2002/framesintro.html.

47. CDC, *Emerging Infectious Diseases: A Strategy for the 21st Century* (Atlanta, Ga.: CDC, 1998), n.p., on-line, Internet, 20 June 2002, available from http://www.cdc.gov/ncidod/emergplan/slideset/1.htm. To keep the increase in perspective, one should note

that the mortality rate in 1992 was only about 60 per 100,000. Contrast this with the rate in 1900 of more than 500 per 100,000 and the rate of more than 800 per 100,000 during the flu pandemic of 1918.

48. Joshua Lederberg, Robert E. Shope, and Stanley C. Oaks Jr., eds., *Emerging Infections: Microbial Threats to Health in the United States* (Washington, D.C.: National Academy Press, 1992), 108, on-line, Internet, available from http://www.nap.edu/catalog/2008. html.

49. Aside from the human toll, these hospital-acquired infections cost Americans more than five billion dollars annually. CDC, "Hospital Infections Cost U.S. Billions of Dollars Annually," 6 March 2000, n.p. on-line, Internet, 20 June 2002, available from http://www.cdc.gov/od/oc/media/pressrel/r2k0306b.htm. In another example of the collateral damage from medical care, one study cautiously concluded that more than 100,000 people in the United States die each year from prescription drug–related deaths. If true, then this would be the fourth to sixth leading cause of death in America. Jason Lazarou, Bruce H. Pomeranz, and Paul N. Corey, "Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies," *Journal of American Medical Association* 279, no. 15 (15 April 1998): 1200–1205.

50. For more homeland security facts see http://www.whitehouse.gov/response/.

51. They may, for instance, change the antigens that they display to the immune system. Because of this antigenic change you must, for instance, get a different flu shot each year. The artificially induced immune memory from previous shots will often not protect you from the changing flu virus.

52. Christopher Walsh, "Molecular Mechanisms that Confer Antibacterial Drug Resistance," *Nature*, 17 August 2000, 776–77.

53. For more information on microbial genetics, see Claire M. Fraser, Jonathan A. Eisen, and Steven L. Salzberg, "Microbial Genome Sequencing," *Nature*, 17 August 2000, 799–803.

54. Walsh, 777.

55. Lederberg et al., 108.

56. In 1990, for example, nearly all Central and South American countries had higher measles vaccination rates than the United States. Cuba's rate stood at 94 percent; the United States at 70. See Lederberg et al., 109.

57. Duffy, 2–3.

Chapter 3

Threats from Within

We share the belief that terrorism is a cancer on the human condition, and we intend to oppose it wherever it is.

—Secretary of Defense Donald H. Rumsfeld

Well, terrorism is the cancer of our age. . . . For the past decade, a lot of countries wanted to deny that, or make excuses for why they could go on dealing with terrorists. But after what's happened in New York and Washington, now everyone knows. This is a cancer. It's a danger to us all. So every country must now decide whether it wants to be a smoking or nonsmoking country, a country that supports terrorism or one that doesn't.

—Foreign Minister Shimon Peres

Cancer is the renegade of cellular society.[1] It subverts the body's normal order of cooperation and communication. "Our bodies are nothing more than highly complex societies of rather autonomous cells, each retaining many of the attributes of a fully independent organism. . . . When, as usually happens, these cells are well-behaved and public-spirited, extraordinarily complex order ensues. But on occasion, a cell may choose to go its own way and invent its own novel version of a tissue or organ. It is then that we see the much-feared chaos that we call cancer."[2] This chaos of cancer begins with the distortion of a cell's genetic message, with the cell's subsequent behavior gone awry.

The Nature of the Adversary

We knew we had cancer. Now we know it has metastasized. The al-Qaeda terrorist network reached into the very systems of cooperation and communication . . . and turned the building blocks of peace into the weapons of war.

—Ambassador John D. Negroponte

The genes encoded in a cell's DNA shape how that cell interacts with other cells and substances in the environment and, consequently, how that cell develops and behaves. All cells in a given human body carry identical sets of genes, but cells differ as to which of these genetic instructions they read and respond to. This selective reading of the DNA text and its resultant effect on cellular development and behavior produces diverse cell types. For example, it makes nerve cells different from lung cells but nerve cells of a given type very much like each other. The normal cellular order arises, therefore, because all cells of a given type respond rather consistently to their environment while performing DNA-directed roles within cellular society.[3]

Within this society, cellular communication and cooperation are the norm. For instance, cells grow and produce new cells only when they receive signals from neighboring cells instructing them to do so. The cells then generally stop growing and replicating only when other cells send them growth-inhibition signals. Biological factors limit the number of times that a cell can proceed through this growth cycle before it dies. A cell may also die by activation of its built-in death program should the cell's behavior go awry.[4] Finally, cells stay within the confines of their own tissues and do not spread.[5]

A cancer cell violates these norms of cellular behavior. It stimulates its own growth and ignores signals from neighboring cells to stop growing.[6] It evades the mechanisms that trigger death in aberrant cells and may replicate indefinitely. It siphons nutrients and other support from the surrounding cell population and, should it need more, induces the body to produce new blood vessels to supply the growing tumor with additional nutrients.[7] The growing tumor invades nearby tissues, and cells separate from it and metastasize, or spread and invade other tissues. "Cells remain confined to their home territory because they are held in check by intercommunication with neighboring cells and with the surrounding extracellular matrix. . . . [whereas] malignant tumour cells can be hypothesized as being resistant to the regulatory signals because they may appropriate, misinterpret, or disregard these signals and dominate the local invaded host-cell populations."[8] The capabilities to proliferate uncontrollably; to appropriate, misinterpret, or disregard regulatory signals; to derive sustainment from and dominate the local host-cell population; and to spread to tissues afar—these are the hallmarks of cancer.[9]

