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TECHNOLOGICAL CHANGE AND GLOBAL BIOLOGICAL DISEQUILIBRIUM

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We are living in a time of explosive manmade change. Breakthrough advances in the sequencing, decoding, and manipulation of genomes of all organisms are occurring at the same time as disruptive changes in the world's ecosystem. We are in the midst of the sixth great extinction, which is predicted to culminate in the elimination of about 30 percent of all ocean corals, sharks, and rays, 30 percent of all freshwater mollusks, 25 percent of all mammals, 20 percent of all reptiles, and about 15 percent of all birds currently alive.[1] Many factors contribute to this global disruption, including increasing carbon dioxide (CO_2) leading to climate change and shifts in ocean chemistry, geopolitical upheavals, poorly controlled intercontinental transport, unsustainable population growth, deforestation, and urbanization. Human actions are behind these factors that are eroding our ecosystem, and it remains to be seen if the coincident advances in technology can mitigate the consequences of the mess we are making.

These disruptions also are having direct consequences on human health. Climate change is a cause of the global redistribution of infectious diseases. Modern mobility facilitates rapid spreading of new diseases or pathogens that emerge from remote corners of the world

or by mutation of familiar diseases. Excessive or inappropriate use of antibiotics anywhere can have dire medical consequences globally. While many medical professionals and biological scientists have become acutely aware of these concerns over the last two decades, the principal responses have been largely reactive. Examples include emerging disease surveillance and response systems, improved clinical hygiene, and international coordination through the World Health Organization (WHO). But there is severe underinvestment in some critical areas. Two examples are surge capacity for global vaccine production to respond to a severe influenza pandemic and investment in basic research and drug development to respond to the ongoing and inevitable decline in effectiveness of current antibiotics.

The Global Redistribution of Infectious Diseases

Even small, one- to two-degree Celsius changes in ambient temperature can alter the habitat and thus the global distribution of viral, fungal, and bacterial pathogens and the birds, mice, ticks, rats, bats, and mosquitoes that carry them. Between December 2014 and June 2015, nearly fifty million domestic poultry in twenty-one American states were slaughtered to stem a raging Asian avian flu contagion. This was the worst animal disease pandemic in US history. How did it happen? Global warming has shifted migratory bird flight paths, leading to an overlap of the south-to-north Asian Pacific flyway and the North American Pacific flyway at the Bering Strait. The Arctic waters are warming faster than other regions on earth so that the Bering Strait has become a meeting and mingling spot for flocks following flyways that formerly rarely mixed. DNA sequencing enabled identification of specific Asian avian flu strains that were hitching a ride in these mingling flocks as well as their sites of origin and their mutation rates. In late 2014, an Asian avian flu virus that was transferred to the North American flock appeared first in Canada, followed by Oregon, Idaho, and Washington State. We were fortunate that the avian flu strains tracked during this period did

not easily infect humans or transfer between humans. However, with continued mutation of the virus and re-assorting of genetic material among mixed viral populations, the generation of a human pandemic strain of flu can happen at any time. The question is not if, but when such a strain will arise.

The organisms of the world that have evolved over millennia are adapted to thrive in local or regional ecosystems. Now, however, we are experiencing rapid global movements of formerly local pathogens and their vectors. These changes affect the health of people, ocean life, and the animals and plants that are our food sources. The living world is in trouble!

Since the 1980s, the annual number of epidemics across the globe has tripled, leading to social and economic disruptions. Fungal infections of corals weakened by warming and more acidic oceans have decimated the coral reefs that are part of the foundation of the ocean food chain. Hundreds of millions of people worldwide depend on them for their food and livelihoods. The death of reefs, from the Australian Great Barrier Reef to the reefs in the Caribbean, is causing a catastrophic disruption in the global food chain.

In addition to humans and animals, plants fall prey to epidemics. The precipitous rise in infections of food plants, such as fungal infection of the world's banana crop and bacterial threats to citrus crops, can cause global disruption of the food supply. And we are forgetting the lessons of the past. The devastating potato famine that killed one million people in Ireland between 1845 and 1852 resulted because of wide dependence on a single strain of a common food staple, the Irish Lumper potato. These potatoes were susceptible to blight caused by the *Phytophthora infestans* fungus that arrived in Ireland in 1844, leading just two years later, in 1846, to loss of three-quarters of the potato harvest to the blight. The unfolding crisis in the commercial banana industry is somewhat similar. Almost all bananas in our stores are the Cavendish variety. Every Cavendish banana plant worldwide is a clone and thus is genetically identical to every other. This is a recipe for disaster as a disease capable of killing one plant can kill them all. There are now fungal diseases that will wipe

out the Cavendish banana within a decade. Sadly, this scenario was both inevitable and predictable.

