Macalester International

Volume 11 *The Body: Meditations on Global Health* Article 19

Summer 2002

Response to Bayer

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It is an honor to be invited to again participate in the intellectual life of the Macalester campus, and to respond to the thoughts of Dr. Bayer.

Multiple interesting and significant themes wind through the sunlight and shadows of Dr. Bayer's essay. The six that most captured my imagination can be capsulized as follows: 1) Confronting illusions of safety; 2) The human propensity for scapegoating in response to fear; 3) The value of worthy adversaries; 4) The difficulty of framing the right questions; 5) The complexity of allocating finite resources in a world of infinite need; and 6) Tensions between our responsibilities to the patients of today and of tomorrow.

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Dr. Bayer begins his portrait by describing the pre-AIDS perception that the advent of the antibiotic era had consigned infectious disease epidemics to history. He ends it by concluding: "The notion of a plague, like the great Bubonic plague of the European Middle Ages, is no longer a metaphor. It is real and it is harsh." This initial summation reflected an underestimation of the power of microbes and an overestimation of the power of modern medical science.

Science is a process of promulgating and testing hypotheses. A primary hypothesis around which our current thinking in biological sciences is organized is the concept of evolution, and of evolutionary change in response to environmental pressure. When worlds are separate and barrier-protected, the ecosystems within them attain a sort of homeostasis. When the barriers are removed and new pressures are introduced, previously stable worlds grow unstable. One way in which they manifest that instability is through the emergence and reemergence of infectious diseases.

Mechanisms of evolutionary adaptation are inherent in both infectious agents and their natural hosts. The disease-producing potential of an infection is a function of the relation between the host and the infecting agent; the biologic features of both are contributory. Thus, the pathogenic potential of an infection can change in an unpredictable fashion when the infecting microbe is transmitted from a host, with which it has co-evolved for millennia, into a different host.

This phenomenon is observed repeatedly in zoonotic diseases. A zoonosis is a disease that is transmitted from one animal species into another. Each of five hantaviruses recognized as causing zoonotic disease in humans is associated with a distinct rodent host. The phylogenetic relation among the viruses mirrors that among their rodent hosts, indicating that they have evolved together. In the rodent hosts, the hantaviruses produce no detectable morbidity or mortality. When the viruses cross species lines into humans, however, they cause disease with mortality rates as high as 50 percent.

Other zoonotic examples are easy to find. In the macaque monkey, its natural host, Cercopithecine herpesvirus 1 (B virus) has a clinical profile very similar to that of herpes simplex infection in humans. However, B virus infection in other primates, including humans, results in an encephalitis for which the mortality rate is about 70 percent. The infection of rhesus monkeys with human measles virus results in mild disease similar to that in humans, but in marmoset monkeys such infection produces severe, frequently fatal disease.

"Microbes don't carry passports" is a common shorthand used to acknowledge that in the modern era of globalization no human subpopulation can expect protection from infection introduced into humans anywhere in the world. Compelling data argue that the human AIDS pandemic began as a zoonotic disease. The human immunodeficiency virus type 2 (HIV-2) epidemic in West Africa began with the transmission of Simian immunodeficiency virus (SIV) from a sooty mangabey monkey into a human, with subsequent transmission among humans. In central Africa, the cross-species transmission of SIV from a different primate species, the chimpanzee, appears to have resulted in the HIV-1 pandemic. Initial infections of humans in Africa before 1970 resulted in more than a decade of insidious human-to-human transmission before AIDS was first identified as a public health problem in the United States in 1981. By the advent of the twenty-first century, it had transformed from a geographically circumscribed zoonotic infection into an endemic human infection of pandemic proportions.

When geographic distance provided a more significant barrier to human interactions, increases in virulence were repeatedly seen when infections that had long been endemic in certain human subpopulations gained initial access to other, previously isolated, human subpopulations. During the century that followed Christopher Columbus's trans-Atlantic passage in 1492, the European mind per-

ceived the universe to consist of two worlds: the so-called "Old World," defined by Europe and its adjacent land masses, and the so-called "New World" that had awaited discovery on the other side of the vast barrier of the Atlantic ocean. As the residents of these two worlds increasingly intermingled, many things changed. The explorers brought with them Old World microbes such as measles and smallpox. These viruses were scourges with which the Europeans had coexisted and co-evolved for millennia. Processes of natural selection had repeatedly resulted in adaptation by both the microbes and the human hosts. On the human side, the biologically most resistant Europeans were the ones most likely to survive infection and contribute to the gene pool of subsequent generations. The immunity to reinfection acquired by individual survivors within each generation collectively resulted in a "herd immunity" that minimized the size and disruptive impact of subsequent outbreaks on society as a whole. When these Old World microbes were introduced into New World human populations with whom they had not co-evolved, and among whom no herd immunity existed, the initial impact was devastating.

