lems by means of any available knowledge, whereas basic biology currently favours certain types of knowledge (for example, reductionist, molecular and obtained under controlled conditions at the laboratory bench). Research on oncogenes, viruses and immunology is highly rewarded; research on methods of coping, patient compliance and motivating people to stop smoking is scorned as 'soft', eligible for no Nobel prizes and little support. In an infintely rich world, one would increase expenditure on prevention and treatment, but an increase in the large US cancer budget cannot be expected when support for other areas of medicine and science is even stingier. Thus, some reallocation of funds from the biochemical/cellular aspects of treatment towards prevention and broader aspects, seems called for. □

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Retroviral vaccines

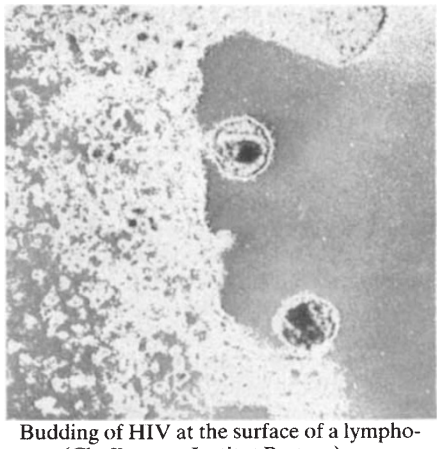
How close is C to D?

from Jerome E. Groopman

PERHAPS the highest octaves in recent meetings in Paris and Cold Spring Harbor, New York were reached in discussions of the development of retroviral vaccines. There has been considerable controversy concerning the optimal approach to the production of a safe and effective vaccine against the human immunodeficiency virus (HIV), the aetiological agent of the acquired immune deficiency syndrome (AIDS), and the significance of neutralizing antibodies. These antibodies are defined by their ability to kill the virus *in vitro* but their role in protection against infection is not clear. Marx, Gardner and their co-workers at the California Primate Research Center in Davis, in collaboration with Syntex Corporation, have now developed a vaccine based on inactivated whole virus that protects monkeys from infection and subsequent immune deficiency related to the simian AIDS serotype 1 virus (Marx, P.A. *et al. J. Virol.* in the press). Although the simian AIDS virus is a type D retrovirus whereas HIV is type C, it may help understand the host immune responses necessary for protection and the significance of neutralizing antibodies.

Lasky and co-workers at Genentech have adopted a different approach to a vaccine against HIV by cloning and expression in mammalian cells of the major viral envelope glycoprotein gp 130 (Lasky, L.A. *et al. Science* **223,** 209; 1986). Immunization of rabbits and guinea pigs with the recombinant gp130 elicits neutralizing antibodies of moderate titre that appear capable of inhibiting not only the HIV isolate used in the cloning but several other isolates as well (R. A. Weiss *et al.*, personal communication). This success in eliciting neutralizing antibodies was repeated by scientists in the National Cancer Institute and Duke University who used gp120 purified from HIV-infected lymphoid cell cultures to immunize goats (Robey, W.G. *et al. Proc. natn. Acad. Sci. U.S.A.* in the press). Similarly, F. Wong-Staal *et al.* (personal communication) have used non-glycosolated HIV envelope fragments expressed in *Escherichia coli* and elicited neutralizing antibodies.

Although these approaches appear to follow the successful development of vaccines for viruses that do not belong to the retroviral family, the significance of the neutralization response as an indicator of success has been questioned. Furthermore, the presence of neutralizing antibodies in patients with AIDS has been taken as evidence of their inability to limit the pathogenic effects of HIV. Cell fusion and syncytia formation, perhaps caused by gp120 interaction with the CD4 determinant on uninfected lymphoctes, is thought to be a mechanism of lymphocyte loss and immune deficiency.



Budding of HIV at the surface of a lymphocyte (Ch. Daguet, Institut Pasteur).

The approach adopted by the Davis group is simple and direct, and is modelled on the Salk vaccine for the poliovirus. Formalin-inactivated simian AIDS virus was used with the adjuvant threonyl muramyl dipeptide to vaccinate six macaques, and a control group received adjuvant alone. Moderate titres of neutralizing antibody were elicited in the vaccinated monkeys. Persistent viraemia was prevented in vaccinated animals and none developed disease, whereas five of six controls were viraemic, with four developing clinical simian AIDS. Although the pathogenesis of simian AIDS resulting from the type D retrovirus may differ from disease related to HIV, the study from California is the first report of a vaccine which prevents spontaneous retrovirus-induced immunosuppressive disease in primates.

Recent data from our laboratory and elsewhere indicate that the humoral neutralizing response in man following HIV infection does not appear until 6–9 months after the primary antibody response. The reasons for this are not yet understood, but it is possible that the presence of neutralizing antibody before exposure to HIV might effectively limit entry and spread of the virus. The ability of human or animal neutralizing sera raised to gp120 to block formation of multinucleated giant cells *in vitro* is being studied in several laboratories. Although it is possible that the configuration of neutralizing epitopes on the viral envelope in the infected cell membrane may differ from those in native or recombinant antigens, it is still unclear whether this is of practical importance in vaccine development.

The direct approach to the development of an AIDS vaccine still has considerable hurdles, most notably strain specificity. It appears that the neutralizing antibodies raised against the recombinant gp130 and the native gp120 will neutralize some but not other geographically distant isolates of HIV (R. A. Weiss *et al.*, personal communication). Again, we can look back to the development of a vaccine against poliovirus where success was achieved after systematic serotyping of numerous strains to give the current trivalent formulation. A polyvalent subunit vaccine encompassing the major serotypes of HIV will probably be required, although how many major strains will be needed is not known.

Other approaches being considered in the development of an AIDS vaccine, such as synthetic peptides related to neutralizing epitopes of the envelope protein and anti-idiotypic antibodies, as well as study of the immune response to proteins other than gp120, should be pursued. Considering that 5 million or more individuals throughout the world are estimated to be infected with HIV, and the continued rapid spread of the retrovirus in the West and in Africa, a variety of approaches should be taken. The next step, trial of prototype HIV subunit vaccines in chimpanzees, will tell us if the direct approach works. This should teach us a lesson in the alphabet of clinical retrovirology. □

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