Cancer behaves as such because it reads and responds to a corrupted genetic text. The corruption consists of a series of mutations and other genetic modifications, which generally occur over many years and originate within a single cell.[10] The genetic changes launch the cell into the characteristic cycles of uncontrolled cell proliferation, with the body consequently harboring scores of renegade clones. Some of the clones, being renegades themselves, may then diverge from the founder.[11] Consequently, the malignant tumor contains subpopulations of cancer cells—each with a unique genetic message and possessing to varying degrees the hallmark capabilities. These subpopulations compete in Darwinian fashion to become the dominant group within the tumor. A single, cancerous mass may thus prove far more diverse and complex than the homogeneous-sounding name cancer implies.

The catchall name cancer masks to an even greater extent the genetic and behavioral diversity among cancers of various types. Many of us view these differences as being largely of disease location—lung cancer, colon cancer, breast cancer, prostate cancer, and so on. While "all share the ability to proliferate beyond the constraints limiting growth in normal tissue," their differences transcend location.[12] Cancer of the lung and cancer of the breast are not the same disease threat in distinct locations.[13] Even cancers with the same name—prostate cancer, for instance—vary from person to person. Some are aggressive, and some grow more slowly. Some quickly spread, and some remain relatively contained:

> The great majority [of cancer cells] will be ill-suited for the rigors of metastatic voyage and settlement in new terrains, so their attempts to colonize distant sites will end up as suicide missions. By now, the primary tumor mass may have grown quite large and can afford to dispatch a large, continuous stream of scouts on these missions. Even a seemingly impossible mission will succeed if tried often enough, so some new colonies will be founded and then thrive at distant sites. Sooner or later, these metastases begin to compromise the functioning of host tissues in which they have taken root. Only then is the cancer patient placed at death's door.[14]

Failure to assess properly the nature of this deadly threat "can lead to poor treatment planning and compromise the ability to cure patients."[15] Therefore, the physician must ask and answer this question: What exactly are the patient and I fighting?

Thus, the "first step in rationally treating" cancer is to classify the disease properly.[16] Classification considerations include determining both the extent of tumor spread, the stage, and the degree of similarity between cancer and normal cells, the grade. Physicians assess the stage by answering three questions: How large is the original tumor and to what degree has it invaded the surrounding tissue or organs? Has it spread to the regional lymph nodes?[17] Has it metastasized to more distant areas of the body?[18] The greater the spread, the greater the danger. Microscopic analysis of the cancer cells yields the grade. High-grade cancers tend to grow rapidly and are more resistant to therapy. Together, the stage and grade help physicians assess how near death the patient may be.

Cancer—a single name but many diseases—signifies a potentially lethal imbalance in cell society, the gross distortion of cell behavioral norms, and the resistance to outside cellular influence. "Each of the 1,268,000 Americans who will be diagnosed with cancer this year will battle a very specific, very personal disease. While the hundred-plus distinct diseases we call 'cancer' have several essential attributes in common, each type of cancer has its own unique characteristics that affect how it arises, how it progresses, and how it can be most effectively treated."[19] The nature of the threat thus demands an array of viable treatments.

Fighting the Enemy Within

> *The dreadful attacks against [the] World Trade Center and the Pentagon unveil, time and again, that the cancer of terrorism can be extensively damaging if left unchecked. It follows that there is a pressing and urgent need to combat world terrorism.*
>
> —League of Arab States, 17 September 2001

> *But what we do want to do, though, is to work with every government in which there is a substantial al-Qaeda presence to figure out a strategy for rooting it out. Because it's like cutting out a cancer now in 60-plus countries. You've got to get to these cells and root them out and disrupt them before they strike again.*
>
> —National Security Advisor Condoleezza Rice

The treatment strategy is "to choose an approach that will remove the tumor, rid the body of wandering cancer cells, and prevent a recurrence."[20] Each of the standard cancer treatments—surgery, radiation, and chemotherapy—contributes by eradicating or controlling cancer cells. But each method proves better suited for some cancer conditions than others do.[21] For instance, surgery remains the frontline treatment for solid tumors. Radiation complements surgery, but each suffers limitations: "In selecting appropriate therapy, surgery and radiation are still the most successful means of treating cancer localized to the primary site and/or regional lymph nodes. Since these forms of therapy exert their effects locally, neither is usually considered curative once the disease has metastasized beyond the loco-regional site."[22] Chemotherapy takes aim at the wandering cells and thus makes its contributions where surgery and radiation may fail, for "therapy with cytotoxic drugs is the basis for most effective treatments of disseminated cancers."[23]

The cancer-fighting weapons in the medical arsenal generally work best when they work together; combination therapy—two or more methods—is accordingly much more common than any therapy alone.[24] Combined surgery and radiation, for instance, can complement each other's effects.[25] Surgery can remove a tumor yet leave microscopic cells behind. On the other hand, radiation lacks effectiveness at a tumor's center but works well at the tumor periphery. Thus, a treatment plan might call for surgery to remove the main tumor and radiation to kill any residual cells.[26] This combination approach can allow for less drastic surgical measures than otherwise necessary and increase the probability of cure. Similar reasons exist to combine surgery or radiation with chemotherapy, which is generally ineffective when confronting a large tumor. Surgery and radiation could, however, reduce the main cancer burden. Chemotherapy would then attack any residual, metastasized cells.[27] In a different form of combination therapy, a physician might use two therapies to attack the same cells. Some forms of chemotherapy, for instance, make cancer cells more susceptible to radiation.[28] Subsequent radiation treatment then proves more effective than radiation alone.