This microbial exchange was not unilateral. The human residents of the New World had also spent millennia co-evolving with their own endemic microbes. During the sixteenth century, a new epidemic disease referred to as "The Great Pox" ravaged Europe and Asia, impacting societies in major ways and resulting in countless deaths. We can never know the origin of this devastating illness with certainty. However, some medical historians believe that it was a virulent manifestation of venereal syphilis, transported from the New World to the Old World by Columbus's fellow explorers. The comparatively mild nature of modern day syphilis may reflect a change in the virulence of the spirochete or an evolutionary adaptation of the human hosts.

This theory is controversial. Other historians believe that syphilis began as a nonvenereal zoonotic infection introduced from nonhuman animals into humans in Asia or Europe, and that it was the advent of urbanization that allowed it to grow to pandemic proportions. Whatever its origin, syphilis continued to rank as one of the great medical scourges of mankind from its first recognition in the 1490s until the advent of penicillin in the last century.

A differential vulnerability of human populations to specific infections has been repeatedly observed in association with human migrations. When Britons departed England to serve as colonial governors in Sierra Leone, West Africa, their average life expectancy dropped to

about six months. The rapidity with which colonial governors succumbed to tropical infections earned colonial Sierra Leone the sobriquet "The White Man's Grave." Europeans who came to the southeastern coast of colonial America as indentured servants also encountered tropical infections, such as malaria and yellow fever, with which they had no prior experience. Fewer than one in seven survived the seven-year term of indentureship, making indentured Europeans a poor economic bargain compared to humans enslaved on the west coast of Africa and transported to labor contemporaneously in the same fields. Africans had a survival advantage conferred by preexisting immunity to these diseases. An infectious disease rewriting the course of history is not a unique occurrence.

Dr. Bayer described initial hopes that the availability of the first antiretroviral drug, AZT, would radically alter the life expectancy of those living with AIDS, and the subsequent dashing of those hopes. The identification of HIV as the cause of AIDS was followed by an announcement from then-Secretary Heckler of substantial financial support for biomedical research with the goal of producing a vaccine within five years. Nearly two decades later, we are still pursuing that goal, with humbled expectations. Is it necessary to have a vaccine that is fully protective or would even a partially effective vaccine be of considerable value? That question was unthinkable in 1985. HIV is not the only threat to human health for which our vaccine development efforts have thus far failed. Further, the pace at which microbes, including HIV, are developing resistance to existing antimicrobials is a major concern among infectious disease professionals.

The Department of Defense has rarely underestimated the power of microbes. Historically, more soldiers have died from infections than from bullets. Products of research funded by the military include the first antibiotics, sulfa drugs and penicillin; a shifting pharmacopeia that produces new treatments as malaria grows increasingly resistant to older remedies; multiple vaccines, including tetanus, rabies, and yellow fever; and much more. As a result, increases in the probability that a child born in the developing world will survive to adulthood may owe more to military research and development than to any other single funding source. U.S. Army research has also contributed much to our understanding of the fundamental biology of HIV. In 2001, Jeffrey Sachs, a developmental economist at Harvard, argued that the provision of AIDS treatment in the developing world was absolutely necessary to preserve the social fabric of societies with high levels of

infection. The CIA had recognized this more than a decade earlier when they identified AIDS as one of the most significant strategic threats to world stability. Ministries of Health worldwide are relatively poor and powerless arms of government. To seriously impact an issue through intergovernmental coalitions, you must move it onto the agendas of the ministries where money and power reside. The destabilizing impact of AIDS in the developing world has been an issue on Department of State briefing documents for both the previous Secretary of State, Madeline Albright, and the current one, Colin Powell.

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Scapegoating is a very common human response to pain or fear. And scapegoating is a recurring motif in Dr. Bayer's essay.

A. Scapegoating the Diseased: Are Homosexuals the Problem?

The early perception of a "Gay epidemic" had a compelling power to make the majority of humankind feel safer. This bias contributed both to significant delays in recognizing the world transforming potential of this pandemic, and to delays in implementing preventive efforts directed toward the numerically largest vulnerable population, heterosexuals. AIDS in the developing world has always been an overwhelmingly heterosexual disease.

B. Scapegoating the Unfamiliar: Are Aliens the Problem?

The ports of entry into the U.S. were rapidly closed to HIV-infected immigrants. This policy negligibly impacted the prevalence of HIV infection within the U.S., but perhaps had some impact on health care costs.

C. Scapegoating the Givers of Incomplete Hope: Are Drug Companies the Problem?

Drug companies produced and marketed AZT and other causes for hope. Patent rights ensure profits to the manufacturers of therapeutic products. Profits ensure the stability of the companies and the capability and incentive to fund new research, offering hope of new cures in the future. If releasing patent rights also decreases the capital available

to support future research and development, it becomes necessary to ask if we are abandoning our responsibility to the patients of the future in response to the agony of the patients of today.

Are pharmaceutical companies and patent rights selfish, profit-driven evils? Or are they additional scapegoats in a complex world where the most painful thing to accept is our own impotence in the face of injustice, vulnerability, disease, and death?

