Vaccines, Vaccination, and Vaccinology

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Although the demonstration in 1796 by Edward Jenner that vaccinia virus could protect against smallpox was epochal, he was following the path opened by the ancients who had used the smallpox virus itself in the practice of variolation. The work of Louis Pasteur on chicken cholera opened the way to vaccine development in the laboratory. In April 1880, Pasteur reported to the French Academy of Science that “…chicken cholera is produced by a microscopic parasite [now known as Pasteurella multocida], that there exists an attenuated virus [Pasteur was using “virus” in the ancient sense of the word] of that disease, and that one or more inoculations of this attenuated virus can preserve the animals from the mortal effects of a later inoculation ... let me be permitted to use the word ‘vaccinate’ to express the act of inoculating a chicken with the attenuated virus” [1]. Thus, the word “vaccinate” was extended beyond vaccinia and came to have its modern meaning.

Today, epidemic infectious diseases of children for which there are vaccines have virtually disappeared from industrialized countries such as the United States. These are remarkable successes, which together with clean water and antibiotics have profoundly affected human society [2]. In addition, a new field of microbiology and immunology has evolved, called “vaccinology,” that comprises not only vaccine development but also the use of vaccines and their effects on public health [3]. Here, I will briefly cover some aspects of the past, discuss 5 current issues in vaccinology, and then turn to the future.

CLASSIC METHODS OF VACCINE DEVELOPMENT

Since the time of Pasteur until recently, there have been 2 paths of vaccine development: attenuation and inactivation [4]. With regard to attenuation (figure 1), heat, oxygenation, chemical agents, or aging were the first methods used, notably by Pasteur for rabies and anthrax vaccines. Passage in animal hosts, such as the embroyonated hen’s egg, was the next method, as practiced by Theiler for yellow fever vaccine. After the development of cell culture in the 1940s, attenuation in vitro was accomplished by a variety of means, including selection of chance mutants, adaptation to growth at low temperatures, chemical mutation to induce inability to grow at high temperature (temperature sensitivity), or induction of auxotrophy in bacteria.

For viruses with segmented genomes, such as influenza virus and rotavirus, reassortment has been used to combine genetic material coding for protective antigens of pathogens, with genes coding for attenuated behavior in the host (figure 2). The resultant reassortants can immunize without causing illness. Reassortants have been fundamental to the preparation of both killed and live virus influenza vaccines.

The second set of strategies is the inactivated organism or subunit path (figure 3). Late in the 19th century, Theobald Smith in the United States and Pasteur’s colleagues independently showed that whole organisms could be killed without losing immunogenicity, which soon became the basis of vaccines for typhoid and cholera and later for pertussis, influenza, and hepatitis A. In the 1920s, the exotoxins of Corynebacterium diptheriae and Clostridium tetani were inactivated by formalin to provide antigens for immunization against diphtheria and tetanus. Later in the 20th century, influenza vaccine progressed to subunit preparations, and pertussis vaccine progressed from bacterial soup to the extracted proteins that we use today in acellular vaccines. Extracted native polysaccharides from the capsules of Haemophilus influenzae type b, pneumococci, meningococci, and typhoid bacilli proved useful in immunizing older children and adults, and more recently, the conjugation of these polysaccharides with proteins have provided us with immunogens that generate T cell memory and are effective even in young infants. Although peptide subunits of proteins have not thus far been successful against infectious diseases, they do offer hope for vaccines against melanoma and other cancers, and both lipidated and mul-
Some Current Issues in Vaccinology

Rotavirus. The most significant debacle in the recent history of vaccination was that of the rhesus rotavirus vaccine. The vaccine was composed of reassortants between a type 3 rhesus rotavirus and 1 gene from each of human rotavirus types 1, 2, and 4. Rhesus rotavirus vaccine was highly effective against severe rotavirus diarrhea both in trials before licensure and in actual use after licensure. However, after licensure, intussusception was found to be a serious adverse reaction to the vaccine, and the vaccine was withdrawn [7]. The attributable risk (i.e., the risk to vaccine recipients minus the background risk of intussusception in the infant population) may have been only ~1 per 10,000 or 20,000 vaccinations, but rotavirus diarrhea is seldom fatal in the United States, and the risk/benefit calculation was not favorable to the vaccine. On the contrary, in developing countries, the same calculation probably would have been favorable, but the difficulties in accepting a product rejected by the United States were insuperable, and those countries refused to adopt the rhesus rotavirus vaccine.

