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Developing countries do not have the same needs as developed countries for AIDS control: interest of future vaccines

'Following a phase of tremendous investigation of vaccines under conventional approaches, it seems necessary to develop alternative vaccination strategies taking into account the variability of the target and its role in the pathogenicity of the virus, the type and location of the immune response, as well as the safety of the vaccine and its cost.'

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AIDS, first involving at-risk subjects in developed countries, now mainly occurs in developing countries. Despite the striking improvement of antiviral therapy, even international assistance will be insufficient to organize medical management on a subcontinental scale. Conversely, research on the prevention of AIDS with a vaccine, aimed particularly at the surface of the mucosa, would be primarily indicated to the fight against this disease in developing countries.

The common opinion is that solidarity between rich and poor countries will allow for the treatment of all patients throughout the world. However, the extent of the spread of AIDS is becoming similar to that of medieval plagues and we have no experience in this problem which is together medical, social and economical.

Epidemiological changes during the last two decades

The first cases of AIDS were observed in male homosexuals and, to a lesser degree, in subjects contaminated with blood or derivatives i.e., transfused patients, hemophiliacs and drug addicts. Patients lived mainly in Europe or in Northern America and therefore benefited from the high level of education and medical organization of these rich countries where mass campaigns for prevention have been successful and where therapy by active drugs emerged. In these countries, the spread of the disease is now maintained at a low percentage of cases in the whole population. If the present conditions of prevention persist, and with further improvements in treatment, the future spread of the disease may be curbed. In contrast, the spread of the pathogen in sub-Saharan and South Asian countries is so dramatic that a large proportion of the whole population could be involved. The high and increasing prevalence of this lethal disease is associated with the general problem of underdevelopment. Transmission most often occurs via heterosexual intercourse – men infecting women. Furthermore, the number of children being born with the disease as a result of mother-to-child transmission is also increasing dramatically. The predictable number of patients and their location in developing countries will impair the feasibility of the treatment even if the cost of the administered drugs is largely decreased by international aid.

Antiviral therapy on a subcontinental scale

Antiviral drugs are not without side-effects and must only be prescribed in diagnosed patients.

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In addition, these patients need a sufficient level of infirmary teaching and medical survey. It is unknown how many doctors, nurses and volunteers will be necessary for this strategy and whether rich countries will be able to meet these demands for staff if the spread of AIDS increases. Moreover, this overload of the international medical resources will be associated with that of the local management of this war-like strategy. Concerning the decrease in the cost of drugs, attention must be directed towards not impairing the research efforts of the private companies. The financial risk of these investments is high and must be taken into account.

Local prevention by condom usage, virucides, or vaginal douching

Local methods of prevention were developed or are under investigation. The use of condoms, promoted by mass campaigns is largely responsible for the maintainence of the spread of the disease in developed countries. Interestingly, sexually transmitted diseases, such as infections by *Neisseria gonorrhea,* simultaneously almost vanished. However, this usage may be limited in developing countries where it would not be readily available and may even be denied by the male partner. In addition, its contraceptive effect is unacceptable in many countries. Application of virucidal drugs in the vagina would be of interest to prevent male-to-female transmission but no significant results have been obtained to date in simian models. The principle of vaginal douching with tap water is to clear the vagina of semen without abolishing the mucosal barrier to infection. This method, which depends on the availability of a fresh water supply, preserves a fraction of the mucus layer and allows the local pH to rapidly recover its virucidal properties. Preliminary investigation of this method in humans seemed to be unsuccessful but, like other local methods, the key point of success is obviously the problem of education in hygiene.

'The aim of the vaccine is to protect against the disease and not to fully clear the body of the pathogen.'

Dead or live vaccines?

Vaccination requires a limited number of health workers and does not need a specialist organization as demonstrated during a similar type of campaign against meningitis in sub-Saharan Africa. The aim of the vaccine is to protect against a disease and not to fully clear the body of the pathogen. This delineation is of importance because the mechanisms of action of the disease and of the persistence of the pathogen are not fully understood in AIDS. The usual method of testing protection is the measurement of the level of serum antibodies to a selected microbial antigen. To date, it has not been proven whether antibodies are protective or associated with another type of protection against AIDS. An alternative method of analysing this protection is the use of experimental diseases, such as infection of monkeys with simian–human hybrids of the virus. This approach is very expensive, difficult to analyze, dependent on simian species and subspecies and has not yet been successful, even in the chimpanzee model. For ethical reasons, it appears that efficacy in simian models is usually considered necessary before human assays although the comparison shows clearcut variations. At variance with ant-viral drugs, vaccines are administered to the whole population, including children. A key point is the choice between dead and live vaccines. Dead vaccines consist of the inactivated pathogen or a purified component usually associated with an adjuvant. Live vaccines are genetically attenuated microorganisms or even a DNA construct encoding for the selected antigen. They have taken advantage of the progress of molecular biology. However, their side effects cannot be predicted on a subcontinental scale. The risk of an iatrogenic infection by live vaccines or inefficacy by lack of immune response in a small percentage of subjects may be significant and detected long after the assays when side effects arise in the vaccinated population, thus leading to a large number of victims. Nonetheless, the measles virus vaccine seems to be a good candidate as a safe vector since it has been worldwide administered without iatrogenic infection and also because it most likely induces both systemic and secretory immunities.