D. Scapegoating Moral Relativism: Is an Absence of Firm Principle the Problem?

Impassioned statements about the treacherous embrace of moral relativism, the failure of moral understanding implicit in inadequate appreciation of context, and the immorality of rigid application of moral principles pervade arguments about what constitutes ethical research on human subjects in the developing world.

It is always easier to work with black and white than to struggle with shades of gray. Rigidity provides a certain sense of safety. But safety carries its own price. Does our allegiance to principles empower or abandon our commitment to the human souls those principles were intended to protect? Does a refusal to bend on principle constitute a triumph of moral will or a failure of moral courage?

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About the ethical debates that surrounded the use of the placebo, Bayer observes, "What made the encounters so intense and furious is that they pitted against each other those who saw themselves as deeply committed to the protection of the vulnerable."

The value of a worthy ally is always obvious. But when the desired outcome is the public good rather than the triumph of the individual will, a worthy adversary who pushes you to examine your reasoning and question your assumptions may be more valuable than any ally.

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Is the existence of any therapy the appropriate standard against which the ethics of using a placebo should be weighed? Or is the existence of a therapy that is available to the community of concern? Does an acceptance of ethical relativism open a door allowing exploitation of

vulnerable populations for research? Or does a refusal to pursue research that requires us to wrestle with moral shades of gray ignore the pressing needs of vulnerable people for the sake of the philosophical comfort of the ethicist?

Were quarantine and other time-honored tools of infection control inappropriate public health responses to AIDS because the nature of the infected was different—or because the nature of the infection was different?

Are drug trials experiments on human subjects or opportunities for health care?

Study of the scientific method teaches us to formulate hypotheses, and then to examine the truth of these hypotheses. The study of philosophy teaches us to maintain vigilance for the begged question. Initial assumptions in both scientific and ethical reasoning are essentially a form of hypothesis, and we should begin by questioning them. Whether the issue at hand is the appropriate use of the placebo in research, the allocation of fiscal resources, or the best public health policy response, the first imperative is to frame the most pertinent questions. When rigorous ethical reasoning based on standard assumptions leads to outcomes that seem to conflict with or ignore the needs of the people most at risk, it is time to reassess whether you are in fact framing the right questions.

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Framing the availability of antiretroviral drugs to the developing world solely in terms of the moral obligation of the wealthiest nations to the poorest is too simple. Moral obligation cannot be discussed meaningfully in a context that fails to acknowledge the complexity of allocating finite resources in a world of infinite need. Very real limitations place a gulf between desire and ability. In real life, the question is never "how do we fix it all?" It is always "what is the best use of the resources we have at our disposal today, given that they are absolutely inadequate to address the evident need?"

A. Left in the Shadows: the Disenfranchised among Us

Bayer describes the emergence of two worlds of AIDS: one where AIDS is treatable and another where AIDS equals death. These worlds are not defined by the geopolitical boundaries that separate the devel-

oped and the developing worlds. Very real inequalities exist within developed nations. The disenfranchised are not just "over there." They dwell with little hope in many pockets of America.

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Implicit in much of Bayer's discussion was a tension between our responsibility to the patients of today and our responsibility to the patients of tomorrow. Was the concept that "drug trials are treatment, too" an empowering benefit to the patients of today or an artifice that offered only the illusion of benefit at the cost of delaying the availability of effective treatment for future patients? When placebo-controlled trial restrictions were loosened, were we responding with reason and compassion to the needs of the vulnerable or were we retreating to an illusion of power in the face of overwhelming powerlessness?

Alteration of the standard approach to drug evaluation through strict placebo control trials — with the intent of opening access to experimental therapy to all who might benefit from it — resulted in both gains and losses. The scientific method is the basis of the power that enables a transformation from medicine that comforts to medicine that cures. Placebo-control trials are not designed either to protect the vulnerable, or to treat the ill. Rather, when current medicine has nothing of proven benefit to offer the patients of today, randomized placebo-control trials are designed to maximize the efficiency with which we meet our responsibilities to the patients of the future.

Shortcutting the randomized placebo-control trial under the argument that all patients deserve access to potentially beneficial therapies is problematic in two ways: (1) it assumes efficacy of experimental approaches while failing to acknowledge fully the potential to do harm, and (2) it undercuts the efficiency with which the efficacy and safety of experimental approaches can be defined.

Triage is a hardheaded necessity on the battlefield and in medicine. The conclusion of the debates about the ethics of developing world trials was that placebo use was crucial to policymakers required to make costly decisions under conditions marked by profound poverty and scarce public health resources. This press for efficiency was driven by an economy of lives, not just an economy of dollars.

Notes and Further Reading

*This work represents the views of the author and not necessarily those of the United States government, the U.S. Public Health Service, or the Centers for Disease Control and Prevention.

Journal Review Article Summarizing Evidence arguing that AIDS is a Zoonotic Infection:

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Marks, Goeffrey, and William K. Beatty. *Epidemics.* New York: Charles Scribner's Sons, 1976.

McNeill, William. *Plagues and People.* New York: Doubleday, 1977.

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