One lesson from this experience is that, if a vaccine has potential to be used in developing countries, trials should be done in those countries before licensure, so that if a problem occurs, the benefits as well as the risks can be weighed in varying circumstances. Another lesson is that rare events cannot be ascertained in prelicensure studies and that careful surveillance in the period just after licensure of a vaccine is mandatory.

Fortunately, alternative live oral rotavirus vaccines are in development: a set of bovine reassortants and an attenuated human strain. The bovine reassortant vaccine was developed in my former laboratory in Philadelphia by Fred Clark and Paul Offit and is based on reassortants of a virus called “WC-3” [8]. The human strain was developed in Cincinnati by Richard Ward et al. [9]. In a phase II efficacy trial, the efficacy of the bovine reassortant vaccines appeared to be equal to that of rhesus rotavirus vaccine, with 75% protection against all rotavirus diarrhea and 100% protection against hospitalization [10]. It is now being tested in 60,000 children, including some in developing countries. As of October 2002, 30,000 children have been vaccinated, with only 4 cases of intussusception, none after the first dose or within 42 days of vaccination. The human strain has also demonstrated efficacy in a clinical trial [11]. Thus, new rotavirus vaccines may soon become available for worldwide use.

Poliomyelitis. Eradication of pathogens and cessation of vaccination have long been goals of public health, achieved in the case of smallpox and sought for in the case of polio. Wild polioviruses are now limited to 2 parts of the world—sub-Saharan Africa and the Indian subcontinent [12]—but some disturbing findings will inhibit us from ceasing to vaccinate even if eradication is accomplished (table 1).
Although the attenuated poliovirus strains were passaged ∼70 times in animals or cell culture, the property of attenuation rests on a small number of mutations [13]. Those mutations change only 1% of amino acids, and most of the changes have nothing to do with attenuation. Moreover, after oral administration to humans, reversion of the few attenuating mutations is a constant feature of replication in the intestine, where neurovirulent viruses have a selective advantage. To show this, we infected explants of fetal intestine with an attenuated type 3 poliovirus and a reverted mutant of the same virus [14]. Although both sub-strains grew in the explants, and maintained their virological markers, mixing the 2, even at a 20:1 ratio in favor of the attenuated strain, resulted in overgrowth of the revertant virus.

The other facet of the problem is that recombination between poliovirus serotypes and between poliovirus and enteroviruses is a regular phenomenon during replication in the intestine. When the 5′ end of a reverted poliovirus combines with the 3′ end of another enterovirus, the result is a virus that not only is neurovirulent but also can be transmitted easily and become epidemic [15]. In fact, epidemic vaccine-derived polio has happened in the past in Egypt, China, Israel, the Dominican Republic, Haiti, the Philippines, and Madagascar, undoubtedly accompanied by hundreds of asymptomatic infections. In addition, rarely persons with B cell deficiencies chronically excrete reverted vaccine virus, for periods of ≥10 years [16, 17].

Moreover, as soon as one stops vaccinating against a pathogen, it becomes a potential weapon. The synthesis of a replicating virulent poliovirus from chemical constituents by Eckard Wimmer’s laboratory [18] removes all doubt about this danger. Poliovirus is far from the ideal bio-weapon, but it becomes more attractive as unvaccinated populations increase in size. Thus, even if eradication is achieved, and vaccination with oral polio vaccine stopped, many countries will choose to continue vaccination with inactivated poliovirus vaccine.

