tion necessary to make plants efficient vaccine production systems.

Many antigenic proteins from infectious viruses are chemically modified in host cells, for example, by the addition of sugars to produce glycoproteins. Although plants will glycosylate proteins, the carbohydrate additions are different from those of mammalian cells. This could be a hindrance in expression of certain immunogens if the sugar component of glycoproteins determines protective epitopes. Ongoing studies with a rabies virus glycoprotein produced in plants may answer this question[6]. Some vaccines require the presence of structural epitopes determined by protein folding and association. Notably, plants produce virus-like particles that mimic the structure of the authentic viral proteins[1,2,4]. In the case of hepatitis B surface antigen, the virus-like particles from plants preserve both the B- and T-cell epitopes that are present in the currently available commercial vaccine[2].

Preclinical studies of plant-expressed bacterial antigens, LT-B and CT-B, have provided indirect evidence for protective immunity in mice. The animals produce antibodies that neutralize the native bacterial toxins in mammalian cell assays and in the fluid accumulated in the intestines of animals challenged with the bacterial toxin[3,5,8]. Based upon animal trials, the U.S. Food and Drug Administration approved human clinical testing of raw potatoes containing LT-B in 1997. The results of this trial are described in the current issue of *Nature Medicine*[9]. The study concludes that edible vaccines are feasible for humans. Volunteers who consumed raw potatoes developed LT-B-specific IgG and IgA; the amplitude of the responses was comparable to a challenge with 10^6 virulent enterotoxigenic *E. coli* (an amount sufficient to induce severe diarrhea). A companion paper in the same issue by Ma *et al.*[10] reports data from another clinical trial that used secretory antibodies produced in transgenic plants to passively immunize human volunteers. The investigators found that colonization of teeth and gums by *Streptomyces mutans*, the bacterium which is the major cause of dental caries, could be prevented by the plant-derived antibodies. This is especially noteworthy because plants offer the only experimental system that can produce these antibodies in a quantity that is pharmaceutically useful.

Research on plant-produced vaccines has moved from theory to proof-of-principle. But challenging questions remain to be answered. Will 'non-traditional' oral subunit vaccines function at effector sites in the gut? Is it possible that oral tolerance[11] could develop with food-borne antigens? Lastly, what is the most appropriate plant tissue to deliver subunit vaccines? Bananas are a particularly attractive choice for developing countries because the fruit is eaten uncooked even by infants[7]. Although many obstacles have yet to be overcome, it is my opinion that they are implementation issues—not roadblocks. Vaccines produced in plants offer a new strategy for safe and cost-effective global immunization against infectious diseases.

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The global vaccine enterprise: A developing world perspective

The industrialization of the vaccine enterprise has implications for the supply of vaccines to the developing world.

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THE MOST IMPORTANT factor driving the transformation of the vaccine enterprise (which encompasses the development, clinical testing, production, licensure and distribution of vaccines) is the increasingly complex scientific and technological base that is required to develop and manufacture the newest generation of vaccines. The traditional (and highly successful) vaccines, such as those against small pox, diphtheria, tetanus, pertussis and tuberculosis, were based on the pioneering work of Jenner and Pasteur. The pathogen was grown in quantity in a simple facility, purified in a few steps, killed with an inactivating agent (where appropriate), and blended into the final product. Within a few decades of Pasteur's death, his disciples established Pasteur Institutes or similar public institutions in many parts of the world that produced vaccines as a public service[1].

In contrast, today's new vaccines are 'high tech' products that require expertise in multiple scientific disciplines, large numbers of skilled staff, and costly advance investment in research and manufacturing facilities. New generation vaccines, such as genetically engineered subunit vaccines against hepatitis B virus, cell-free vaccines against whooping cough (pertussis), and the protein-polysaccharide conjugate vaccines against invasive bacterial diseases, for example those caused by *Haemophilus influenzae* type b (a major cause of bacterial meningitis in small children) and *Streptococcus pneumoniae*, bear little resemblance to the traditional vaccines in the way that they are produced.

