VACCINES

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Prospects for the prevention of disease and for sustaining better health are steadily increasing as we progressively expand our knowledge of the determinants of disease. However, of all the tools available in our medical armamentarium, none can begin to compare with vaccines in terms of cost benefit ratios or in the simplicity of individual or community wide application. With effective use of smallpox vaccine, we were able to eradicate a disease which as recently as the mid-1960's caused 2 to 2.5 million deaths annually. Poliomyelitis has vanished from the United States and, in fact, the last case in the Western Hemisphere occurred more than two years ago. In this country, we have witnessed a precipitous decline, as well, in the numbers of cases of rubella, mumps, whooping cough, tetanus, diphtheria and, most recently hemophilus influenza. In fact, the decrease in incidence of these diseases has been so dramatic that during the 1980's, parents and physicians alike began to assume that these too were diseases of history. Complacency prevailed and with complacency, came a decreased attention to immunization. A rude

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reminder that these diseases remain a lurking threat came with the major measles epidemics of 1989-1990 when over 43,000 children became ill and more than 100 died. In examining this problem in 1990, the National Vaccine Advisory Committee pointed out that the readily and rapidly transmitted measles virus was a harbinger for possible outbreaks caused by other less readily transmitted vaccine-preventable infections--rubella, mumps, pertussis, poliomyelitis and diphtheria--unless action was quickly taken to improve immunization levels. Indeed, this concern was the genesis of the decision by President Clinton to make immunization a priority initiative of his domestic policy program.

The Administration's immunization initiative extends far beyond the achievement of better levels of vaccination coverage with existing vaccines. Advances in biomedical research, especially in biotechnology and immunology, open the prospects for use of other antigens to prevent other serious disease problems. Hepatitis B vaccine is already in widespread use; hepatitis A vaccines may soon be licensed; rotovirus and respiratory syncytial virus vaccine studies are underway in a number of laboratories as well as studies on pneumococcal and streptococcal vaccines. There are, of course, many more prospective new vaccines for community-wide use already on the drawing boards which address the most important infectious disease problems of this and other countries throughout the world. NIAID's Program

for the Accelerated Development of Vaccines, just over a decade old, has provided an enormous impetus, as well as leadership, to these activities.

Priorities in our research agenda over the coming decade have been thoroughly and thoughtfully examined by Committees of the Institute of Medicine and the National Institute of Allergy and Infectious Diseases. Highest on everyone's priority list is a vaccine to prevent HIV infection. This is proving to be a far more difficult task than any had anticipated but I personally am convinced that we will eventually have such a vaccine. Efforts devoted to this end have never been more intense. And in the course of research leading to its development, we will, of course, explore and identify new avenues for the attack on other diseases. In the global scheme, vaccines against major, systemic parasitic infections command the highest priority along with vaccines against tuberculosis as well as HIV.

New methods to produce vaccines have opened a whole new array of possibilities for vaccine development. Until recently, vaccines consisted of inactivated (killed) bacteria and viruses (such as the Salk vaccine or pertussis vaccine); altered or weakened variants of the naturally occurring organism (such as current vaccines against polio, rubella, mumps and measles); or inactivated toxins such as vaccines against diphtheria and tetanus.

Recent research has focused on vaccines that use only part of the infectious agent; by so doing, undesirable effects produced by the whole organism can be avoided. Such vaccines are called subunit vaccines and are now beginning to be tested or used for protection against meningitis, pneumonia, hepatitis B, typhoid and others. One can predict confidently that there will be many more.

A second important development has been the production of conjugate vaccines--vaccines which combine antigenic material from one organism with proteins or toxins from a second. Such vaccines induce protective responses especially in the very young and the elderly which the unconjugated antigen cannot do. The recently licensed and introduced hemophilus influenza B is such a vaccine and undoubtedly the harbinger of a number of other vaccines which will be able to be administered at or soon after birth.

Finally, a broad new scope of possibilities is provided to us through recombinant biotechnology. We now have an ability to take organisms such as vaccinia or salmonella and to replace a portion of their genetic material with key antigens from other organisms. It is not science fiction to imagine the creation of a genetically engineered organism carrying as many as 5 to 10 antigens of other microbes producing infection and immunity against 5 to 10 diseases in the young child.

With our growing knowledge of how, specifically, immunity is produced, we have come to recognize that antibody secreted on the mucosa is immensely important to protection--in many cases, more important that immunity resulting from protective antibodies in the blood stream. This has opened up other avenues of research directed toward methods to immunize by mouth or by inhalation. Such would be far easier and more acceptable to providers, parents and children alike, than immunization by inoculation.

Quite as exciting as these developments has been the discovery that vaccine antigens could be incorporated within minute absorbable spheres made of synthetic substances identical to those which are used in absorbable sutures. Such material can be fabricated such as to permit gradual release of antigens over a year or longer or as pulses every few weeks or few months. With vaccines so prepared, one can readily envisage a single inoculation of an inactivated vaccine which would have the same effect as perhaps three or four inoculations of presently available conventional vaccines.

The potential for protection against many additional diseases is certainly evident. An important challenge will be to combine many such antigens into a single inoculation or, better yet, a single oral feeding. Unless we do, we are inviting every infant to become a veritable pincushion--not appreciated by either mother or child. But such multi-antigen preparations should be

possible. In fact, an ultimate goal would be to concoct a single multi-antigen preparation which, given once by month, would protect a child for life against as many as 30 to 40 different diseases. Some have suggested that this could be the ultimate communion wafer. Such an achievement unquestionably will require time and effort but certainly not a Nobel caliber scientific breakthrough.

The bottom line to this very abbreviated tone of the further horizons of vaccine research is that we are now at the dawn of a new era which promises infinitely better prevention of disease in our own country and around the world. The principal engine driving the research to make this possible is NIH and NIH-funded research linked with a world class pharmaceutical industry.

Should this be a priority in our prevention research agenda? We need to recognize that today's vaccines, the ones now in widespread use, have already resulted in far more savings from death and disability than everything we have done to date in such areas as cancer or cardiovascular disease, and at far less cost. Much more can be done. A principal problem in developing a research agenda is that there are so many encouraging opportunities of such diverse type that it is difficult to choose among them.