A physician must consider more, however, than the threat and potential cure. He must also consider risk—that of treating too aggressively versus the chance of not treating effectively at all. Patients respond differently to the same treatments. For instance, identical radiation or chemotherapy treatments for identical cancer types and locations can produce very different side effects—both in terms of type and severity—in different people. The side effects, indicative of radiation and chemotherapy toxicity to normal cells, range from relatively minor to significant: hair loss, nausea and vomiting, fatigue, reproductive dysfunction, and damage to healthy cells.[29] Additionally, both chemotherapy and radiation may increase a patient's risk of developing a second cancer.[30] Finally, too high a drug dosage can prove lethal.[31]

While seeking over the years to avoid the undesired and sometimes devastating damage that treatment can impose, physicians have developed more precise ways to target cancer cells at the same time sparing healthy ones. Surgery, for instance, was likened by a famed eighteenth-century practi-

tioner of the art to "an armed savage who attempts to get that by force which a civilized man would get by stratagem."[32] Surgery is now far less a brute-force strategy. Advanced surgical techniques and technologically sophisticated tools (e.g., laser surgery) allow precision that early practitioners would find unfathomable. Radiation therapy may also precisely target cancer cells: "The goal of treatment planning is to uniformly irradiate a specified target while minimizing the dose to surrounding normal tissue."[33] These refined, brute-force approaches may minimize, to the extent technologically possible, the collateral damage to tissue in the immediate area of a localized tumor. However, precision is relative. Compared to older surgical and radiation tools and procedures, the new methods are incredibly precise. Compared to needs—to find and eradicate small pockets of metastasized cells that mix with healthy ones—the precision offers relatively little help. Therefore, physicians often turn to chemotherapy for metastases; however, precision targeting with chemotherapy also proves problematic.

In developing precision chemotherapeutic agents, "the critical issue is to identify how tumor cells differ from normal cells and how those differences can be exploited therapeutically."[34] Cancer exacerbates this problem because the once-normal rogue cells retain most of their normal features. The resultant drug-targeting difficulties explain why metastasis is the chief reason for cancer deaths and treatment failure.[35] Precision and effectiveness largely elude us when the renegade cancer cells disperse, prove difficult to locate, and intermingle with healthy cells.

This may soon change. The problem of finding ways to target precisely diseased cells with fewer side effects to the healthy remains, but the phenomenal gains in understanding of the genetic differences between normal cells and cancer cells provide promising prevention and treatment opportunities. On the prevention side, molecular diagnostics—characterizing a cancer by its genetic fingerprints—could revolutionize care. "For most people, the diagnosis of cancer comes unexpectedly. But as scientists have learned, the cellular changes that lead to cancer probably have been developing slowly in a person's body over several decades. This discovery raises a window of opportunity to catch the cancer cells before they ever become a threat to a person's health."[36] We already glimpse this potential as physicians identify people with genetic predispositions to certain cancers and provide the option to act before the potentially deadly threat emerges.[37] For example, some women with family histories of ovarian or breast cancer opt for hysterectomies or mastectomies.

Unfortunately, the decision to preempt cancer may not always prove easy. When facing a high probability of fighting a deadly, treatment-resistant cancer, the decision to opt for preventive surgery is relatively easy, particularly if the risk and side effects are acceptable. However, the decision would become vastly more complicated if confronting less lethal or less probable cancers, particularly if the surgery is risky or if the cancer type is often—but not always—treatable.[38] Moreover, once action is taken, one would never know

whether the threat might have materialized nor to what degree—and what was lost to the surgery?

Should cancer arise, the increasing ability to collect and analyze genetic information about a particular cancer may make it easier to diagnose and treat effectively. Medical imaging techniques revolutionized medical care, and the ability to refine images to the molecular level would revolutionize diagnostic procedures again. New precision targeting treatments "enlist a patient's immune defences in fighting cancer."[39] With such immunotherapy, "toxins can be linked to [certain types of] antibodies. This converts the antibodies into 'smart bombs' that guide the toxins to the tumor cell targets."[40] Cancer vaccines offer the promise of the body protecting itself as they try to stimulate the immune system to attack cancer cells. Some gene therapies even attempt to convert a cancer's distorted genetic message by inserting the proper genetic information.[41]

Even the old tool of chemotherapy is being transformed. New drugs try to attack cancer's ability to induce blood vessel formation and thus interdict the tumor's nutrient and oxygen supply lines. Others try to disrupt the internal signals that govern a cancer cell's spread. More weapons are on the way: "We are entering an era in cancer research that holds the potential for an exciting new approach to drug development for cancer prevention and treatment. These drugs will be designed to target specific molecular features of cancer cells, such as small but critical errors in genes or proteins that lead to tumor growth. By selectively attacking cancer cells, these revolutionary agents promise to be less toxic and more effective than current drugs. This extraordinary opportunity of molecular targeting has been generated by knowledge."[42] It has been generated by knowledge that cancer is not one threat from within but many, by knowledge of the genetic message at the heart of the renegade cell, and by knowledge that adds new tools and transforms our old tools to tackle new tasks.