Lyme disease. The Lyme disease *Borrelia burgdorferi* outer surface protein A (OspA) vaccine was recently taken off the market by the manufacturer. The reasons for this are multiple and probably include lawsuits arising from unsubstantiated claims that the vaccine induced autoimmunity. However, more important, in my opinion, were 2 errors. The first was the lukewarm recommendation issued by the Centers for Disease Control and Prevention [19]. In effect, they proposed that the vaccine was only “to be considered” for people at risk and indicated preference for attempts to reduce tick exposure and use antibiotics for prophylaxis, despite weak evidence that Lyme disease cases can actually be reduced by such measures [20, 21]. The second error was made by the manufacturer’s marketing department, which predicted a high demand by the public in states with endemic Lyme disease. Such patient demand never materialized, despite an annual and continuing total of >17,000 reported cases/year of Lyme disease, because the manufacturer did not convince physicians of the value of vaccination. Consequently, the vaccine did not prove profitable and was withdrawn. Whereas the efficacy of the OspA vaccine was only moderate, in view of this experience, the likelihood that manufacturers will seek to develop a better vaccine against Lyme disease is small. Beyond the issue of Lyme disease, this experience will have a negative effect on development of so-called lifestyle vaccines for other non-

Table 1. Phenomena that may lead to persistent circulation of virulent poliovirus and thus require continued vaccination.

<table>
<thead>
<tr>
<th>Phenomena</th>
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<tbody>
<tr>
<td>Reverse mutation of oral poliovirus vaccine to virulence</td>
</tr>
<tr>
<td>Recombination between oral poliovirus vaccine types</td>
</tr>
<tr>
<td>Recombination between oral poliovirus vaccine and other enteroviruses, enhancing transmissibility</td>
</tr>
<tr>
<td>Persistent excretion by B cell–deficient children</td>
</tr>
<tr>
<td>Bioterrorist introduction of poliovirus synthesized in laboratory</td>
</tr>
</tbody>
</table>

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*Figure 3.* Methods to develop inactivated (killed) vaccines and examples, given in a semi-chronological fashion. Hib, *Haemophilus influenzae* type b; Meningo, Meningococcal; Pneumo, Pneumococcal; Vi, typhoid virulence antigen.
fatal diseases [22]. These are vaccines for nonfatal diseases in high-risk groups, such as anti–dental caries and anticontraceptive vaccines [22].

**Measles and rubella.** The control of measles and congenital rubella in developing countries is an important program. Vaccination coverage against measles in children must be extraordinarily high to prevent the virus from spreading, and it must also be high against rubella to prevent a paradoxical increase in the susceptibility of women because of decreased exposure to natural infection. Mass vaccination by injection is difficult and risky in some settings. Years ago, Albert Sabin showed that aerosol administration of measles vaccine is feasible [23], and during the development of RA 27/3 rubella vaccine, we showed that its administration by nose drops, no less than injection, resulted in successful vaccination [24]. Recently, Mexican researchers led by Sepulveda-Amor and Valdespino-Gomez [25–27] have administered a combined measles-rubella vaccine to children by means of a simple aerosol apparatus and have succeeded in immunizing against both infections in >90% of cases. This opens the way to simpler mass vaccination campaigns and to the simultaneous control of both measles and congenital rubella syndrome.

**Combination vaccines.** There is currently a gap between Europe and the United States in the use of combination vaccines. Two hexavalent vaccines covering diphtheria, tetanus, pertussis, polio, hepatitis B, and *H. influenzae* type b (Hib) are licensed in Europe for routine pediatric vaccination. Compared with monovalent Hib vaccine, they give lower responses to the Hib polysaccharide, and the US Food and Drug Administration (FDA) has been reluctant to license them. Although vaccine recipients obtain higher

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**Table 2.** Newer strategies for vaccine development starting from information on microbial genome (DNA, cDNA, or RNA).

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live recombinants</td>
<td>Dengue virus, parainfluenza virus, <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Recombinant protein production</td>
<td>Hepatitis B surface antigen, pertussis toxin, <em>Borrelia burgdorferi</em> outer surface protein A</td>
</tr>
<tr>
<td>Replication-defective particles</td>
<td>Human papillomavirus, herpes simplex virus</td>
</tr>
<tr>
<td>Alphavirus replicons</td>
<td>HIV, hemorrhagic fever agents</td>
</tr>
<tr>
<td>&quot;Naked&quot; DNA plasmid</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>Recombinant vectors</td>
<td>Cytomegalovirus, human immunodeficiency virus</td>
</tr>
<tr>
<td>Prime-boost with DNA and/or vectors</td>
<td>Human immunodeficiency virus, malarial parasites</td>
</tr>
<tr>
<td>Reverse genetics</td>
<td>Influenza virus, parainfluenza virus, respiratory syncytial virus</td>
</tr>
<tr>
<td>Peptides</td>
<td>Cancer</td>
</tr>
<tr>
<td>T cell receptor</td>
<td>Multiple sclerosis</td>
</tr>
</tbody>
</table>