Global climate change contributes to unprecedented exposure of crops, livestock, wildlife, and humans to new viral, bacterial, and fungal pathogens as well as their vectors. This abnormal mingling in the biosphere causes rapid emergence of novel pathogens and the appearance of old pathogens in new places. The changing pattern of wildfowl migrations is just one example where the distribution of global wildlife is being disrupted. Weather pattern changes bring insect vectors that carry viruses into new population centers. We routinely share living quarters with the *Aedes aegypti* mosquito, which has adapted to life in urban areas, doesn't wait till evening to bite us, and carries multiple dangerous viruses. Examples include dengue (also called breakbone fever), chikungunya, yellow fever, and Zika viruses. These are just a few of the viruses we know about! The breeding habits of *A. aegypti* are sensitive to temperature: when ambient temperature increases, their gestation time decreases and their breeding seasons become longer. They like warm weather and standing water, and changing weather patterns are now providing plenty of both.

Counterintuitively, drought conditions can also lead to increases in mosquito-borne infections. An example is West Nile virus. This virus first made landfall in the Northern Hemisphere in 1999, with the sudden appearance of dead birds in New York's Bronx Zoo. The West Nile virus is transmitted by mosquitoes to both birds and humans. During droughts, birds and the water-loving mosquitoes are frequently together at the scarce water containers, leading to increased chance of virus transfer and propagation.

The tropical areas around the middle of the globe are the traditional habitat of the *A. aegypti* mosquito. Over the past several years, concurrent with the dramatic retreat of the Arctic and Antarctic glaciers caused by the warming of the oceans, there has been an equally dramatic change in the geographic distribution of mosquitoes and the pathogens they carry. Because of the temperature-induced migration of the mosquito vector, many disease-causing microbes have moved out of the tropics

and into the temperate zones. The establishment of new disease zones is further enhanced by the high mobility of modern human populations. A case in point is dengue fever, with over four hundred million people infected per year in tropical zones worldwide. Dengue is now newly established in the Caribbean and throughout the state of Florida as well as increasing in multiple southern US states and California, coinciding with the new distribution of the *A. aegypti* mosquito. Chikungunya, a mosquito-borne tropical virus, has emerged in South America and the Caribbean, with over a million infected people. Hundreds of chikungunya infections of people who have not been previously exposed to this disease have been reported in the continental United States. Zika virus, another tropical virus spread mostly by the bite of an *Aedes* species mosquito, was first identified in the 1950s in the monkey populations of equatorial Africa. It began its rapid migration a few years ago, first to Polynesia, then to Brazil, Central America, the Caribbean, and finally to the US mainland. Zika can be transmitted by sexual contact or blood transfusions. Zika can also be passed from an infected pregnant woman to her fetus to cause devastating effects on the fetal brain and nervous system.

Currently, there are no effective vaccines or drugs on the market for the dengue, West Nile, chikungunya, or Zika viruses, although international R&D efforts are in place to address these challenges. There are parallel efforts to control the mosquito populations. An effective method, previously used in Brazil and just approved for a small trial run in a southern Florida county, releases mutant male mosquitoes that, when bred with wild-type female mosquitoes, produce nonviable progeny, yielding a 90 percent suppression of this insect vector. Although the method is safe and effective, there has been public resistance to this remedy. Even with advances in vaccine technology, the revolution in gene sequencing and gene editing, and mosquito control measures, staying ahead of the current outbreaks, not to mention those that will inevitably appear, is a significant challenge.

Malaria, which is transmitted among humans by the *Anopheles* mosquito, claims the lives of 650,000 people per year worldwide. Millions

more survive with debilitating disease. The dependence of malarial outbreaks on weather conditions is not a new phenomenon. In recent decades, malaria has been primarily restricted to tropical and subtropical environments where outbreaks followed the patterns of rains and floods. Now, however, malarial outbreaks have moved, for the first time, into the highlands of East Africa owing to recent warmer and wetter weather. This has had devastating effects on the newly exposed populations. They have no immunity built up from past exposure and thus are unable to mount an immune response. The result has been a sharp increase in illness and death.

