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emergency threats of emerging infections in the future. For example, scientists can perform relevant research and can warn; agencies can inform and advise top government officials; presidents can initiate emergency responses; Congress can carry out emergency legislation; industry can produce vaccines in substantive amounts, if given 6 or more months' notice; state and local health organizations can deliver vaccines; and the public can be informed. These essential elements can potentially be accomplished successfully in case of an emergency, since they were achieved in 1976.

But, what went wrong? The judgments of 1995 can benefit from the clarities of hindsight (Figure). The principal reality, perhaps, is that a hard core of well-intentioned scientists and agency personnel, working with theory and limited data, exercised substantial clout to establish and maintain a changeless agenda for vaccination without meaningful periodic review and reevaluation. This reality was despite an early and increasing disenchantment in the larger scientific community with the idea that there was a real threat of pandemic influenza. No one could reasonably fault the initial concerns and actions of February and March 1976, even though built on a dubious concept that an antigenic difference alone would suffice to drive an animal influenza virus through a human population with pandemic force. The swine virus was zoonotic of origin and was of limited communicability in humans since there was no evidence for spread beyond Fort Dix. The centrist determination for immu-

nization prevailed even though there was reason to question the initiative by June and certainly to end the program in September before the October immunization campaign began.

The lessons of 1976 will provide valuable guidelines for decisions and handling of future threats from emerging disease. Such planning will benefit by obtaining a broad scientific and technical consensus and by conduct of periodic review and reevaluation that was not part of the 1976 initiative.

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Editorials

Editorials represent the opinions of the authors and THE JOURNAL and not those of the American Medical Association.

Infection Emergent

The depredations of the global HIV pandemic have been a humbling experience for the scientific infectious disease community and the public health authorities. This can hardly be compared with the human suffering induced by this alien surprise, and what may still lie ahead. However, it may yet have some salutary effect if it alerts us to still further hazards that we face as a species in our competition with microbial competitors, who crowd us at the summit of the terrestrial food chain.

This month, *JAMA* and 35 other journals worldwide will document the occurrence, causes, and consequences of emerging and reemerging infections. This resurgence of scientific interest has been matched in popular media, in the pages of newsmagazines, newspaper headlines, best-selling books, TV shows, and movies like *Outbreak*. Tangible responses by governments in the form of budgetary or staffing commitments remain negligible, and political debates about health have focused on billions of dollars for health care insurance while millions for public health are in the main ignored.

The catalog of potential and actual agents of communicable disease is congruent with large monographic texts: if any of them have been dormant for a while, some one or another is

likely to reappear in the coming months. Most importantly, the process of emergence and reemergence is a coevolutionary one. No genomes are more plastic than those of viral predators: even within a single infected individual, genomic change plays a large role in the pathogenesis of HIV, as well as in malaria or trypanosomiasis. We are likely to find that this is a more general rule even for bacterial infections; and if not within the individual, larger bacterial populations have exhibited dramatic shifts in antibiotic resistance. These resistant bacteria can then display promiscuous genetic exchange and reshuffling through conjugal plasmid transfer.¹

Similar processes are mobilized in our own somatic cell populations as our mechanism of immune response: we depend on blind luck that an immunocyte conjures up a DNA combination that will match the epitopes of the invader. The microbe's soma and germ are one, and a new selective advantage is passed on to subsequent generations; for us the rule is that we cannot rely upon the germinal transmission of our educated immunocytes to the next generation.

For our part, accommodation by compensatory biological evolution is too costly to contemplate. Setting aside calculated genetic engineering, with its own host of problems, human gene frequencies would diverge only after drastic natural selection, the sacrifice of a substantial part of the susceptible herd. Nevertheless, while Darwin never mentioned infectious disease as a selective factor, it has left its mark on human evolution. Most of the authenticated examples are erythrocyte

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modifiers in response to malarial infection; many others are sure to be discovered. Whether they will also be such mixed blessings as hemoglobin S, thalassemia, or erythrocyte G6PD deficiency remains to be seen. Arguably, cystic fibrosis might fall in this category as a prophylaxis against cholera.²

At any rate, human genomic change is not the answer for the foreseeable future. Most of human culture transcends the biological, with transmission through learning, artefactual technology, and social institutions. In that sense, as I believe was said by the anthropologist Alfred Kroeber, "man is a manmade species," for better or worse out of nature, and with many penalties in store for that hubris. In purely biological terms, we face a war of attrition against a foe that can crowd billions of microbes into a single test tube. While some may deplore the military metaphor, preferring the harmony of nature and a symbiotic détente with the microbial world, whether "Nature" is inherently benign is already beside the point for a world population that since the Neolithic has expanded a hundred- or thousandfold over its primitive bounds in a Rousseauesque-mythical State of Nature. Many aspects of emerging infection can be viewed as diseases of civilization, if we understand what embraces the invention of agriculture and then of urban life. To turn back the clock, to return to the Garden of Eden, would also be to dispose of most of now-living humanity.