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**Figure 4.** Effect of immunization with recombinant parainfluenza virus (hemagglutinin-neuraminidase genes of PIV-1 and PIV-2 each inserted into attenuated PIV-3) on response to subsequent challenge with PIV. Monovalent viruses provided protection against homotypic challenge, but triple recombinant protected hamsters against all 3 PIV serotypes [36].

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levels of antibodies to Hib after receipt of combined vaccines containing Hib capsular polysaccharide (PRP) coupled to tetanus toxoid than after licensed vaccine containing Hib PRP coupled to an outer membrane complex of Neisseria meningitidis group B [28], as well as show immune memory and anamnestic responses [29], the FDA has insisted on “noninferiority” with respect to geometric mean titers. The absence of combinations in the United States created the need for numerous separate injections, which in my opinion was a situation inimical to public health. Fortunately, the FDA very recently licensed a combination diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and hepatitis B vaccine. However, a more general question that needs discussion is whether regulation and public health are now in conflict, without malicious intent on either side.

NEW TOOLS FOR VACCINE DEVELOPMENT

Genetic engineering. There are still many important diseases that are not controlled by vaccination. Why is this so? One reason is that we are now seeking to prevent infections that do not have extracellular, viremic, bacteremic, mucosal or toxemic phases, during which pathogenicity can be neutralized by antibodies in the serum or on the mucosae [30]. Second, although molecular biology permits us to construct just about any antigen, in many cases we know little about the pathogenesis of the target disease and therefore do not know which antigen to choose. More young investigators are needed in the field of pathogenesis.

Nevertheless, molecular biology and its tool, genetic engineering, have now provided additional paths to vaccine development. Although induction of antibodies is still a major goal, a particular aim of much of these efforts is to induce cytotoxic T cell responses and other T cell functions for prevention of diseases in which cellular immunity is crucial.

Knowledge of the base sequences of genes of microbes and the ability to manipulate them has been useful in many ways, starting from DNA, cDNA, or even RNA [31] (table 2). Several recombinant strategies are possible. To develop live recombinants, genes from heterotypic viruses can be inserted into an attenuated virus. As examples, to produce a candidate dengue vaccine, the envelope genes from 3 dengue virus serotypes have been inserted into a fourth attenuated serotype [32, 33]. Also, dengue virus genes have been inserted into the attenuated 17D yellow fever virus as a carrier [34]. A candidate West Nile virus vaccine also is based on the 17D carrier [35].

Recombination also has been used for respiratory agents. The laboratory of Brian Murphy at the National Institutes of Health created a recombinant parainfluenza virus types 1, 2, and 3 by inserting the hemagglutinin-neuraminidase gene from parainfluenza virus types 1 and 2 in an attenuated parainfluenza virus type 3. This recombinant prevented all 3 parainfluenza viruses from replicating in the lungs of hamsters (figure 4) [36].

Genes also can be inserted into animal, plant, bacterial, viral, or yeast cells for expression of proteins, as is the case for hepatitis B surface antigen produced in yeast. In some cases, the proteins so produced will self-assemble into viruslike particles that are useful for immunization, despite the absence of a nucleic acid. For example, the L1 protein of human papillomaviruses will form noninfectious particles, which are the basis of a preventive vaccine against human papillomavirus infection of the cervix and subsequent cervical cancer; this vaccine gave high efficacy in a phase II