The example of the recently approved drug Gleevec offers insight into both the promise and drawbacks of the emerging precision-targeting approaches. Gleevec attacks a single, vital molecular target in a particular form of leukemia. During clinical trials, 98 percent of patients with an early stage of leukemia responded positively within three weeks of treatment—all remained in remission during the nearly yearlong follow-up. However, among those in various later stages of the disease, between 55 and 70 percent went into remission but nearly all relapsed within a few months. A single mutation in the cancer cells caused the relapse—the molecular target mutated and endowed the cancer with resistance.[43]

Cancer cells, like any determined adversary, will resist, adapt, regroup, and reattack. When Gleevec attacks a single, vital cell target, those cancer cells that adapt will survive. The drug resistant cells remain and the vulnerable ones die. Eventually the tumor regrows, with the resistant cells dominant.[44] Administration of another drug in sequential fashion could produce the same resistance effect. An alternative approach might require a simultaneous targeting strategy—the targeting of many cancer cell mechanisms si-

multaneously with a combination of drugs, each designed to strike a specific cell mechanism. Alternatively, "several drugs that hit different parts of the same target might be ideal" because cancer cells resistant to one of the drugs would unlikely be resistant to all.[45] This outlook is promising, but cancer has dashed many promises and hopes.

When President Richard M. Nixon signed the National Cancer Act of 1971, he made the "conquest of cancer a national crusade."[46] A supportive nation readily embraced the act's promise and followed Nixon into the newly declared war on cancer. What the nation declared war against was, as we now know, not a single disease but a concept, one of cancer as an aberrant and unwanted condition of the human body. It was a new war against an old enemy, but it was an enemy little understood at the time. At the signing ceremony, President Nixon, perhaps waxing rhetorical, put the crusade into perspective: "I hope in the years ahead we will look back on this action today as the most significant action taken during my Administration."[47] Perhaps one day we will; we have seen many successes since that year. For now, the war on cancer drags on into its fourth decade.[48] The verdict is out as to whether we are winning.

The data are mixed. On the downside, cancer accounts for nearly 10 percent of all disease-related treatments in the United States.[49] Its overall economic costs tallied slightly more than $180 billion in 2000, which is enough money to fund the nation's traditional war-fighting requirements for six months. Currently, cancer is the second leading cause of US deaths; by 2010, it may surpass heart disease. Cancer also claims the lives of more women aged 35 to 74 than does any other disease. Although rare in children, cancer still takes those under age 15 at a rate second to no other disease. Every 30 seconds, another American hears the cancer diagnosis; every three minutes, two of the stricken will die.

Hopeful signs do exist. Both cancer incidence and death rates peaked in the early 1990s and now move slightly downward.[50] More people survive cancer than ever before.[51] Physicians cure about one-half of all patients.[52] New treatments, the fruits of research in the 30-year-cancer war, promise to grant life to even more. Still, the war drags on.

When will the war on cancer be won? How will one know? When can victory be declared? Will it be when more cancers are prevented than need treatment? How does one know how many cases were prevented? Will the war be won when most cancers are eradicated but some few others remain resistant? How many types? Will the war be won when most cancers can be maintained in a chronic state? When cancer kills only 300,000 Americans each year rather than 500,000? When HIV/acquired immunodeficiency syndrome (AIDS) or another disease overtakes cancer as chief villain and the medical community shifts focus? Perhaps one can only know in hindsight when the war is won. Even if the war on cancer is someday declared over and won, deadly malignancies will occasionally arise. The permanent elimination of all types of cancer seems naïvely remote. Moreover, what of the case of remission from a metastasized cancer? Can one

truly know that all of the cancer cells are forever gone and thus will not again threaten? One waits, hopes, remains vigilant, and goes on living.

Notes

1. Robert A. Weinberg, *One Renegade Cell* (New York: Basic Books, 1998). The term *renegade* is taken from Weinberg. This book, written by this internationally known cancer researcher, provides an exceptionally readable yet scientific account of how cancer begins.

2. Weinberg, 2.

3. For an undergraduate-level introduction to genetics, see Anthony J. F. Griffiths et al., *An Introduction to Genetic Analysis*, 7th ed. (New York: W. H. Freeman and Co., 1999), n.p., on-line, Internet, available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books. For a basic science introduction to cancer and related issues, see the National Cancer Institutes (NCI), Science Behind the News, n.p., on-line, Internet, available from http://press2nci.nih.gov/sciencebehind/.

4. This is the "cell suicide" program that killer T cells trigger in a viral-infected cell (chap. 2). In this context, a cell may initiate this program if, for example, it experiences severe, irreparable problems in its DNA.