We come then to social intelligence as our remaining option to counter the evolutionary drives of the microbial world. That intelligence must include a profound respect for the ecological factors that enhance our vulnerability. Many have commented about the disturbance of natural environments and the lash-back of arthropod vectors and zoonotic parasites³; and the consequences of global warming are mainly unpredictable (hence, probably harmful).⁴ Nevertheless, the preponderant changes are the sheer expansion of our species, with high population densities, and much the worse, egregiously stratified by standards of economics, nutrition, housing, and public health. At the same time, we have unprecedented mixing of people: a million passengers a day cross national boundaries by air, not to mention the movements of armies, refugees, and road transport as well-documented vehicles for the rapid spread of disease. One could hardly have concocted a better-calculated recipe for a tinderbox, as AIDS already harshly teaches. From this perspective, we have never been more vulnerable; this vulnerability must be matched against the extraordinary sophistication of the science and technology that we are, in principle, able to pit against the threats.

Doubtless, much of the "emergence" is that of reassessment of the ongoing situation. Lyme and legionnaires' diseases and *Hantavirus* infection were surely with us for many years before modern diagnostic technology enabled their more precise delineation. Most peptic ulcer disease will now be correctly reclassified as a *Helicobacter* infection. These included, many of our concerns would hardly pass for newsworthy in the developing world, in the poorest countries, where baseline communicable disease accounts for almost half of mortality, as a primary cause of death. This is in contrast to less than 10% in the developed world, according to traditional scorekeeping.¹ The toll, year in, year out, of tuberculosis, malaria, and diarrheal disease far exceeds in the developing world what would be labeled elsewhere as a shattering pandemic. "Emergence" is in fact regression, a return to the standard that prevailed universally in the previous century. It is the deviation from our accomplishments of the 1950s through the 1980s that we now assess a current crisis. And

we arrive at the realization that world health is indivisible, that we cannot satisfy our most parochial needs without attending to the health conditions of all the globe.

One line of social thought would argue that the only answer is a fundamental convergence on population and poverty. Even were the will to do so to exist, and that will needs every encouragement, the history of social experiment in the 20th century would leave one in despair. Health is also a precondition to economic development, so that more modest and selfishly motivated measures can be a great beneficence to the overall human condition.

The current situation in the United States is surveyed throughout this issue of *JAMA*. Infectious disease remains a tertiary category for mortality, still far behind heart disease and cancer.⁵ But it is rising, in important measure from AIDS, but also in a range of other categories. Outbreaks of new, or newly recognized, diseases have been seen throughout the world, some regionally grievous—eg, cholera O139—or in even more ferocious but thus far mostly localized style—Ebola in Zaire. The United States has had its own examples: *Hantavirus*, *Escherichia coli* O157, *Cryptosporidium*, which, because of their smaller numbers, have not shown up in overall vital statistics. On a substantially larger scale, the genomic innovations of antibiotic resistance are becoming increasingly troublesome, especially for nosocomial infections and for multidrug-resistant tuberculosis. We do not as yet have a quantitative measure of their impact on mortality through treatment failure, but a potential collapse of medical management of some bacterial infections is in sight.

Likewise, we have had several cycles of antigenic drift, and a few episodes of shift for epidemic influenza: these do show up as measurable spikes in seasonal mortality statistics for more elderly age groups. Whether more intensive vaccination could have prevented these consequences for familiar strains is an open question, but the answer is presumably yes, at least in partial measure. Almost certainly, a recurrence of pneumonogenic influenza like that of 1918 could well overtake the research and development cycle of new vaccine development as now constituted, taking into account the acceleration of spread that derives from present-day travel. Recall that the 1918 pandemic claimed about 20 million lives worldwide, notable for its attack on the young and vigorous, and sparing no nation. As backup to new vaccines, we do have some chemotherapeutics, but as with the viral armamentarium generally, these are imperfect, partial measures at best, though perhaps still worth stockpiling. And while we may have learned better medical management of pneumonia than was known in 1918, just visualize how that would overwhelm our hospitals.

So our prospects are, at minimum, rising exposures to familiar agents globally spread and increasing treatment failures with antibiotics. We are at plausible risk from uncontrollability of, say, pneumococcal pneumonia, and from the resurgence of a 1918-like flu pandemic. There is an outside chance of a zoonosis like Ebola escaping more broadly, with increasing adaptation to person-to-person spread, and perhaps some muting of mortality that would keep the virus from burning out before it spread further. Existing viruses might mutate or recombine to present new challenges to our control measures, or perhaps simply diffuse to areas like the southeastern United States, which already harbors many competent mosquito vectors.