<table>
<thead>
<tr>
<th>Month, vaccine dose</th>
<th>Seronegative placebo recipients (n = 7)</th>
<th>Seropositive vaccine recipients (n = 4)</th>
<th>Seronegative vaccine recipients (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/7</td>
<td>4/4</td>
<td>0/14</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>3</td>
<td>0/4</td>
<td>2/2</td>
<td>8/8</td>
</tr>
<tr>
<td>4</td>
<td>0/5</td>
<td>4/4</td>
<td>14/14</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0/7</td>
<td>3/3</td>
<td>13/13</td>
</tr>
<tr>
<td>12</td>
<td>0/7</td>
<td>3/3</td>
<td>14/14</td>
</tr>
<tr>
<td>26</td>
<td>0/3</td>
<td>1/1</td>
<td>5/5</td>
</tr>
</tbody>
</table>

NOTE. NT, not tested. Data are from [62].
* Not all subjects tested at each time point.
clonal immunity to control CMV infections, we placed the gene for the matrix applied, particularly to negative-stranded RNA respiratory viruses such as influenza virus, parainfluenza virus, and respiratory syncytial virus [25, 54–57]. This technique depends on inducing mutations at specific sites in cDNA and reconstituting a new virus by furnishing nonstructural enzymes, in a cotransfection with the modified genome segments. The rescued virus can then be examined for its phenotypic qualities.

Another powerful strategy to induce cellular responses uses vectors, microbes that are naturally or artificially attenuated for humans, in which foreign genetic information has been inserted [58]. Experimental vectors include a wide range of viruses and bacteria, but the ones most explored are poxviruses, alphaviruses, flaviviruses, adenoviruses, bacille Calmette-Guérin, and Shigella and Salmonella species. The enteric bacterial vectors are given orally and depend for their action on the injection into intestinal cells of DNA plasmids carrying foreign genes [59, 60].

An example of vector use for vaccination comes from experimental cytomegalovirus (CMV) vaccines [61]. Intrauterine infection with CMV is the most common infectious cause of deafness and mental retardation in countries that have eliminated rubella. In view of the importance of cellular immunity to control CMV infections, we placed the gene for the matrix

Table 5. Neutralizing antibody responses to human immunodeficiency virus (HIV-1) 2 weeks after prime with canarypox-HIV vector or control vector and second boost with recombinant glycoprotein (rgp) 120.

<table>
<thead>
<tr>
<th>Vaccine group</th>
<th>No. with neutralizing antibody to HIV-1, GMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canarypox HIV + rgp120</td>
<td>21/21 323</td>
</tr>
<tr>
<td>Canarypox rabies + rgp120</td>
<td>2/6 &lt;10</td>
</tr>
<tr>
<td>Canarypox rabies</td>
<td>0/6 &lt;10</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from [67]. GMT, geometric mean titer.

Figure 5. Effect of preimmunization against human adenovirus type 5 (AdHu5) on response to challenge with 10^6 TCID50 of either human or chimpanzee (Ch) adenovirus type 5 vector containing gene for rabies glycoprotein. Rabies virus neutralizing antibodies (VNA) were measured after challenge. Monkeys immune to human virus responded poorly to rabies protein produced by gene carried by same virus but as well as naive monkeys when gene was carried by chimpanzee virus [72].
protein pp65, a principal target of cytotoxic T cell responses against the virus, in a canarypox vector. Strong pp65-specific cytotoxic T cell response was elicited in all CMV-susceptible human volunteers after 2 injections [62] (table 4).

The success of this experiment justifies a digression. Over many years, my colleagues and I, as well as other laboratories, have tried to develop a vaccine against CMV to protect women during pregnancy [63]. Safety and moderate efficacy were demonstrated with an attenuated live virus vaccine. Also, workers at Chiron generated a line of Chinese hamster ovary cells transfected with the gene for the principal viral surface glycoprotein, gB. When the glycoprotein was combined with an adjuvant, it was highly immunogenic and generated neutralizing antibodies [64].

Questions remain about the ideal composition of a vaccine against CMV, but although there are experimental antigens that produce neutralizing antibodies and cell-mediated immunity, vaccine development has been slow. The perception of marketing departments was that a CMV vaccine to prevent intrauterine infection would not be used. However, a committee of the Institute of Medicine recently published an analysis of priorities for new vaccines [65]. They put CMV in the highest category of need and concluded that a successful vaccine would save society money as well as suffering. The report by the Institute of Medicine has changed the picture, and now at least 4 different manufacturers have CMV vaccine development programs. This history illustrates the necessity for public health authorities and opinion leaders to clearly indicate to manufacturers what vaccines are wanted. Manufacturers can then avoid investing millions of dollars in developing a vaccine that will not be welcomed by the public health community, such as the Lyme disease vaccine, or worse, to ignore a public health need, such as a CMV vaccine.

