Letters

Effectiveness of AIDS Vaccines

The News & Comment article by Jon Cohen (19 Oct., p. 369) about the third annual International Conference on Advances in AIDS Vaccine Development shows that the investigators regard achievement of the following goals as important indicators of the potential effectiveness of AIDS vaccines: (i) neutralizing antibodies for different serotypes of the human immunodeficiency virus (HIV-1), (ii) cytotoxic lymphocytes capable of specifically destroying cells infected with HIV-1, (iii) resistance of vaccinated chimpanzees to experimental infection with HIV-1 or, in work with the simian immunodeficiency virus (SIV) model, resistance of vaccinated monkeys to experimental infection with SIV.

Synthetic peptides containing epitopes of the GP120 envelope antigen of HIV-1 have been reported to induce high titers of neutralizing antibodies in rhesus monkeys (*1*). Although passively transmitted, high-titered human neutralizing antibody failed to protect chimpanzees against experimental HIV-1 infection (*2*) and certain immunogens have also failed to protect chimpanzees, there have been two recent reports of resistance of vaccinated chimpanzees to experimental infection (*3*). At the conference mentioned above, Jim Stott of the U.K. Medical Research Council was said to have reported that, "using a whole, killed SIV vaccine, his group protected monkeys against a challenge with a strain *different from the one used to formulate the vaccine*" (emphasis mine).

I regard these tests as improper criteria for judging the potential protective effectiveness of an experimental vaccine against natural infection in human beings because the two most important vehicles of infection in human beings—semen and blood—contain large numbers of *virus-infected cells* in addition to smaller amounts of cell-free virus (*4*). Up until now the vaccinated chimpanzees and monkeys have been challenged only with cell-free virus given intravenously. It has long been known that intracellular viral genome or mature viruses are not affected by neutralizing antibodies. Virus-specific cytotoxic cells can attack infected cells, in which the viral antigens are expressed on the cell membrane. The HIV-1 genome exists in many latently infected lymphocytes only as integrated proviral DNA (*5*), or when the proviral DNA is activated to produce viral RNA (*6*) and viral antigens, they may not reach the membrane of the infected cell. It is well known that mothers naturally infected with cytomegalovirus (CMV) transmit not only antibody but also infected cells to the fetus and that these infected cells then transmit the infection to the cells of the urinary tract in the presence of maternal antibodies; the newborn babies then excrete CMV in their urine (*7*).

In my judgment, vaccinated chimpanzees and monkeys need to be challenged intravenously with infected cells carrying integrated HIV-1 or SIV proviral genome. If they prove resistant (which is highly improbable), then one can speak of an experimental AIDS vaccine that might be protective in human beings. It is also important to remember that in human beings there may be no resistance to HIV-1 infection by semen (containing free virus, infected cells, or both) in the colorectal area, even in those who may resist an intravenous dose of contaminated blood. It is well known that polio and other entrail viruses can multiply in the intestinal tract in the presence of antibodies in the blood.

Along the same lines, the assumption that flooding the circulation with free CD4 virus receptors (natural or synthetic) could prevent HIV-1 infection disregards the cell to cell transmission of the virus genome without intervention of specific viral receptors.

Previous experience has shown that effective human vaccines have been produced against infectious diseases (for example, polio and measles) that are transmitted only by cell-free viruses that produce a primary natural infection followed by lasting immunity.

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"Sequence-Gazing?"

In the last few years, a series of papers has been published in leading journals, including *Cell* (*1*), *Nature* (*2*), and *Science*, that use sequence similarities to seek components of the secretion machinery of *Escherichia coli*. Specifically, open reading frames (*ffh* and *fisY*) for two proteins and the gene for an RNA molecule (4.5*S* RNA) were found in *E. coli* that have substantial sequence similarity to genes for components of the eukaryotic signal recognition particle (SRP). On the basis of these sequence comparisons it is postulated that the gene products play a role in bacterial protein export.

Most recently, M. A. Poritz *et al.* (Research Article, 23 Nov., p. 1111) show that a mutant affecting the function of 4.5*S* RNA does not block protein secretion, except in the case of β-lactamase, where the authors assume that the block is an *indirect* effect of induction of the heat-shock response. Many would conclude that the proposition for a role in secretion had been tested genetically with this mutant and that the results were negative, thus falsifying the proposition. The authors instead propose that these factors *are* involved in secretion and postulate a set of hitherto unidentified proteins that depend on the proposed bacterial SRP for their export.

While this interpretation may turn out to be correct, without substantiating biological evidence for a role of this presumed bacterial SRP in protein export other than sequence comparisons, it is quite premature. The discovery of sequence similarities should be a guide for doing genetic experiments to test hypotheses based on these similarities, not a criterion for defining the function of a protein. Proteins with extensive sequence similarities may have different functions, and the similarities may reflect some aspect of their interaction with other cellular components.

The concern is that scientists and referees may be caught up in the attraction to conclusions inferred from "sequence-gazing" rather than those derived from solid biological approaches.

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2. H. D. Bernstein *et al.*, *Nature* **340**, 482 (1989); K. Romisch *et al.*, *ibid.*, p. 478.

