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EDITORIAL

Coexisting with viruses

'No matter how selfish our motives, we can no longer be indifferent to the suffering of others. The microbe that felled one child in a distant continent yesterday can reach yours today and seed a global pandemic tomorrow. "Never send to know for whom the bell tolls; it tolls for thee".'

Joshua Lederberg
Medical Science, Infectious Disease and the Unity of Humankind
J. Am. Med. Assoc., 1998, **260**, 684;
Current Contents, 1989, **12**, 145

'The United States should be investing efforts and funds to strengthen the health structures in countries around the world. If we were to help train experts in epidemiology and surveillance, strengthen laboratories in key regions and link them to the best labs in this country and around the world, and support WHO, we would help to create a true global health network. This investment would protect our country and every other against global epidemics, save millions of lives and change the US image from one of self-interest to one of human interest'.

Barry R. Bloom
Lessons from SARS
Science, 2003, **300**, 701

The first descriptions of acquired immune deficiency syndrome (AIDS) appeared in 1981. By 1984 it became clear that the causative agent of AIDS was a retrovirus, christened the human immunodeficiency virus (HIV). In the two decades since its discovery, HIV and AIDS have occupied centre stage in most discussions of public health. At times, the perceived importance of AIDS as a threat to human health has diverted public attention and research funds from diseases which afflict larger populations, exact a heavier human toll, but are restricted to the less developed countries. In a remarkably prescient address at a conference of Nobel laureates in 1988, Joshua Lederberg emphasized that 'the ravaging epidemic of acquired immunodeficiency syndrome has shocked the world. It is still not comprehended widely that it is a natural, almost predictable, phenomenon. We will face similar catastrophes again, and will be ever more confounded in dealing with them, if we do not come to grips with the realities of the place of our species in nature'. Lederberg posed the problem of our relationships with our microbial environment with great clarity: 'Human intelligence, culture and technology have left all other plant and animal species out of the competition. We also may legislate human behaviour. But we have too many illusions that we can, by writ, govern the remaining vital kingdoms, the microbes, that remain our competitors of last resort for dominion of the planet. The bacteria and viruses know nothing of national sovereignties. In that natural evolutionary competition, there is no guarantee that we will find ourselves the survivor'.

Lederberg's concerns voiced even as the AIDS scare peaked in the late 1980s, seem particularly relevant today, as a new viral disease, Severe Acute Respiratory Syndrome (SARS), appears to have emerged from the southern Chinese province of Guandong, with its first public victims having been identified in Hong Kong. SARS is accompanied by the commonplace symptoms of influenza and is an airborne disease. In today's world SARS has spread quickly through the Far East and even beyond; Toronto becoming an outpost in the Americas. The rapid spread of infection has been facilitated by air travel; infected individuals become viral reservoirs, transported in hours across continents. The SARS outbreak appears to be under control, a tribute to the stringent public health measures adopted in several Southeast Asian countries, whose discipline and organization would be hard to replicate in many less developed areas of the world. Even more strikingly, the response of the biomedical research community to SARS demonstrates the enormous power of the tools of modern biological research. The first clinically diagnosed cases of SARS appeared in hospitals in Hong Kong in late February. On 31 March researchers in Hong Kong reported that 'SARS appears to be infectious in origin' and noted that 'the microbiologic origins of SARS remain unclear' (K. W. Tsang *et al.*, *New Engl. J. Med.*, 2003; published at www.nejm.org). A week later, the clinical, laboratory and radiologic features of 138 patients was reported (N. Lee *et al.*, *New Engl. J. Med.*, 2003; published at www.nejm.org on 7 April). Barely ten days later, the causative agent had been identified as a 'novel coronavirus' (T. G. Ksiazek *et al.* and C. Drosten *et al.*, *New Engl. J. Med.*, 2003; published at www.nejm.org on 10 April). One of the authors, Carlo Urbani had already succumbed to the infection. The two simultaneously published papers,

which establish the viral etiology of SARS, have authors with affiliations to institutions in Atlanta, Hanoi, Singapore, San Francisco, Taipei, Hong Kong, Bangkok, Hamburg, Frankfurt, Marburg, Paris and Rotterdam remarkable testimony to the power of purposeful international collaboration. Three weeks after the identity of the SARS agent was established the complete genome sequences of distinct viral isolates were reported by two independent groups (Sciencexpress/www.sciencexpress.org/1 May 2003). The viral genome has a length of about 29,700 nucleotides, a tiny fraction of the over three billion bases that specify our genetic program. The analysis of the SARS virus genome reveals no similarity to other known coronaviruses, promising to keep biologists busy establishing the significance of the many unique features of the organism's genetic makeup.