**Prime-boost strategies.** Although immune responses and protection afforded by DNA vaccines or vectors alone are often insufficient, the combination of modalities in a prime-boost configuration is more promising [66]. The prime-boost approach works both for generating antibodies and for generating cell-mediated immunity. For example, one of the earliest trials of the prime-boost concept involved priming with canarypox vectors containing human immunodeficiency virus (HIV) genes and boosting with injections of the envelope glycoprotein 120 of the virus (table 5) [67].

Enhancement of cellular immunity can also be achieved by priming with DNA containing an HIV gene and boosting with the same gene carried by a vector. In experiments in monkeys by Harriett Robinson’s group [68], the prime was DNA coding for several proteins of HIV that induce cellular immune responses, and the boost was an attenuated vaccinia virus vector strain called “MVA,” coding for the same proteins. In contrast to the high HIV loads developed after challenge by control monkeys, vaccinated monkeys showed no or low virus loads. Human clinical trials are now being conducted in England and Africa making use of a similar DNA-MVA prime-boost sequence. Workers at Merck have also achieved efficacy in monkeys with use of a DNA prime but followed by a boost with an adenovirus vector [69].

Two different vectors carrying the same genes can also be combined in a prime-boost format. The prime-boost approach may also work for other diseases; in fact, clinical trials of a malaria vaccine that use...
DNA priming followed by boosting with MVA are now in progress [70].

However, a major problem with vectors is that they are usually good producers of immunity against themselves as well as against proteins of inserted genes. This so-called vector immunity may make it problematic to use as vectors agents to which populations are naturally exposed. Ertl and her colleagues at the Wistar Institute have come up with an ingenious way to circumvent this difficulty [71, 72]. They have isolated and characterized chimpanzee adenoviruses, which are antigenically distinct from human adenoviruses. In one experiment, monkeys immune to human adenovirus type 5 or naive to that virus were vaccinated either with the human virus or with a chimpanzee adenovirus, both carrying the gene for rabies virus glycoprotein. Whereas immune animals barely responded with rabies antibodies to the human adenovirus, the chimpanzee adenovirus vector was equivalently immunogenic in immune and naive animals (figure 5) [72].

Miscellaneous strategies. New technologies that will help vaccine development are microarray analysis [73] to define virulence genes and in silico epitope analysis to predict T cell epitopes [74, 75]. In addition, the burgeoning of proteomics, the field of protein analysis that parallels genomics, is promising to help define proteins that are important to pathogenesis [76].

Among the important proteins frequently identified by proteomics are bacterial adhesion proteins, antibodies against which prevent bacteria from attaching to mucosal cells [77]. This is the basis for an experimental vaccine against recurrent urinary tract infections [78, 79]. Immunization against T cell receptors may help us to decrease immune responses in situations in which they are pathological [80].

Although there is insufficient space to discuss the important subject of adjuvants, it is noteworthy that an entire arm of the immune system, the heretofore-neglected innate immunity, can be brought into play through the use of unmethylated cytosine–phosphorothiolated guanine (CpG) oligonucleotide motifs from bacteria [3]. The stimulation of both innate and acquired immunity is particularly attractive as a method to protect against agents of bioterrorism. Figure 6 [81] illustrates the concept that although adaptive immunity would arrive too late to prevent replication of a pathogen, innate immunity stimulated by CpG could act to restrict the growth of a pathogen until the subject could develop adaptive immunity from vaccination [81].