5. Tissue is an aggregate of a single type of cell. Collections of tissues form organs that perform various functions.

6. It could stimulate its growth by many mechanisms. One suggestion is that the cell triggers its growth without any signaling from neighboring cells. On the other hand, it can induce those cells to unnecessarily release growth signals. The cancer cell would then respond to the signals in normal fashion—grow and replicate. See Douglas Hanahan and Robert A. Weinberg, "The Hallmarks of Cancer," *Cell 100* (7 January 2000): 60.

7. This process of blood vessel formation is called angiogenesis. Once a tumor grows beyond a certain size, the cells in the center of the mass become oxygen starved. By stimulating blood vessel formation into the tumor itself, the tumor satisfies the need for oxygen and continued development. It is an interesting question as to whether this support from the normal host cells makes them somehow complicit in the tumor's continued existence.

8. Lance A. Liotta and Elise C. Kohn, "The Microenvironment of the Tumour-Host Interface," *Nature*, 17 May 2001, 375.

9. Hanahan and Weinberg, 58. These authors developed this hallmark model and called these the acquired capabilities of cancer. They "suggest that most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies."

10. Cancer does not have a single cause. Rather, numerous risk factors—heredity, lifestyle, environmental exposure, and viral—can trigger mutations in virtually every mammalian cell (hair, nails, and teeth excepted). See the US NCI's Surveillance, Epidemiology and End Results (SEER) Program Training Web site, n.p., on-line, Internet, available from http://training.seer.cancer.gov/. Hereafter referred to as NCI/SEER (training module name). For more detailed information on cancer genomics, see Lance A. Liotta and Edison T. Liu, "Essentials of Molecular Biology: Genomics and Cancer," in *Cancer: Principles and Practice of Oncology,* ed. Vincent T. DeVita Jr., Samuel Hellman, and Steven A. Rosenberg, 6th ed. (Philadelphia, Pa.: Lippincott Williams and Wilkins, 2001), 17–29.

11. The genome of cancer cells is inherently unstable and undergoes more random genetic changes than do normal cells.

12. Gerard I. Evan and Karen H. Vousden, "Proliferation, Cell Cycle and Apoptosis in Cancer," *Nature*, 17 May 2001, 343.

13. The common names for cancers indicate where the original tumor originated. If for instance, the tumor originated in the breast and then spread to the brain, the patient would not then have both breast cancer and brain cancer but would have metastatic breast cancer.

14. Weinberg, 149. *The Merck Manual of Diagnosis and Therapy,* 17th ed., chap. 142, n.p., on-line, Internet, available from http://www.merck.com/mrkshared/mmanual/

home.jsp. The manual points to another interesting characteristic of metastases: "Experiments suggest that metastasis is not a random event and that the primary tumor may regulate the growth of metastatic tumors. . . . Theoretically, removal of the primary tumor can result in rapid growth of the metastases."

15. Steven A. Rosenberg, "Principles of Cancer Management: Surgical Oncology," *Cancer*, 260.

16. Carlos Caldas and Samuel A. J. Aparicio, "The Molecular Outlook," *Nature*, 31 January 2002, 484.

17. Spread to the regional lymph nodes often indicates distant, unseen metastases.

18. Although metastases were discovered in the nineteenth century, we still know relatively little about them. Some clinical observations follow: Metastases do not spread randomly; for instance, a certain cancer of the eye metastasizes almost exclusively to the liver. In addition, metastases themselves can also later metastasize.

19. The specific nature of each cancer led the NCI to promote both general and disease-specific cancer research. NCI, *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2003* (Bethesda, Md.: NCI, 2001), 93, on-line, Internet, 20 June 2002, available from http://plan.cancer.gov/pdf/bypass.pdf.

20. NCI/SEER (Cancer treatment: overview).

21. This is why staging is so important.

22. Raphael E. Pollock and Donald L. Morton, "Principles of Surgical Oncology," *Cancer Medicine*, ed. Robert C. Bast Jr. et al., 5th ed. (Hamilton, Ontario: B. C. Decker, 2000), n.p., on-line, Internet, 19 June 2002, available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books.

23. Chemotherapy acts systemically—throughout the whole body—as opposed to the local action of surgery and radiation. See, Charles S. Morrow and Kenneth H. Cowan, "Drug Resistance and Its Clinical Circumvention," in *Cancer Medicine,* n.p., on-line, Internet, 20 June 2002, available from http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=cmed.chapter.d1e333588.

24. Each therapy can achieve success on its own. For instance, surgery alone cures many skin cancers. Radiation therapy can eradicate some forms of breast and prostate cancer. Chemotherapy cures some forms of leukemia. However, some cancers are inoperable, some radioresistant, and some chemoresistant.

25. For a general discussion of combined uses of radiation with other treatments, see Samuel Hellman, "Principles of Cancer Management: Radiation Therapy," in *Cancer,* 285–86.

26. Just a note for some in the military audience: Given that a cure is impossible without eradicating all of the cancer cells, ask yourself which treatment is the dominant or more decisive one. Is it the surgery, which removed, say, 95 percent of the cells? Alternatively, is it the radiation, which killed the rest? The patient might think it a silly or even meaningless question.

27. Even with chemotherapy, the "complete eradication of metastatic disease by currently [2001] available therapeutic strategies [is] extremely difficult." Moreover, 90 percent of drug cures occur in just 10 percent of cancer types. William G. Stetler-Stevenson and David E. Kleiner Jr., "Molecular Biology of Cancer: Invasion and Metastases," in DeVita et al., in *Cancer,* 123; and Edward Chu and Vincent T. DeVita Jr., "Principles of Cancer Management: Chemotherapy," in *Cancer,* 290.

