SERIES INTRODUCTION

New directions in vaccine research

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J. Clin. Invest. **109**:1517–1518 (2002). doi:10.1172/JCI200215876.

During the past 100 years, the widespread use of vaccines has begun to ameliorate the devastating effects of infectious disease, increasing the average life expectancy and enhancing the quality of life of those who have been vaccinated. During the 20th century, more than twenty vaccines were introduced, and in the US and Europe these vaccines dramatically curtailed (or nearly eliminated) diphtheria, tetanus, pertussis, measles, mumps, rubella, poliomyelitis, and diseases caused by *Haemophilus influenzae* type b. In addition, the global eradication of smallpox through vaccination has been one of the great triumphs of modern medicine.

Nevertheless, there are at least three reasons to renew our efforts to develop new and better vaccines. First, with the notable exception of smallpox, the organisms that cause most of these diseases continue to circulate in the population worldwide. Second, in addition to these persisting scourges, new diseases continue to emerge. Perhaps the most frightening example is AIDS, with its devastating effect on millions of people throughout the world. Third, as both scientists and the public have recently come to appreciate, the use of infectious agents as bioterrorist or biowarfare weapons represents a potent threat to individuals and society. Thus, there is an urgent need to maintain and improve vaccinations against circulating agents, to develop vaccines against emerging diseases, and to hone our ability to respond to novel biological threats, whether of natural or unnatural origins.

Better, and safer, mousetraps

Despite the extraordinary success of many currently used vaccines, there is a need for improvement. A case in point is the influenza vaccine. The presently approved inactivated vaccine requires injection by needles, as well as annual administration. Clearly, a safe vaccine that could, for example, be administered by nasal spray and be effective for several years would represent a major step forward. Such a vaccine would also reduce concomitant cases of bacterially caused otitis media in children and pneumonia in the elderly. Fortunately, with the advent of genetic engineering techniques, it is now practical to alter the viral genome. Drawing on parallel developments that have greatly deepened our understanding of the immune system, we can redesign natural influenza virus strains to improve the efficacy of vaccines (1). Such approaches may soon result in safe and commercially viable vaccine products that will be usable in developing as well as developed countries. Likewise, the development of respiratory syncytial virus vaccines, based on genetically engineered strains, will likely replace the only currently available prevention modality, passive vaccination using intravenous or intramuscular injection of antibody preparations (2).

New and better vaccine approaches are also needed for many bacterial diseases (3) against which we now have only partially effective vaccines, or against which our major weapons of defense are antibiotics. The latter approach may lead to selection for drug-resistant mutants, whose antibiotic resistance genes can blunt or eliminate the effectiveness of the therapy and can be transmitted horizontally to other bacterial pathogens. The use of appropriate bacterial vaccines may actually result in a decrease in antibiotic use. Such a reduction in antibiotic prescriptions was observed following the introduction of the *H. influenzae* type b vaccine in the US. Bacterial vaccines that can and should be improved include those for salmonella and anthrax (4).

Vaccines where none existed before

Conquering AIDS has become an unprecedented challenge for the scientific community. Despite the progress represented by the development of antivirals, the best approach to curb this devastating disease would be through effective vaccination (5). Efforts by legions of laboratories will no doubt succeed eventually, if not in preventing the disease, then at least in slowing its progress more easily and effectively than antivirals can. One important result of these efforts is that major progress has been made in our fundamental understanding of the immune systems, especially the cellular immune system (5). Possibly even more difficult is the task of developing effective vaccines against malaria. There is an extremely complex relationship between the malarial parasite and humans, which is

governed by the genetics of the host and the infectious agent (6). This parasite–human host interaction is further complicated by the existence of a second host, the mosquito. Eradication of this disease is therefore even less likely than eradication of AIDS, for which humans appear to be the only host.

As demonstrated by smallpox, diseases caused by agents limited to the human host are indeed candidates for elimination by vaccination. Whether this will ever be accomplished for many of our human infectious diseases remains to be seen. For example, the obstacles to the development of effective vaccines against herpes or cytomegaloviruses, which are obligate human pathogens, remain high at this time, with no solution in sight for the near future (7).

Unorthodox approaches and the future of vaccine design

We begin this Perspective series with the accompanying discussion by Steinman and Pope of the promise of harnessing dendritic cells in vaccine design. These antigen-processing cells, sometimes described as natural adjuvants, can be loaded ex vivo with native or altered antigenic peptides to foster immune responses to pathogens or tumor antigens (8, 9). Other intriguing approaches will exploit the vast quantity of genomic and proteomic data that is now coming to light for engineering vaccines to target specific host-pathogen interactions (3).

Although the advantages of vaccines are obvious and compelling, there appears to be a huge lag time between what has been done in the laboratory and what has become available to patients. While fascinating unresolved scientific puzzles abound in this field, much of this delay can be attributed to the barricades of legal threats and governmental regulations that make it difficult to translate the benefits of research into medical help for patients. A case in point is the recent development of human papilloma virus vaccines. Two hundred thousand women die annually of cervical carcinoma worldwide. This cancer is almost 100% associated with infection by the oncogenic types of this virus. After painstaking research efforts, a vaccine against papilloma virus has been developed that appears to be safe and to prevent a large percentage of this disease. It would only be appropriate if the anthrax cases that followed the terrible events of September 11, 2001, were to smooth the path that brings research from the bench to the bedside.

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