Changes in distribution of mosquito-borne viruses are just one consequence of climate change. Ticks also transmit viral and bacterial pathogens. In the American Midwest, the season for ticks that carry Rocky Mountain spotted fever now starts earlier and ends later. *Ehrlichiosis*, a bacterial pathogen carried by ticks, had been dubbed the "summer flu" because it traditionally appeared only during the warm summer season, while it now occurs any time of the year. In addition, the fungal infectious agent that causes valley fever in California and the Southwest has changed its infectious season. Eleven states in the US and multiple local governments have developed surveillance and containment plans to cope with the spread of the vectors that carry pathogenic agents. We can expect increasing awareness of the geographic change in pathogen distribution as these disease vectors march out of the tropics, and municipalities are faced with providing the funds needed to diagnose, contain, and treat new disease outbreaks.

Headlines announcing the sudden appearance and spread of diseases such as West Nile virus, the viral pneumonia-like SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), Ebola, and Zika at new global locations have become an almost yearly occurrence. Climate change is just one of a confluence of factors that have enabled this disruptive migration of infectious agents. Deforestation and population growth push pathogens and their vectors into new environments. Rapid movement of people, goods, and food through porous borders transports the co-traveling pathogens and their vectors.

The twin problems of new infectious diseases and old diseases in new locations are made worse by the growing resistance of pathogens to antibiotics, antivirals, and antifungals. Resistance to the most effective antimalarial agent, artemisinin, is growing rapidly. Owing to the rise in antibiotic resistance, we are now moving precipitously toward a return to the pre-antibiotic era. That would be a medical catastrophe with deaths from infections predicted to exceed cancer deaths and greatly increased risk for even minor surgeries. Again, it is not if, but when.

I do believe we have some evidence on global pandemics that we've responded fairly quickly. My point is, we ought to be having these conversations on a regular basis, whether they're cyber-oriented challenges or whether they're biological or chemical or whatever. I don't think we do that. Every time we have a crisis, it seems as though it's a pickup game. —James O. Ellis, Jr.

Rising Antibiotic Resistance

Antibiotic resistance is increasing in parallel with the increasing incidence of infectious diseases. US hospitals see two million cases of antibiotic-resistant infections each year that cause one hundred thousand deaths annually. Overuse or improper use of antibiotics is a major factor that can increase the rate of evolution of resistant bacteria. A pathogen can become resistant to an antibiotic in two principal ways: (1) the target organism can evolve a mutation in a gene associated with the structure or function of the antibiotic cellular target; or (2) the bacterium can acquire genes encoding antibiotic resistance mechanisms by importing foreign DNA segments that encode such mechanisms. As one example, bacteria often acquire in this manner a capability to "pump" the antibiotic molecules out of the cell. This bacterial technique for importing DNA is called horizontal gene transfer (HGT). The DNA segments with the resistance mechanisms that are imported by HGT

were evolved in other bacterial species that previously encountered the antibiotic in other animals. The resistance mechanism imported by a bacterium infecting a human could have evolved during infection of a different animal by a different bacterial strain. This is how a resistance mechanism that evolved in a bacterium infecting, say, chickens that have been fed antibiotics (a common agricultural practice) can end up in a bacterium that infects humans.

In the quest for economical production, over 70 percent of the antibiotics used annually in the United States are fed to farm animals. This practice inevitably leads to bacterial evolution of resistance mechanisms that can then be passed on to human pathogens as discussed above. There is thus a trade-off between having larger and healthier livestock and the global availability of effective antibiotics. In the short run, we have more meat on the table, but in the long run we will lose the antibiotics that are vital for human health with catastrophic consequences.

HGT is dependent on small circles of DNA called plasmids that carry genes encoding proteins that make a given antibiotic ineffective. Plasmids can be transmitted from one bacterial pathogen species. Thus, when a bacterial pathogen carrying plasmids with resistance genes appears in an environment, these plasmids can spread into all the pathogenic bacterial strains in the area. There are now even "super resistance plasmids" that carry up to fourteen different genes encoding proteins that produce different types of antibiotic resistance. A bacterial pathogen that acquires one of these super resistance plasmids will then be resistant to most antibiotics. A person with an infection of a bacterium carrying such a plasmid is likely doomed.