The second factor driving the transformation of the vaccine enterprise is the changing nature of technology ownership. Even though the basic research supporting development of vaccines is conducted at public and academic research centers supported by public funds, vaccine development has become primarily the purview of large industrial laboratories, often augmented in key segments by specialized biotechnology companies funded by venture capital. Thus, most key technologies for future vaccines will be developed and owned by companies that will diligently protect their new inven-

tions through internationally enforced patents. In Pasteur's day, and even as recently as forty years ago when the polio vaccines were first developed, most of the new technologies needed to manufacture vaccines were owned by the public. The scientists and organizations that developed them often assisted and funded the technology transfer to institutions in developing countries. It is improbable that the developing world will have such easy access to key vaccine technologies in the future.

The third factor is the globalization of international commerce. In order to compete successfully, vaccine companies have been consolidating on an ever larger scale. The global vaccine industry in 1998 is thus dominated by a small number of large multinational companies, instead of the smaller, publicly owned and public-spirited national vaccine production centers that until recently were the norm. Consequently, some of the key decisions regarding which vaccines to develop and how to distribute (market) them are no longer made by scientists and public health officials but by business executives in board rooms who must answer to their stockholders.

Finally, the increasingly stringent international product safety standards required of vaccines has particular implications for the supply of vaccines to developing countries. Heightened international standards for vaccines may be only a reflection of the larger trend of higher safety standards for consumer products in general, but the issue of product safety for vaccines is much more complex than for other pharmaceuticals.

Traditionally, the protection of the public against major infectious diseases was the primary goal of public vaccination efforts. The provision of vaccines was often viewed by national governments as an essential public service. In an age of widespread public concerns about paralytic polio, for instance, the public was more willing to accept a vaccine that could save a million lives even if it might cause inadvertent but unavoidable harm to an unfortunate few. However, when polio is no longer a threat to most people because of the very success of polio vaccination, even a few cases of vaccine-associated polio may be deemed unacceptable. But in developing countries where polio is still a potential public health concern, protection of the general population has to take precedence over the avoidance of a few adverse reactions. In many industrialized countries, public pressure to minimize vaccination-associated risks as well as ever-increasing concerns over product liability and lawsuits are forcing the vaccine industry to adopt the maximum defensive policy, by opting for the highest possible level of product safety. Because

The new buildings of the International Vaccine Institute (including a small pilot plant) on the campus of Seoul National University in Korea are due to be completed by the year 2000.

the safety-related technology keeps improving, the product safety requirements concomitantly become more stringent. The added cost will eventually be passed on to consumers everywhere as higher vaccine prices.

Newly introduced international safety requirements have the effect of making older vaccines, produced according to previous standards, potentially obsolete. Several of the larger developing nations together produce as much as 65 percent of the world's total output of traditional childhood vaccines used in the Expanded Program in Immunization (an international effort to increase vaccination coverage for six major childhood diseases coordinated by the World Health Organization and UNICEF). But few of these vaccines are exported to other developing countries because of their inability to meet the current international safety standards[2]. Meeting these requirements is not an easy task for most Third World vaccine producers. Their facilities were established many years ago and would require major new investments in personnel training and new construction, as well as the introduction of national safety control laboratories. Reaching an acceptable balance between the need to keep up with the evolving technologies in vaccine production and the need to make vaccines affordable to the greatest number of people will be a continuing policy challenge for developing nations.

The key concerns of the developing world in the areas of vaccine production and supply can be summed up as access, affordability, equity and national autonomy.

A highly effective and safe vaccine against hepatitis B was developed in the early 1980s, but its incorporation into immunization programs in developing countries was long prevented by its high cost. It took a major concerted effort by an international group of dedicated people to introduce the vaccine to several developing countries in Asia and Africa but the key element in its eventual success was a drastically lower price[3]. However, more than 15 years after its development, the hepatitis B vaccine is not as broadly available today as it should be, and the price factor is often cited as the most important reason. Other vaccines of importance to developing countries, such as the new acellular pertussis vaccines, the conjugate vaccines against *Haemophilus influenzae* type b and, we hope, an AIDS vaccine, will not be widely available for the world's poorer citizens unless they are affordable. A stark example of the national choices that developing countries are facing is the recent announcement that India will launch its own program to develop an AIDS vaccine[4].