28. Hellman, 286.

29. Michael B. Kastan and Stephen X. Skapek, "Molecular Biology of Cancer: The Cell Cycle," in *Cancer,* 107. Radiation kills both healthy and normal cells. Chemotherapy damages healthy cells, but they generally can repair themselves. Physicians thus will often use the maximum safe dosage even in the presence of side effects because they are generally temporary.

30. This produces an interesting predicament: The treatment that saves you now may generate worse circumstances and kill you later. If you do not take the treatment now you may never live to worry about a second cancer. The increased risk of second cancers inherent in certain treatments must be balanced against several competing factors: age of

patient, severity of illness, likelihood of improved survival from treatment, and so on. The efficacy of treatment of the first cancer is the primary concern. Flora E. Van Leeuwen and Lois B. Travis, "Second Cancers," in *Cancer,* 2939, 2960.

31. Even while surgery avoids the toxicity side effects, it introduces other drawbacks—loss of organ function a prominent one as seen in hysterectomies and mastectomies, for example. One benefit of surgery is that the surgeon can often reconstruct what he or she damaged with curative surgery.

32. Quoted in Rosenberg, 261.

33. Arno J. Mundt, John C. Roeske, and Ralph R. Weichselbaum, "Physical and Biologic Basis of Radiation Oncology," in *Cancer Medicine,* n.p., on-line, Internet, 20 June 2002, available from http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View. ShowSection&rid=cmed.section.d1e274582.

34. Evan and Vousden, 343.

35. The patients die from organ failure associated with the disease or from systemic treatments directed at the disease. Stetler-Stevenson and Kleiner, 123.

36. NCI "Future Plans" fact sheet, n.p., on-line, Internet, 20 June 2002, available from http://cra.nci.nih.gov/index.shtml.

37. Ibid. The assessment of risk is extremely difficult. Susceptibility genes and environmental factors—within the body and without—interact in mostly unknown ways.

38. For examples of the uncertainty associated with early detection and prevention measures, see Gina Kolata, "Test Proves Fruitless, Fueling New Debate on Cancer Screening," *New York Time*s, 9 April 2002.

39. Drew Pardoll, "T Cells and Tumours," *Nature,* 28 June 2001, 1010.

40. Weinberg, 160.

41. The difficulty is in achieving this genetic conversion in all of the cancer cells present. Interestingly, scientists are using one human threat to combat another—viruses serve as one of the vehicles, or vectors, to insert the desired genes into cancer cells.

42. NCI, *The Nation's Investment in Cancer Research,* 78.

43. Brian J. Druker, "STI571 (Gleevec) as a Paradigm for Cancer Therapy," *Trends in Molecular Medicine* 8, no. 4 (1 April 2002): S14–18.

44. Evan and Vousden, 347.

45. Frank McCormick, "New-Age Drug Meets Resistance," *Nature,* 19 July 2001, 282.

46. Quoted in National Institutes of Health, "Executive Summary: National Cancer Act of 1971," n.p., on-line, Internet, 20 June 2002, available from http://www.cancersource.com/nclac/1971canceractsummary.doc.

47. Quoted in NCI/SEER (Cancer as a Disease: War on Cancer).

48. The goal in 1971 was to defeat cancer in five years. NCI, *The Nation's Investment in Cancer Research,* 98.

49. All data in this paragraph from NCI/SEER (Cancer as a Disease: War on Cancer).

50. The incidence and death rates climbed 45 and 10 percent, respectively, from 1950 to 1990. They dropped 6.4 and 2.4 percent, respectively, from 1992 to 1996. NCI, "Types of Cancer," n.p., on-line, Internet, 20 June 2002, available from http://cra.nci.nih.gov/index.shtml.

51. Ibid. The five-year survival rate increased from 35 percent to 60 percent from the 1950s to the early 1990s.

52. NCI, *The Nation's Investment in Cancer Research*, 98.

Chapter 4

Redefining War

We are, in a sense, seeing the definition of a new battlefield in the world, a twenty-first century battlefield, and it is a different kind of conflict.

—Secretary of Defense Donald H. Rumsfeld

As the pain of 9/11 subsides, the fevered demand for justice and a sense of traditional victory lessens. Scholars may one day debate whether the event should have triggered a war schema at all, but at this point, Howard's words stand true: "The *W* word has been used and now cannot be withdrawn."[1] Without doubt, America is at war. However, it is not a war that lends itself to any established characterization. To be understood fully, it needs to be described and classified properly, but, and herein lies the critical focus of this study, can—and should—the *W* word be redefined?

Members of the Bush administration apparently believe so. At the president's lead they remind us that this is a different kind of war, unlike any other that recent generations faced, and it requires us to think differently. Many people naturally grasp for the familiar to help explain and guide when confronting something new. Pearl Harbor passed across many lips even before the first World Trade Center tower fell. As Dr. Rice later explained, 9/11 was no Pearl Harbor—not because the place, means, or human toll differed but because the enemy did: "In that case, we had a country with a capital, with marching armies and beaches to storm, and islands to take, and in the last war, deserts to cross. That is not the nature of this war."[2]

The nature of the enemy and of a war are inextricably linked. Should we now face an adversary with marching armies and beaches to storm then we might profitably invoke memories of military victories to explain the task at hand: It will resemble the Persian Gulf War; it will be like Normandy. Of course, it would not be literally so. Details would differ, maybe substantially. The analogies would, however, help explain the general road ahead in familiar terms. They might even suggest other issues for further consideration, each to be subsequently analyzed outside of the analogical frame and in the relevant context. But where should we turn if, as the president has told us, recent military memories will not suffice? Perhaps, as Haass suggests, images from our metaphorical wars can hint at explanation or posit major challenges ahead in the terror war. Perhaps they can suggest areas that merit further study.