The good news is that modern medicine can extend human life spans by transplanting organs and even control cancer by means of sophisticated immunotherapy and chemotherapy. The bad news is that use of these medical advances can lead to populations that are immunocompromised and thus unusually susceptible to infections that must be treated with antibiotics. It is a sad fact that these immune-compromised patients also provide highly effective venues for generation of even more antibiotic-resistant bacteria.

It is important to realize that the recent rapid rise in bacterial resistance to antibiotics is not due to some newly emerged biological phenomenon. Rather, it is a perfectly normal and predictable consequence of widespread unsound clinical and agricultural practices. Clinicians often overprescribe antibiotics, in many countries antibiotics that are available without prescriptions are misused, and the agricultural industry abuses are indefensible. Compounding the problem, for decades funding for basic research in microbiology and training of microbiologists has been in decline due to a misguided belief that the problem of infectious diseases had been "solved" by antibiotics and vaccines. Further, the question of what to do about the rise of antibiotic-resistant bacteria is quite complex. An antibiotic is simply a chemical compound that disrupts some vital biochemical process in the bacterium but is harmless to human biochemistry. But a large majority of the biochemical and genetic mechanisms in human cells are very like the comparable functions in bacteria. We are, after all, descendants of bacterial cells! As a consequence, there are a finite and relatively small number of potential distinct mechanisms that antibiotics can target. The "easy" targets, the low-hanging fruit, were targeted by the antibiotics developed long ago. These older antibiotics are, of course, the ones where antibiotic resistance is more likely to be high since evolutionary selection for resistant bacterial strains is inevitable. We can slow that natural selection process, but we cannot stop it.

The traditional method for finding new antibiotics was to screen literally millions of natural compounds for effectiveness in killing pathogenic bacteria. Those found to have lethal activity were then tested for toxicity in animals and eventually in humans. Unfortunately, this method is no longer productive. The well is running dry. Use of combinations of antibiotics shows some promise for extending the life of older antibiotics. There has also been some success from combining antibiotics with new drugs that attack mechanisms the bacteria have acquired to protect themselves against antibiotics. These are all promising avenues that are effective for some, but by no means all, antibiotic-resistant bacteria.

Each of these new strategies requires R&D funding: basic research funding to discover novel strategies, development funding to reduce them to practice, and clinical trials to demonstrate safety and efficacy. As noted above, basic microbiological research at the federal level has been underfunded for decades. Over the past decade, two-thirds of the antimicrobial research and development programs in big pharmaceutical companies have been downsized, due in large part, but not solely, to the economics of drug discovery. Good medical practice now requires that new and effective antibiotics be kept on the shelf and used only as a last resort. This is to delay the development of resistance. But this practice severely reduces the potential sales and earnings of the new antibiotics that were developed at great expense. Also, antibiotics that are generally taken for just a few days or a few weeks are far less profitable than drugs taken for decades for chronic ailments such as diabetes, heart disease, cancer, and neurological disorders. From the standpoint of business considerations, drug companies' reluctance to invest in development of antibiotic drugs is a rational decision. However, from the standpoint of society's interest in responding to the looming threat of radical increases in the number of deaths from untreatable infections, the situation is insane.

Lucy is telling us that the ultimate arms race is going on right now, and the bugs are ahead. —Jim Hoagland

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The Specter of an Influenza Pandemic

Viral influenza, or flu, is an infectious disease of great global concern. Strains of this small RNA virus mutate frequently, changing both the characteristics of the H (hemagglutinin) and N (neuraminidase) proteins that sit on the surface of the spherical virus shell and of the ferocity of the infection. A new flu vaccine is created each year to target the flu strain expected in the coming season. In the 1918 flu pandemic, the

H1N1 strain killed fifty million people worldwide. Subsequent pandemics occurred in 1957 (two million deaths) and 1968 (one million deaths). Not all flu strains are easily transmitted from person to person, but when a mutation in a flu strain causes it to be transmissible, a pandemic can ensue. The story of one flu strain, H5N1 (which is endemic among migratory birds but not currently transmissible among humans), illustrates the hope that biotechnology intervention can enhance viral surveillance, provide a means of containment, and establish effective treatment following an infectious outbreak. It is also a story that raises questions about how, or if, research with infectious agents should be regulated.

