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Eradicating infectious disease: can we and should we?

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"*Eradication of microbial disease is a will-o'-the-wisp; pursuing it leads into a morass of hazy biological concepts and half truths.*"

These are the pessimistic words of René Dubos in 1965, encapsulating the challenges of attempting to eradicate infectious disease. In 1979, smallpox became the first infection to be eradicated, a huge triumph for science and humanity. Sadly, this impressive feat has only been replicated once since then with the eradication of rinderpest virus in 2011, and the words of Dubos seem as relevant today as they did in 1965.

As the only two infections eradicated to date are viral, it is tempting to assume that viruses are the ideal candidates for eradication. To some extent, this is true. Viruses are obligate intracellular pathogens and if denied access to host cells through immunization by vaccination, transmission is prevented, and the virus will be unable to replicate, leading to its extinction. Smallpox was a sensible target for eradication as the virus had no animal reservoir or latent phase, an effective single dose vaccine existed and infection produced obvious clinical signs, allowing effective surveillance for infection (Henderson, 1998). By 2006, eradication efforts had reduced the worldwide incidence of poliomyelitis infection by 99% through the oral polio vaccine (OPV; Arita et al., 2006). The remaining 1% seems to be clustered in endemic areas (India, Pakistan, and certain African countries) and the main barrier now is not biological, but operational, e.g., security issues in Afghanistan and a funding deficit. However, a problem with live vaccines such as the OPV is that the strain can potentially revert back to a pathogenic form and this has been encountered with the OPV. Furthermore, unlike smallpox, poliomyelitis can be subclinical, making vaccine targeting difficult. On a positive note, the complete eradication of polio from the Americas suggests poliomyelitis eradication is possible.

However, eradication of viral diseases is not a straightforward process. Indeed, there are viral diseases that appear impossible to eradicate due to certain characteristics of the causative virus. Herpes simplex virus resides latent in neurons, from where infection can reactivate. One cannot identify latently infected individuals clinically but they have the potential to become infective when the virus reactivates. If a vaccination program was stopped before all latently infected members of a population had died, reactivation of latent infections would result in the infection of naïve, non-vaccinated individuals, taking the program back to square one. Influenza A is an RNA virus whose antigens are constantly changing due to antigenic shift and drift (Carrat and Flahault, 2007). Antigenic drift involves point mutations in the hemagglutinin and or neuraminidase genes, encoding envelope glycoproteins, thus reducing the binding affinity of antibodies raised against previous strains. This explains why individuals can be reinfected with influenza and why the content of the seasonal vaccine must be altered annually. Antigenic shift is the genetic reassortment of genome segments between animal and human strains leading to the expression of novel hemagglutinin subtypes. It essentially creates a "new" virus to which no pre-existing immunity exists and is the process behind dangerous pandemics such as the 1918 "Spanish Flu." The net result of this antigenic instability is a virus that is constantly changing and can thus evade immunity to a previous variant. Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are other RNA viruses that pose similar problems in terms of their rapid rate of evolution, outpacing the immune system. The use of more conserved antigens may provide a solution to this problem but the error prone nature of the RNA dependent RNA polymerase used by influenza and HCV represents a fundamental problem in that even conserved genes have the potential to mutate rapidly under correct selective pressures. HIV causes the acquired immunodeficiency syndrome, resulting in 2 million deaths per year. HIV-1 was first identified in 1983 and is thought to have first entered the human population in 1931 following simian immunodeficiency viruses making a species jump from primate to man (Gao et al., 1999; Korber et al., 2000). This cross-species transmission event was followed by adaptation of the virus to its new host, giving rise to the HIV strains seen today, capable of human–human transmission. Similarly, the 2009 pandemic swine-origin influenza A (H1N1) virus originated from recombination between several influenza virus strains circulating in swine. This antigenic shift resulted in a virus with the potential for human–human spread at a pandemic level, fine tuned by selection pressures following the cross-species transmission event (Smith et al., 2009).

Bacteria represent a bigger problem in that, unlike viruses, few pathogenic bacteria are obligate pathogens. Many are opportunistic pathogens: these can be members of the normal flora that only cause disease if the host is immunodeficient or they access a normally sterile area. An example is *Staphylococcus aureus*, which can be found asymptomatically colonizing the nasopharynx. Bacteria such as *Pseudomonas aeruginosa* and spores of *Bacillus anthracis* can survive in the environment, without infection of their host. A further complication is that many bacteria have animal reservoirs, e.g., *Escherichia coli* O157 asymptomatically colonizes the terminal rectum of cattle (Naylor et al., 2003). Cattle are well controlled animals and a vaccine program in cattle stands a better chance of eradicating infection than, for example, eradication of *Yersinia pestis* from it's rodent reservoir. Therefore, the nature of the bacteria–host relationship is a significant barrier to eradication of most bacterial infections. On the other hand, *Chlamydia trachomatis* is an obligate intracellular pathogen that has undergone genome reduction, losing its capability for free living. Since humans are an essential part of its lifecycle and it has no known animal reservoir, it appears potentially eradicable. A successful vaccine

has not yet been produced and future hopes include DNA vaccines or a live attenuated vaccine (Brunham et al., 2000; Schautteet et al., 2011).