New candidate vaccines against major infectious diseases will need to be evaluated among the populations of the developing world where they will be most used. This is particularly true for vaccines against HIV, malaria, tuberculosis, diarrheal diseases, and acute respiratory infections, which have global significance but predominantly affect the developing world. However, research involving human subjects raises complex ethical issues, as was highlighted recently by the heated debate regarding the testing of potential AIDS vaccines[5].

Many developing countries appear to hold the view that vaccines are an essential public commodity and that a degree of national autonomy in vaccine production capability must be maintained, even at considerable economic cost. There is often a sense that a populous sovereign state should not become overly dependent on foreign (particularly commercial) suppliers for something as critically important as vaccines. In fact, many countries, including China, India, Indonesia, Brazil, Cuba and Mexico, have recently strengthened vaccine development and production, even though it could be more economical to import some of these vaccines from a foreign supplier. Whether it is justified or not, it is unlikely that the desire for national autonomy will disappear soon.

To seek creative solutions to some of these problems, the United Nations Development Program, with the help of many other organizations and major financial support from the Government of Korea, has created the International Vaccine Institute (IVI). This research center will be headquartered in new buildings on the campus of Seoul National University in Korea and will provide assistance to individuals and institutions in the developing world, so that they may become active participants in the evolutionary process that is reshaping the vaccine enterprise. The constitution of IVI (http://www.ivi.org), embedded in a United Nations-sponsored international agreement, has been signed by more than 30 countries and the World Health Organization and was ratified in 1997.

Is protection from diseases that can be prevented by vaccination a universal human right? If the answer is even partially yes, we must look for ways to ensure that a reasonable minimum level of access, affordability and equity for essential vaccines is provided for all. The transformations now taking place at the global level are inevitable. So will be the demand to find realistic solutions to address the legitimate needs of developing nations. The solutions must be acceptable to both the public and the private sectors, and to both the developed and the developing worlds.

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Recruiting HLA to fight HIV

HLA-restricted peptides from HIV-resistant individuals may act as guides to immunogenic regions of viral proteins.

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CERTAIN INDIVIDUALS, WHO are consistently exposed to the human immuno-deficiency virus (HIV), do not succumb to infection[1,2]. The factors responsible for HIV resistance fall into two groups: protective mutations in chemokine co-receptors[3] and the presence of certain allelic specificities of the histocompatibility complex such as HLA-A28 (ref.4). The protection conferred by particular HLA alleles is induced by the corresponding HLA-restricted peptides. These peptides may serve as guides to the identification of the immunogenic regions of HIV proteins, an important step in vaccine development.

The HLA genes involved in processing, transport and presentation of peptides are polymorphic resulting in the presentation of different peptides in individuals infected with the same virus (see figure). Analysis of Kenyan and Gambian prostitutes continually exposed to HIV, who remained HIV-seronegative and PCR-negative for reverse transcriptase, revealed a strong cytotoxic T-cell immune response against various HIV peptides associated with HLA-A28 and HLA-B35 (refs 4,5). HLA-A28 is also protective in Caucasians (R. Wank, unpublished). Sequence-based typing indicates that the alleles A*68012 and A*6802 are associated with HIV resistance whereas A*68011 is not.

It should be possible to identify the different HIV peptides that are presented in the context of A*68012 and A*6802. The viral regions marked by these 'pilot' peptides can then be evaluated for their capacity to prime T lymphocytes. Identification of virus-derived, HLA-restricted 'pilot' peptides from individuals who are immune to a specific virus has potential for the development of vaccines against many viral diseases. That such an approach might work is suggested by data from cancer vaccine studies. HLA-restricted peptides of the E7 protein of human papilloma virus, which stimulate a strong T cell response, have been used in a vaccine to protect mice against cervical cancer[7].

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

Viral proteins are degraded to different peptides by the proteasome subunits, LMP2/7. Variants of the transporters TAP1 and TAP2 bind different peptides and translocate them to the endoplasmic reticulum (ER), where they become incorporated into HLA molecules. The HLA-selected peptides are then presented on the cell surface.

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