The development of technology to sequence DNA and manipulate genomes has been a fundamental breakthrough in the biological sciences. The genome of a virus can now be sequenced in a few hours and the DNA of a bacterium in a day. This technology permits rapid pathogen identification and detailed tracking of disease spreading. The genomes of disease vectors and of humans can also be sequenced accurately and relatively cheaply. Research using these capabilities has produced a much deeper understanding of host-pathogen interactions. Genetic engineering and gene editing have also enabled the design of methods to control the infection process and the viability of pathogen vectors. The databases resulting from this work are the basis of global diagnostics networks for rapid pathogen identification and response intervention. The initial identification and characterization of a new pathogen starts the process of vaccine and drug design and production. Although pathogen identification can be rapid, at least six months of preparation are needed for the design, validation, and ultimately FDA approval for the delivery of a new vaccine. Production and distribution of the quantities needed for a widespread vaccination program take additional months. Development and approval of new antibiotics and antivirals take much longer.

The H5N1 flu strain, first detected in 1997 in Hong Kong, is now carried by poultry and migratory bird populations worldwide. Though there have been just a small number of H5N1 human infections among

people in very close contact with infected poultry, the death rate among those who have been infected is over 50 percent. The death rate of the 1918 pandemic flu H1N1 was only 2 percent, but it was wildly contagious, so a vast population was infected. As of now, there has been no known transmission of H5N1 from person to person, but the virus has significant potential to become a transmissible pandemic strain.

Scientists, considering how to respond to this threat before a transmissible human strain develops, are asking three critical questions:

- What is the genetic signature (genome sequence) of a potential pandemic H5N1 strain that can be used for global surveillance?
- Is there a genetic signature that can be used to identify an H5N1 strain with a high kill rate?
- Would a newly evolved pandemic strain be sensitive to existing antivirals and vaccines?

In 2011, experiments in two labs, one in Wisconsin and the other in the Netherlands, addressed these questions by attempting to evolve a laboratory strain of H5N1 that was transmissible from human to human. Their work caused a public conflict relating to the right to perform "knowledge-driven science" versus perceived ethical and security concerns. The ultimate objective of the experimenters was to genetically engineer and evolve a strain of the H5NI flu virus that would be transmissible among ferrets. Why ferrets, and what do they have to do with human transmission? Ferrets were chosen because their response to infection by the flu virus closely resembles the human response. In contrast to infection in birds, infection in both humans and ferrets occurs by inhalation of virus-laden respiratory droplets and subsequent infection by virus attachment to cells in the airways. Then, infected ferrets, like humans, sneeze, spreading potentially infective droplets in their vicinity. The researchers found that it took only five mutations in two genes to generate an airborne transmissible strain of the H5N1 virus. While these mutated viruses are transmitted among ferrets and are sen-

sitive to existing vaccines and drugs, their ability to be transmitted to humans by respiratory droplets is conjecture and not tested.

When researchers from the two laboratories attempted to publish the viral sequence for their potential pandemic strains, the NSABB (National Science Advisory Board for Biosecurity) blocked publication. The NSABB rationale was, first, that there might be an accidental release of the evolved strain and, second, that a published viral sequence might be used to deliberately duplicate the potentially pandemic strain as a biological weapon. A group of prominent scientists called for a moratorium on further H5N1 experiments and for blocking publication of the mutated sequence. This action was reminiscent of calls for a moratorium on applications of genetic engineering at the Asilomar Conference in 1973.

After public discussion and many heated debates, the moratorium was lifted when, in 2012, the US government established an oversight committee that mandated rules limiting the types of experiments that can be conducted with pathogenic strains. Publication of the original H5N1potential pandemic strains was allowed in 2013, and flu research was resumed. Then, in 2014, two things happened. The same lab that had evolved a potentially pandemic H5N1 flu strain succeeded in the reconstruction of the H1N1 1918 flu strain from material obtained from frozen bodies. Second, multiple events involving mishandled pathogens were reported at both the CDC (Centers for Disease Control and Prevention) and at an FDA (Federal Drug Administration) lab.

In response, the Office of Science and Technology Policy and the Department of Health and Human Services mandated a one-year pause in flu research, as well as research on SARS and MERS viruses aimed at eliciting enhanced transmissibility via a respiratory route. Eventually, after two workshops conducted at the National Academy of Sciences and an extensive risk assessment study, the NSABB found that only a small subset of experiments continued to be of concern, including those that "generated a pathogen that is highly transmissible and highly virulent." A plan for oversight of federally funded research in this arena is now in place.