Within the current international context, Haass rightly notes that our old language does not fully capture the tasks ahead. Traditional war images—with the promise of high-profile battles and decisive military victories—could produce false expectations in an untraditional war waged covertly, oftentimes with nonmilitary means. A new language will, however, effectively represent the nature of this new enemy and new war only if it resonates with

the American people. In an age of bioterror, emerging disease, the human genome, and a metaphorical cancer war, the administration might look further to the language of disease to better communicate the challenges of the war on terrorists.

The infection and immunity metaphors described herein illustrate a threat from without the body, a contagion from "over there." Infectious diseases and international terrorists each represent potential global threats. They slip through borders, evade detection, circumvent protective measures, and often derive resources from their targets by turning a potentially hostile environment to their advantage. Both disease and terrorists kill men and women, old and young, rich and poor alike. Failure to eradicate either could allow the remaining hardy cells to adapt, to resist once-effective treatments, to multiply and strike again, perhaps lethally. New threats of each type, facilitated by technological and social change, can emerge and spread—at the same time old threats reemerge in stronger form—in unpredictable ways.

The cancer metaphor is about a threat from within, malignants in the global body. Cancer cells and terrorist cells are the renegades of their respective societies. They subvert normality, and their distorted internal messages alter behavior in harm-inducing ways. The cancer proliferates uncontrollably; we fear the terrorists may also proliferate uncontrollably. Each disregards the regulatory signals sent out from normal neighbors; instead, the renegades derive sustainment from, and may even dominate, those neighbors. Then they spread, often undetectably, and kill indiscriminately.

Parallels also exist beyond the nature of the enemy; they extend to what many foresee as the nature of the war ahead. For instance, protective measures will not suffice to counter the disease or the terrorist killers that can subvert, evade, or rapidly overwhelm even strong defenses. These cases demand prevention or intervention; we must act before attacked. Sometimes, for example, preventive surgery provides the only means to ensure one does not succumb to a specific form of cancer. While preemption may sound appealing, in both medicine and war, it can prove difficult; such situations are fraught with risk and uncertainty.

The nature of disease battles and the terror war mirror each other in a more fundamental way. The core problem in attacking microbial cells, metastasized cancer cells, and dispersed terrorists cells is the same: to find and selectively target the threatening cells while minimizing damage to healthy human cells or innocent human beings. Whether treating viruses or cancer, this can be a long, difficult, and sometimes insurmountable task. While it appears the problem is essentially similar, we cannot be sure that the prognosis or solutions will so precisely overlap, but the possibility is intriguing. Might it be the same for treating terrorists?

Additional questions predictably arise when considering the metaphors. For instance, just as various infectious agents range from highly lethal to relatively harmless, terrorist groups also differ in their capacity to injure. Nonetheless, we do not actively seek out and destroy all types of microbes. Some may even be beneficial, strengthening our immunity and symbiotically

working to ward off more deadly agents. Should we then seek out and destroy all terrorists? Furthermore, neither all infectious agents nor all terrorists have global reach; each demonstrates patterns of spread—some localized, others global.[3] To which groups should efforts be directed? President Bush noted, "we cannot single-handedly wage a successful campaign against international terrorism. In this respect, terrorism is like many other challenges of this globalized era, like combating HIV/AIDS."[4] If our goal is, as the president has said, to eradicate terrorists of "global reach," then do we necessarily, for sake of attaining international assistance, commit ourselves also to combating terrorists with only local reach, to include those that do not target US citizens or property?[5] Moreover, how do we convince our indispensable international partners that we will not, as we did with infectious disease, close the book on terrorism should the terrorist plague cease to rage within our borders but continue to do so in theirs?

While we struggle with differences between types of terrorist groups, should we consider that the term *terrorist,* like cancer, is a catchall term that says little about a prognosis or the treatments needed to counter specific terrorist cells, groups, and state sponsors? Therefore, do we need a taxonomy of terror that clearly identifies the most lethal and widespread terror cells and differentiates among the lesser, albeit still terrorist threats and the more traditional state sponsors? Moreover, who might be the terrorist carrier states—the states in which terrorists exist and possibly multiply but which show few or no ill effects from the terrorist presence? These states may be, such as Saudi Arabia perhaps, with us and against the terrorists, but they harbor the infectious threat nonetheless and, in doing so, permit it to infect others. How do we treat them, and will they accept our prescriptions? If not, should they be quarantined or have treatment measures forcefully imposed?

Even within state borders, can a democratic population and its government remain resolute, or will cycles of public health apathy and crisis response so evident in national policy also plague homeland security? Will terrorist activity and the national response, such as disease awareness and prevention, wax and wane perpetually? Perhaps a human adversary will instill more determination—and hate—than a microbial one. If not, how do we best institutionalize protective measures so that future generations take them for granted, just as we do many of the public health measures of earlier generations?[6] Will we waver in long-term effort yet steadfastly cling to traditional and ineffective interventionist treatments? On the other hand, how much folly is closing the book on traditional killers or threats to shift all of our emphasis to the new?