### Table 7. New targets for vaccination.

<table>
<thead>
<tr>
<th>Target</th>
<th>Example</th>
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<tbody>
<tr>
<td>Adolescents</td>
<td>Human papillomavirus, cytomegalovirus, pertussis</td>
</tr>
<tr>
<td>Adults</td>
<td>Herpes simplex, herpes zoster, pertussis</td>
</tr>
<tr>
<td>Hospital patients</td>
<td>Staphylococcus, Pseudomonas, and Candida species</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Group B streptococci, respiratory syncytial virus, parainfluenza virus type 3, Haemophilus influenzae type b, pneumococcal polysaccharide, pertussis</td>
</tr>
<tr>
<td>Bioterror threats</td>
<td>New smallpox, anthrax, plague</td>
</tr>
<tr>
<td>Noninfectious diseases</td>
<td>Cancer, diabetes, Alzheimer’s disease</td>
</tr>
</tbody>
</table>

### ROUTES OF ADMINISTRATION

In addition to new strategies for vaccine development, to avoid injections there will also be new delivery technologies and routes of administration. Transcutaneous, oral, and even rectal routes of immunization are under active investigation [82, 83]. Transcutaneous vaccination can be aided by adjuvants, a low electric current, or simply application to the skin of a sufficient dose, as shown by studies of adenovirus vectors [84, 85] (table 6).

In the category of oral vaccination is the feeding of vaccine antigens produced in transgenic plants, as illustrated by hepatitis B surface antigen in lettuce [86–88]. Chimeric plant viruses containing genes from animal pathogens also provide an approach to oral immunization [89].

### NEW TARGETS

As vaccine development progresses, the target diseases and populations (table 7) are broadening beyond the traditional pediatric targets to adults in specific risk groups (such as hospitalized patients) or to adults in general (e.g., for pertussis) [90].

Noninfectious diseases will also become the target of immunization strategies [91]. Cancer prevention is already provided by hepatitis B vaccine, which is reducing the incidence of hepatic neoplasms [92], and the recent preliminary success of a human papillomavirus vaccine in preventing infection [93] augurs well for specific protection of cervical carcinoma. In addition, the isolation of antigens specific for trans-

### Table 8. Some vaccines being tested for therapeutic effect against chronic infection.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Antigen(s) of interest</th>
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<tbody>
<tr>
<td>Hepatitis B</td>
<td>PreS1 and S2 core</td>
</tr>
<tr>
<td>Human immunodeficiency virus type 1</td>
<td>gag, tat</td>
</tr>
<tr>
<td>Herpes simplex virus type 2</td>
<td>Glycoprotein D</td>
</tr>
<tr>
<td>Human papillomavirus type 16 and others</td>
<td>Early protein 6 and 7</td>
</tr>
</tbody>
</table>
formed cells allows for the possible development of vaccine therapy for cancer. Immunization may also be useful in situations in which infection plays no role, such as to prevent conception [94] or to neutralize drugs in the bloodstream to treat addiction [95].

The application of vaccines to pregnant women has been inhibited by medicolegal concerns. Vaccination in pregnancy has as goals either to protect the newborn (e.g., group B streptococcal disease) or to protect the woman herself (e.g., influenza). Candidate vaccines that might be used late in pregnancy to protect the neonate during the early months of life include those against respiratory syncytial virus, pertussis, pneumococcal polysaccharide, and group B streptococcus [96].

Therapeutic vaccination against chronic infections is an entirely new field of vaccinology [97]. Therapeutic immunization protocols are currently being tested in at least 4 viral diseases (table 8), on the basis of the idea that whereas in chronic infection the host is unable to mount an effective immune response, external administration of antigens may induce cellular responses that suppress viral replication [98]. Therapeutic immunization may also be useful in chronic bacterial infections, such as that due to *Helicobacter pylori*.

### SOCIAL ISSUES FOR THE NEW CENTURY

Finally, we must not forget that the 21st century must deal with 3 major social issues in vaccinology: safety and the rise of antivaccinationism, cost for developing countries, and adequacy of supply. These issues could be the subject of a separate article. Although solutions have been proposed, considerable wisdom will have to be exercised to put those solutions into place.

Despite these many problems, vaccinology continues to advance through its peculiar combination of fundamental research and empiricism. As W. H. Auden remarked in a wider context, “We may not know very much, but we do know something.” Vaccination has come a long way since Jenner, and we can be confident that vaccinologists will continue to extract beautiful melodies from the orchestra of the immune system.

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