> *The way that government takes action is through legislation and implementing policy. . . . What feels to me missing from our government though is an articulation of objectives and values that would guide the thinking of people who are in decision-making roles.* —Christopher Stubbs

Yogurt and the Discovery of Gene Editing

As stated earlier, the ability to rapidly and cheaply sequence the genetic material of all organisms has enabled identification and tracking of the migrations of pathogens and their vectors in our increasingly unstable ecosystem. Genetic engineering—the ability to design mutant proteins with altered functions and to move genes from one organism to another—has led to a deeper understanding of how viruses and bacterial pathogens interact with host cells in humans to generate altered modes of pathogen transmission and infectivity. A holy grail of genetic engineering was development of the means to directly edit the genes in chromosomes of all living entities and thus to change the instructions encoded in our DNA. Over the past several years, the ability to edit genes easily and accurately has become a reality. The ultimate impact of gene editing on global health and agriculture is not yet known, but its promise is so far-reaching that understanding how it came about and its potential uses is relevant in any discussion of our technologically driven world. In this regard, the story of the discovery of the CRISPR/Cas9 genome editing technology is a wonderful illustration of the role of serendipity in biological sciences.

The manufacturing process for yogurt uses special bacterial strains to produce the lactic acid that gives yogurt the tang and taste that customers enjoy. But, just as human cells are subject to attack by pathogenic viruses, bacterial cells can be attacked by viruses known as bacteriophage (or phage) that have evolved the ability to attack specific strains of bacteria. Phage infection of the lactic acid bacteria required for the

yogurt manufacturing process can bring production to a halt. Between 2003 and 2007 at Danisco, a Danish yogurt company, researchers in the corporate laboratory were studying this viral infection process and seeking a method to protect the lactic acid–producing bacteria. They discovered a previously unknown mechanism that these bacteria have evolved to fight viral infection. As it happened, these Danisco researchers found a bacterial immunity system, and the repercussions of their discovery have been monumental.

When the Danisco scientists investigated the DNA sequences in lactic acid bacteria that were resistant to phage infection, they found something odd. The bacterial genome contained short repeated DNA sequences that were exact copies of pieces of phage DNA. The bacteria had captured and stored a short fragment of the DNA of past viral invaders in their chromosomes, and they had also evolved a molecular mechanism that used these stored fragments to recognize DNA from new infections and destroy the invading virus. These "immunized" bacteria could quickly produce an RNA copy of the stored viral DNA segment that could find and match the corresponding segment on the foreign viral DNA. The bacteria also produce an enzyme, Cas9, that cuts and destroys the viral DNA at the tagged site. This defense mechanism protects the lactic acid bacteria and serves to immunize the bacterial culture against infection by the viral strains common in their environment. Discovery of this bacterial immunization mechanism, and characterization of its mechanism for editing foreign DNA, soon led other scientists to develop the technology that we now know as *gene editing*. The technique, referred to as CRISPR/Cas9, can modify any target gene in humans, plants, livestock, pathogens, or pathogen vectors. If, for example, a gene contains a mutation that causes an inherited disease, gene editing could destroy this deleterious gene and replace it with a "normal" gene, thereby restoring function.

"Genetic engineering" has been practiced since the eighteenth century, when farmers discovered how to use breeding programs to produce livestock with desired characteristics. But now, our ability to sequence full genomes and to use gene editing to target individual genes

opens an entirely new era in the manipulation of the instructions of life. This breakthrough technology expands the tool kit for basic research in living systems. Importantly, gene editing enables the correction of mutations in specific genes that endanger survival of our sources of food and of us as a species.

Gene editing can reengineer the genomes of animal and insect disease vectors that normally harbor the pathogen. In some instances, specific changes in the genome can be propagated rapidly through a population of, for example, the mosquito that carries the Zika virus. Another potential strategy might be to edit the genomes of food plants to generate resistance to pathogens. However, any genetic change made using the CRISPR/Cas9 technology that is propagated to all descendants of the modified plants must be approached with great caution since CRISPR/Cas9 might also introduce changes into the genome far from the targeted site with totally unpredictable consequences to descendant plant generations.