Response: In independent studies (*1*) we identified two *Escherichia coli* gene products, 4.5*S* RNA and *Ffh*, that bear a striking similarity to two subunits of the mammalian signal recognition particle (SRP), 7SL RNA and SRP54. These discoveries enabled us to design genetic *and* biochemical experiments (*2*) to begin assessing their function. We showed that, like their mammalian counterparts, 4.5*S* RNA and *Ffh* are associated in a ribonucleoprotein complex in vivo. Furthermore 4.5*S* RNA binds specifically to SRP54 and can replace 7SL RNA in an

enzymatic assay. We also presented genetic arguments that even though 4.5*S* RNA is known to interact with the translational machinery (*3*), it is not required for protein synthesis per se. By combining these experimental data with the results of previous studies on 4.5*S* RNA and the observation of evolutionary conservation, we developed a model in which the *Ffh*–4.5*S* RNP, by analogy to the mammalian SRP, acts in the earliest step of the secretory pathway. As we acknowledged, other models could also be proposed. The observation that the three *E. coli* periplasmic and outer membrane proteins tested to date may not require the *Ffh*–4.5*S* RNP to cross the inner membrane is a negative result. However, it certainly cannot *falsify* our hypothesis, which already takes these data into account. Indeed we stated in our paper that, in agreement with existing genetic data, many proteins may use a posttranslational targeting pathway rather than the putative *Ffh*–4.5*S* RNP dependent pathway.

We agree that it would have been rather premature to present our hypothesis as a conclusion. However, it is appropriate to propose the most plausible model consistent with the available data, especially if so doing will stimulate thinking about a difficult problem. There is no question that further experimentation using all available approaches will be crucial to settle these issues. The judicious use of "sequence gazing" has already enabled us to isolate the corresponding components of a SRP from yeast, in which a clear link to protein translocation is now apparent (*4*).

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Unus et Triginta Quoque Anno?

Readers of *Science* should be grateful to Stephen Jay Gould for his gracefully written comment on the meaning of the Royal Society's motto, "*Nullius in verba*" (Letters, 11 Jan., p. 142). In the interest of historical fairness, however, it should be noted that the same point—that this motto should be understood as a rejection of authority—was made previously in the pages of the same journal by the late Henry Allen Moe (16 Dec. 1960, p. 1817).

Gould should not, of course, be distressed at the repetition after a gap of 31 years. What this happening points up is the inadequacy of scientific abstracting and indexing services, particularly when it comes to contributions to learning that appear in Letters. A pessimist may well suspect that the same contribution will be published again, without citation of either Gould or Moe, about the year A.D. 2022.

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Steroid Therapy Publication Delay

Joseph Palca, in his 30 November article "A storm over steroid therapy" (News & Comment, p. 1196), discusses allegations in the *New York Times* that news of a consensus conference favoring steroid therapy in the treatment of AIDS-related pneumonia was deliberately delayed, at least in part, on account of concern about publication priorities. I am described in the article as being "anxious to clarify" the remarks I had made to the *Times*, "telling *Science* that although the issue of publication status came up, it did not contribute in any appreciable degree to the delay."

Since the article leaves the impression that this last comment was an afterthought on my part, I want to make it clear to *Science* readers, as I did to Palca, that this is exactly what I told the *Times* in the initial interview.

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Buckyballs and Double Bonds

Buckminsterfullerenes (C_{60} and other carbon clusters) are an excellent choice for one of 1990's top ten molecules (12 Dec., p. 1640). However, the structure depicted on page 1641 is incorrect. There are no "double bonds" in buckyballs. What is shown is the formula of $C_{60}H_{36}$, obtained from C_{60} by Birch reduction with Li, NH_3, t-BuOH (*1*). This hydrocarbon, with one double bond in each of the five-membered rings, has a hydrogen atom attached to each carbon that is *not* part of a double bond (a mixture is obtained, and the exact locations of the double bonds is not known). The structure shown destroys the magnificent I_h symmetry of C_{60}, which has all the C-C bonds identical. Readers who want to picture the correct structure should remove all the double bonds; or they can just look at a soccer ball and imagine a carbon atom at each of the 60 vertices.

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GABAergic Pathway from Zona Incerta to Neocortex: Clarification

Concerning our report of 22 June 1990, "A major direct GABAergic pathway from zona incerta to neocortex" (p. 1553), we would like to point out that the pathway we observed in the adult rat had previously been noted in several other publications. I. Divac *et al.* (*1*) reported that injections of horseradish peroxidase (HRP) into different neocortical areas in the rat resulted in retrograde labeling of small numbers of neurons in the zona incerta (ZI). L. L. Porter and E. L. White (*2*) later noticed small numbers of labeled neurons in mouse ZI after HRP injections into the somatosensory cortex. Most recently, C. B. Saper (*3*) and others (*4*) have carried out extensive neuroanatomical mapping of neocortical projections from the hypothalamus, including the ZI.

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Erratum: In the article " 'Nuclear winter' from Gulf war discounted," by Eliot Marshall (News & Comment, 25 Jan., p. 372), Tica Novakov's affiliation should have been given as the Lawrence Berkeley Laboratory, not the Lawrence Livermore National Laboratory. The concentrations of airborne soot reported at various locations should have been given as follows: for greater Los Angeles (summer), a daily average of 5 micrograms per cubic meter; Beijing (winter), a monthly average of 50 micrograms per cubic meter; Yugoslavia (winter), a daily average of 60 micrograms; and London (1-day winter peak in 1952), 750 micrograms, now reduced to less than 15 micrograms.