The progress in understanding the SARS virus has been breathtakingly fast, demonstrating the virtues of networking and cooperation in an increasingly interdependent world. In the case of AIDS, two decades ago, it took about two years to identify HIV as the infectious agent; at that time competition won over collaboration (*Science*, 2002, **298**, 1726–1731). The SARS episode, by contrast has, thus far, been a model of enlightened scientific cooperation.

AIDS and SARS are viral threats that emerged with frightening rapidity, reminding us of the vulnerability of the human species to variant microbes, which can overwhelm our immune defences. Curiously, even as SARS edged Iraq from the headlines, an article in *American Scientist* (2003, **91**, 122) highlighted the problem of influenza, claiming that 'the world is teetering on the edge of a pandemic that could kill a large fraction of the human population'. The authors, R. G. Webster and E. J. Walker, trace the influenza epidemics of the 20th century, noting that the epidemic of 1918–1919 affected '500 million people across the globe and killed at least 20–40 million – more than twice the number who died on the battlefields of World War I'. The influenza viruses that cause human disease have their origin in avian viruses, migrating from birds to humans through intermediate hosts, 'usually domestic fowl or swine'. Webster and Walker note that 'most pandemics originate in China, where birds, pigs and people live in close proximity. Hong Kong's 1997 "bird flu" was an avian influenza virus that probably attained virulence through reassortment of genes from geese, quail and teal'. A rapid response to an emerging infection, by local public health authorities, effectively contained the 1997 influenza outbreak in Hong Kong. The ability of these viruses to mutate and undergo 'antigenic shifts' permits them to evade human immune systems and makes vaccination a poor strategy for combating infection.

The SARS outbreak has focussed attention on the problems of infectious disease. Over the last couple of years there has been much public discussion on the subject of bioterrorism, where a dangerous pathogen may be intentionally released into the environment. The countries with the greatest capabilities in the areas of biological weapons are also the ones who appear to perceive the greatest threats. The report of the United States, Institute of Medicine on *Microbial Threats to Health* (March 2003) begins with these words: 'Infectious diseases continue to be a serious burden around the world, in developing and industrialized countries alike. Whether naturally occurring or *intentionally inflicted* (italics mine), infections can cause illness, disability, and death in individuals while disrupting whole populations, economies and governments. And because national borders offer trivial impediments to such threats, especially in the highly interconnected and readily traversed "global village" of our time, one nation's problem soon becomes every nation's problem'.

The spectrum of biological infectious agents which can emerge from the cauldron of nature's evolutionary processes, pose a continual threat to the well-being of humans. In the struggle between microbes and man, who will prevail? A study of our shared evolutionary past may provide a glimpse of what awaits us in the future. On the broad canvas of a biology driven by Darwinian imperatives, there may be the prospect of a not entirely benign equilibrium. Lederberg strikes a positive note in his essay: 'Many defense mechanisms inherent in our evolved biologic capabilities, thus mitigate the pandemic viral threat. Mitigation is also built into the evolution of the virus: it is a Pyrrhic victory for a virus to eradicate its host! This may have happened historically, but then both the vanquished host and victorious parasite will have disappeared'. Lederberg adds: 'At evolutionary equilibrium we would continue to share the planet with our internal and external parasites, paying some tribute, perhaps sometimes deriving from them some protection against more violent aggression. The terms of that equilibrium are unwelcome: present knowledge does not offer much hope that we can eradicate the competition. Meanwhile, our parasites and ourselves must share in the dues, payable in a currency of discomfort and precariousness of life'.

The public health and biomedical research response to the SARS episode has been spectacular in its speed and efficiency. There has been little doubt about the nature of the disease and the causative organism; a sharp contrast to the 1994 Surat 'plague'. The sudden emergence of new infectious agents may exact a higher toll if the outbreak occurs in the more populous, less organized and underdeveloped parts of world. But even here, nature may have the final say. A constant exposure to pathogens can serve to enhance the level of natural immune competence. Lederberg must have the last word: 'Paradoxically, improvements in sanitation and vaccination sometimes make us more vulnerable because they leave the larger human herd more innocent of microbial experience'.

P. Balaram