Most of these contingencies are, in principle, manageable with the old standbys of vaccines, passive immune globulins, and antibacterials. These can be reinforced with very exciting

fruits of biotechnology, both for parasite control and for modification of the pathogenic processes. Most of the "new" microbial agents do not display HIV's nasty evasions of the immune system; but they could still go a long way before we actually mounted a response unless we are nimbler and more foresighted than has been evidenced so far.

The program needed in response follows fairly self-evidently from the delineation of the problem:

1. Concerted global and domestic surveillance and diagnosis of disease outbreaks and endemic occurrence. This must entail the installation of sophisticated laboratory capabilities at many centers now lacking them.

2. Vector management and monitoring and enforcement of safe water and food supplies.

3. Public and professional education.

4. Scientific research on causes of disease, pathogenic mechanisms, bodily defenses, vaccines, and antibiotics.

5. Cultivating the technical fruits of such research, with the full involvement of the pharmaceutical industry, and a public understanding of the regulatory and incentive structures needed to optimize the outcomes.

Largely through the diligent work of the National Center for Infectious Diseases at the Centers for Disease Control and Prevention, there are clearly outlined plans for epidemiological surveillance,⁶ and most of the other elements fall within the established responsibilities of government, particularly the National Institute of Allergy and Infectious Diseases. These simply await political decisions about the allocation of resources to bolster existing programs. Other forms of surveillance and intervention will require devoting substantial new resources and personnel.^{7,8} Conceptually, we probably have the least clarity about the evident market failure in the pipeline for new antibiotics. We need to learn how best to orient the industrial sector, and its inevitable coupling with the Food and Drug Administration, to efficient attention to developing new antibiotics and vaccines.

Understandably, private entrepreneurs are unlikely to invest in purely anticipatory development, the equivalent of war reserves for the military, against future and problematic contingencies. When the volcano does erupt, the industrial sector will be denounced for profiteering when it prices the priceless in accord with market principles, at levels justified by the risks to which it puts its capital. So there is an unavoidable responsibility for the public sector—hard news at a time when disinvestment is the political name of the game in Washington. This is compounded by the status of public health as a poor relation of remedial health care, a subordination that is bolstered by the long-standing economic and political structures of our medical establishment and its associated educational institutions.

Hence the importance of this Emerging Infection Month, the reinforcement and clarification of our consensual medical scientific perspectives, and the reinforcement they give to public explicators of contingencies. These are often the hardest to convey with balance, without gratuitous scares, with simply a hard-nosed prudence to anticipate threats we hope will never materialize, but some of which surely will.

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Infectious Diseases

A Global Approach to a Global Problem

A little more than a decade ago, *Harrison's Principles of Internal Medicine*¹ proclaimed that "infectious diseases are more easily prevented and more easily cured than any other major group of disorders. . . ." A new disease called "acquired deficiency of cell-mediated immunity in young homosexual men" occupied less than a column of text. "Slim disease," recognized possibly as early as 1962,² did not warrant an entry, but the dramatic decline in tuberculosis seen during the previous decades was noted to have "leveled off." This complacency, reflected in the textbook and documented throughout this issue of *JAMA*, allowed a greater focus on heart disease and cancer. Ten years later, cardiovascular disease mortality has declined, and much of the public knows that high cholesterol and blood pressure should be controlled. Infectious disease mortality, meanwhile, has climbed to the third leading cause of death in the United States.³

In 1996, we view infectious diseases with a humbler eye. The

victories of a quarter century ago ring hollow as AIDS ravages,⁴ enterococci become resistant to all standard treatments,⁵ and the once easily treated pneumococcus gains a plethora of antimicrobial drug resistance.⁶ Unknown diseases develop with disconcerting frequency,⁷ and Ebola virus has been identified outside the confines of Zaire.⁸ Once considered unique and isolated, these events penetrate every corner of the globe. As was recognized in 1892 when the first international sanitary convention on cholera was adopted,⁹ infectious diseases cannot be observed, battled, or understood street by street or country by country. A global approach is necessary.

With this perspective, three editors set about creating the first-ever global theme issue of medical journals. Last December, Linda Hawes Clever, MD, editor of *The Western Journal of Medicine*, Magne Nylenna, MD, editor of the *Journal of the Norwegian Medical Association*, and George D. Lundberg, MD, editor of *JAMA*, contacted the editors of 78 journals worldwide to invite them to participate. Now, 1 year later, 36 journals in 21 countries have agreed to devote all or part of one of their

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