Vaccination of the secretory immune system

At variance with the usual vaccination by immunization of the systemic immune system either by intramuscular or subcutaneous administration, oral and nasal administrations of the antigen were found to allow an alternative mechanism of protection. The mucosal immune system is involved in the first steps of transmission of the pathogen by decreasing the size of the inoculum to a harmless level. This factor seems to be critical in AIDS transmission. Indeed this disease is not easily transmitted and the mucosal immune barrier, with the help of nonspecific mechanisms, may be sufficient to prevent local transmission of the disease. Interestingly, the mechanism of protection by the secretory immune system, such as immune exclusion and elimination, are different from those of the systemic immune system. An increasing interest progressively emerges for this type of immunity which does not seem to depend on microbicide properties of the response. Viral protection by the secretory immunity was demonstrated by efficacy of the oral polio vaccine. However, this success was not reproduced in other attempts at preparing oral vaccines and no other human mucosal vaccine is presently commercialized. One of the problems is to induce a secretory immune response. This can be optimally obtained by colonization with a live vaccine. Unfortunately, colonization is most often associated with a residual level of pathogenicity, which renders the vaccine unsuitable for protection. Recent progress in this field focused on adjuvants of the mucosal response, especially the inactivated cholera toxin and its derivatives chemical linked to dead vaccines or genetically combined with live vaccines. These adjuvants are of high interest but their efficacy also depends on the method of

administration. Besides the oral route, which can be impaired by enzymatic degradation in the gastrointestinal tract, other mucosal or nonmucosal routes are under investigation. The nasal route avoids degradation, whereas transcutaneous and i.m. routes allow, under certain conditions, to immunize the mucosal immune system with peptides.

Choice of epitope

A major concept of a vaccine study against AIDS is to define the viral target. This structure must be solvent exposed, invariant and a protection inducer. Exposition to solvent indicates that antibodies and T-cell receptors can recognize and bind the epitope at the surface of the pathogen. Invariance implies that all isolates will be recognized. Neutralization is required for systemic immunity but not for secretory immunity which primarily acts as an immune barrier. In the case of HIV, the glycoprotein, gp120, contains a short sequence, ELDKWA, which exhibits all of these characters. gp120 is surface-exposed, consensual and involved in the mechanisms of pathogenicity. Moreover, passive immunization with the corresponding monoclonal antibody, 2F5, is associated with a protection in simian experimental models. The risk of an immune escape to an anti-ELDKWA vaccination does not seem to be consistent. Indeed, all the rare variants cross-react with ELDKWA. This suggests that the noncross-reactive mutations are incompatible with the pathogenicity of the virus. It is possible that consensual epitopes are associated with key functions in the replication or transmission of the virus and cannot accept mutations which strongly modify the shape of the site. Similarly, the vaccinal interest of an epitope could be predicted by *in vitro* experiments. Investigation of candidate invariant peptides and choice of the best size and sequence will certainly develop in the future.

Vaccination with proteins or peptides

Vaccination with recombinant molecules containing the target site may be a good direction for future research under defined conditions. Ideally, the protein should not aggregate in the nonglycosylated form, should not induce allergy or cross-react with human components. Furthermore, immune competition should occur between the target epitope of the vaccine and other epitopes unrelated with protection. Small peptides are classically known as haptens and are therefore incapable of inducing antibodies when administered under a free form. However, it has been recently demonstrated that transcutaneous administration of small peptides with cholera toxin induces antibodies in mice. Moreover, a parenteral immunization of mice by ELDKWA, synthesized in line with an artificial peptide, called PADRE (Pan DR epitope), induces a systemic secretory immunity in mice. This parenteral immunization with synthetic peptides leads to predict a promising direction for future vaccines, allowing a defined composition and a control of the amount of the administered antigen, as well as a drug-like examination of toxicity and allergic risks. The cost of peptides is high at the level of a research laboratory but decreases strikingly at the industrial level.

Conclusions

In both rich and poor countries, prevention of AIDS is presently based on hygienic improvement by condom usage and possibly by vaginal douching. However, approaches to the fight against this disease differ according to the socioeconomic conditions of the countries. The outcome being maintained at a relatively and constant prevalence in industrial countries, all patients from these countries can benefit from the improvement in therapy. The corresponding researchers therefore focus on the study of new mechanisms of inhibition and on new drugs. In contrast, despite the efforts of international solidarity, the dramatic spread of the disease in developing countries will obviously overload the possibility of administration of these therapies on a subcontinental scale. These conditions support the first step in the development of vaccinal strategies. Following a phase of tremendous investigation of vaccines under conventional approaches, it seems necessary to develop alternative vaccinal strategies, taking into account the variability of the target and its role in the pathogenicity of the virus, the type and location of the immune response, as well as the safety of the vaccine and its cost.

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