Particularly problematic are the consequences of editing genes in the germ line of humans with the chance of unpredictable off-target changes to the person's DNA. Changes in the chromosomes of eggs, sperm, and embryos would be inherited by all future generations. Before this technology can be widely used to modify heritable characteristics, its level of accuracy must be thoroughly understood. Unintended changes to an individual's genome in somatic cells could be deleterious to that individual, but this would be balanced by saving the life of the individual. However, if unintended edits to DNA in germ line cells and embryos were to be passed down to future generations, these descendants would inherit both the desired beneficial change and an unknown number of unintended and unexpected changes with unpredictable, but possibly harmful, consequences. In response to these concerns, global scientific communities and ethicists are discussing how and whether these gene-editing applications should be controlled. The NIH has called for a moratorium on using NIH funds for editing human embryos. Recently, DARPA (US Defense Advanced Research Projects Agency) has ear-

marked funds to improve the accuracy of gene editing. The goal is to ensure beneficial use and contain accidental or nefarious misuse.

> *I'm sitting here thinking this is like the first chapter of Genesis—where the world is created in seven days, and then Adam and Eve say, "We'll take it from here. We thank you for everything up to now." But now with 3D printing and AI and robotics and nukes and gene editing—it's kind of like we're writing the new Bible.* —Bishop William Swing

Where Do We Go from Here?

Whether we're dealing with manipulation (and possible eradication) of an entire species of mosquito, generating a prototype pandemic flu strain, or correcting a single mutant gene in a child with cystic fibrosis, any policy decisions will affect all nations and the global population. The breakthroughs in biotechnology and their targets of intervention have global impact, as do any attempts to enact moratoriums on scientific exploration that is believed by some to be dangerous.

It is commonly said that we live now in a global village. The effects of climate change on the geographic distribution of insect and animal vectors and their accompanying viral and bacterial pathogens know no borders. The spread of antibiotic resistance is an irreversible global phenomenon. Unsafe poultry or swine farming practices in, say, Vietnam, China, Greece, or Italy could facilitate the growth of antibiotic-resistant bacteria, and the plasmids carrying the resistance mechanisms can show up in drug-resistant bacteria infecting a child in Toronto. Or an immune-compromised TB patient in, say, an Illinois prison could, just by chance, provide the environment for evolution of a new drug-resistant *Mycobacterium tuberculosis* strain. The corollary to

these observations is that the response also must involve an international global effort.

We see some of this happening already. We now have global networks that report outbreaks of disease integrating data provided by the CDC, WHO, the Pasteur Institute International Network, and multiple clinic sites, including those in East Asia, Africa, and South America. During the SARS pandemic there was international cooperation in establishing border monitoring to detect infected persons and follow up with actions to stop spread of the infection. Computer networks and databases are being developed that have the potential to quickly identify and track the spread of new pathogens worldwide. But there is a problem. We can identify new pathogens and we can rather quickly become aware of disease outbreaks anywhere in the world. But that does not mean we have effective means to respond.

Medications to respond to new diseases or to old diseases that have become resistant to established treatments will only come from expensive R&D programs. As we noted, "market solutions" for these problems will not be forthcoming as the business risk and return numbers are not favorable. So, who will provide the necessary funds for disease treatment and containment? Currently, the United States pays 60 percent, the Gates Foundation 10 percent, Britain 13 percent, and five other countries provide the rest of the $4 billion used per year globally for pandemic mitigation. Six nations—the United States, Finland, Saudi Arabia, Pakistan, Eritrea, and Tanzania—have begun establishing fiscal plans for dealing with possible human and animal disease outbreaks. The World Bank supports the creation of emergency funds to deal with disease outbreaks anywhere in the world.

And where will we find the trained and talented research scientists who can develop the solutions to these problems? They will have to come from the international community. In 2012, on international standardized tests, US fifteen-year-olds ranked twenty-first in science and twenty-sixth in math among the thirty-four nations in the Organisation for Economic Co-operation and Development. Over the past twenty years, we have moved from first to tenth place in R&D invest-

ment as a percentage of GDP among industrialized nations.[2] There is a great need in these times for farsighted leaders and legislators who can respond with vision and national resources to these looming global health challenges.

In the United States, we need to think much more carefully about what our strategy is for ourselves and the world, and how are we going to take care of ourselves best. There are all kinds of dimensions to that. This topic is one example why acting as though the world doesn't exist is not an option. —George P. Shultz

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