Environmental efforts can be used toward eradicating an infection, as exemplified by dracunculiasis, caused by *Dracunculus medinensis*. Humans are the only host for *D. medinensis* but no vaccines exist. Infection occurs through drinking contaminated water and thus filtering water to remove infectivity can prevent transmission (Cairncross et al., 2002). This operates in tandem with efforts to remove the worms from blisters; preventing them entering water.

So far, we have considered some of the practical problems with eradicating an infection, assuming that eradication is indeed desirable. Whilst for some infections such as HIV, eradication is clearly a desirable goal, there are others that may require more careful thought. *Clostridium difficile* pseudomembranous colitis is an obvious example of the dangers of broad-sweep microbe killing in humans. A less obvious example is the case of *Streptococcus pneumoniae* vaccination. *S. pneumoniae* is the main etiological agent of pneumonia and the pneumococcal vaccine is used in individuals with pre-existing lung disease to protect from infection by virulent strains of this bacteria. However, *S. pneumoniae* is a member of the endogenous flora of the nasopharynx, colonizing this site asymptomatically. It appears that colonization by *S. Pneumoniae* strains found in the vaccine is negatively associated with *S. aureus* colonization, possibly due to the two bacteria being in competition with each other in the nasopharynx (Regev-Yochay et al., 2004). It is interesting to consider the role this may have in driving the rise in incidence of community acquired methicillin resistant *S. aureus* infection (Blaser and Falkow, 2009). *Helicobacter pylori* chronically colonizes gastric mucosa and is associated with 95% of duodenal and 75% of gastric ulcers and also with gastric cancer. *H. pylori* gastric colonization has fallen markedly, thanks to antibiotic treatment and reduced transmission, and this has culminated in a welcome decrease in the incidence of peptic ulcer and gastric cancer (el-Serag and Sonnenberg, 1998). However, there is evidence that this is associated with a reciprocal rise in the incidence of the constellation of gastro-esophageal reflux disease, Barrett's esophagus, and esophageal adenocarcinoma (el-Serag and Sonnenberg, 1998; Blaser and Atherton, 2004). Furthermore, *H. pylori* clearance appears to result in increased ghrelin secretion by the stomach (a hormone that stimulates hunger). It is hypothesized that this lack of *H. Pylori* mediated ghrelin downregulation in children (due to reduced *H. pylori* transmission) could be related to the increasing incidence of obesity in children, along with the metabolic syndrome (el-Serag and Sonnenberg, 1998; Blaser and Atherton, 2004; Falkow, 2006). In an experimental model of chronic *Salmonella typhimurium* infection in mice, a significant peripheral blood transcriptional profile signature can be seen even by the time there is no bacteremia and only low numbers of bacteria are found in the organs. This signature involves genes of both the adaptive and innate branches of the immune system. Therefore, this model system shows that persistent infection results in a long-term, potentially lifelong effect on host immune regulation (Falkow, 2006). Taken together, all of these examples show how the microbe–host interaction is more complex than previously thought. Bugs don't equal disease. In some instances, infection by pathogenic organisms appears to have beneficial effects for the host and this must be fully explored to fully understand the consequences of eradicating any infection.

Louis Pasteur stated that "*it is within the power of man to eradicate infection from the earth.*" Currently, this is far from the case. Viral disease may represent an easier target than bacterial disease, but there are many biological properties of viruses that stand in the way of eradication using current technology and current ways of thinking. Infectious diseases that cannot be eradicated can usually be controlled to some extent, be it through the use of antimicrobial chemotherapy, vaccinations, or behavioral changes. A major barrier to such control is inadequate healthcare provision in developing countries, who bear the brunt of most infectious disease. Therefore, eradication of such healthcare inequalities would help a long way toward relieving the global burden of infectious diseases. Furthermore, antimicrobial drugs must be used more carefully and new compounds must be developed; lest resistant strains of microorganism nullify the efficacy of these drugs as a control measure. However, something that Pasteur may not have considered is the possibly deleterious effect to man of eradicating certain infections. This school of thought is currently not far from the "*morass of hazy biological concepts*" of Dubos but ongoing research into the symbiotic interactions between even pathogenic bacteria and their hosts is likely to yield very interesting data. Humans have co-evolved with microbes and it is too simplistic to consider the eradication of microbial disease entirely beneficial.

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