As these emerging threats increasingly assail our homeland, will we notice only the protection failures, taking for granted all the times that our protective systems worked without our awareness? How much collateral or healthy tissue damage will we accept as inevitable side effects of a successful protective response? Can we boost the protective systems of those countries lacking proper resources to protect themselves? Should we? Are we vulnerable to hypersensitive reactions to foreigners, and might an

overreaction to a misperceived threat damage our body politic? If so, how might we prevent such a response? Is it possible in our society that protectors could turn against the protected, a form of political autoimmune disease? In an era of fear, how do we wield protective powers sufficient to counter terrorists without jeopardizing the stringent constitutional controls that prevent protective functions from going awry? If we loosen those controls, how much and for how long? At what point is the treatment more burdensome than the disease?

Is international terrorism an acute ailment (e.g., many infections) or is it likely to be a chronic societal ill? If the latter, what symptoms are endurable and acceptable? What long-term treatments—such as raising the level of economic development in poverty-stricken areas to ward off disease and despair, thus lessening the sense of helplessness that incubates terrorism—are most cost-effective?[7] Perhaps we are witnessing only a terrorist epidemic or pandemic, one that will run its course and subside. In this case, how will we know it is over? Moreover, can we ensure it does not reemerge, possibly in a more deadly form?

Here the cancer metaphor may be especially apt: even in the absence of symptoms, will we truly know that we have eradicated all of the metastasized terrorist cells? Can we ever be sure? Might our remission from fear be only temporary? Whether short or long, probably we can know this war is over only in retrospect. Ultimately, will we begin assessing terrorist cures as we do cancer—in terms of five-year, incident-free periods? If "a *permanent* victory over international terrorism is unlikely," then how do we justify normally acceptable wartime restrictions on civil liberties?[8] At what point do we restore the liberties lost? It is a vicious cycle. The liberties that give disease and terrorism such easy entrance to the body politic are among our most cherished. Again, at what point is the treatment less tolerable than the disease?

Few of these concerns are new; the disease metaphors may add little insight for experienced policy makers.[9] The metaphors are not shortcuts to solutions—they are merely tools for education and exploration. They illustrate important facets of the nature of our current adversary and the nature of the war. As such, disease imagery can frame the core war issues in a comprehensive and easily understandable way: immunity as protection, public health as prevention, and medical treatment as intervention. While these metaphors suggest immediate organizational and policy responses to terrorism, they are not definitive or narrowly prescriptive.

Rice, Haass, and Wolfowitz correctly applied aspects of these metaphors to enrich public understanding of the tasks ahead in this new war—a potentially long struggle, one often unseen, one without clear terms of victory. The disease metaphors clearly resonate with many leaders; maybe they will with the public as well. If so, they can fortify resolve and summon long-term support, a critical base for whatever treatment strategy might be selected. In the end, perhaps this new language can help redefine our expectations of war. Perhaps that is enough.

Notes

1. Michael Howard, "What's in a Name? How to Fight Terrorism," *Foreign Affairs* 81, no. 1 (January/February 2002): 10. Howard gives credit to the Bush administration for trying to explain that "this will be a war unlike any other, and that they must adjust their expectations accordingly." Nevertheless, he sees the war mentality pushing us inexorably toward major military action.

2. Dr. Condoleezza Rice, national security advisor, press briefing, 19 September 2001, n.p., on-line, Internet, 20 June 2002, available from http://usinfo.state.gov/topical/pol/terror/01091921.htm.

3. The parallel also arises for cancer, thus the importance of staging a cancer to determine the degree of its spread.

4. Quoted in Richard N. Haass, "The Bush Administration's Response to Globalization," 21 September 2001, n.p., on-line, Internet, 20 June 2002, available from http://www.state.gov/s/p/rem/5508.htm.

5. For example, see George W. Bush, "President Bush, Prime Minister Sharon Discuss Middle East," 7 February 2002, n.p., on-line, Internet, 20 June 2002, available from http://www.whitehouse.gov/news/releases/2002/02/print/20020207-15.html. Could not global reach effectively emerge as a property of a network of otherwise local groups? Also, given international travel, can we ever eliminate global reach of suicidal radicals? Even if we could eliminate the global spread of specific terrorists groups, would not local groups retain the ability to threaten US interests outside the homeland?

6. For example, such protective measures as sewers, clean water, routine vaccination of infants, and mandatory rabies vaccines for pets.

7. One unnamed Bush administration official reportedly called these weak states "petri dishes" for terrorist cells. David E. Sanger, "Bush to Formalize a Defense Policy of Hitting First," *New York Times,* 17 June 2002.

8. Haass.

9. For instance, people invoke the Japanese internment, the excesses of the J. Edgar Hoover Federal Bureau of Investigation, and the Red Scare to illustrate the potential threats to human rights posed by a war on terror. Moreover, some military officers note that the problem of identifying unlawful combatants hidden in a civilian population is—as with the war on terror—the core issue in combating insurgencies, conflicts that may simmer for decades.

Malignants in the Body Politic

Redefining War through Metaphor

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