AIDS vaccine predictions

SIR—Coates *et al.* recently suggested that a *gag* p24 vaccine might prevent the onset of AIDS (acquired immune deficiency syndrome) in human immunodeficiency virus (HIV) carriers[1]. Their proposal was based on the well-known observation that clinical progression to AIDS is often associated with a reduction in antibodies to p24, the major HIV capsid protein. Whereas this association has been described in AIDS patients from the United States or Europe[2-6], we briefly report that an absence of antibodies to p24 is not found in African AIDS patients.

Sera positive for antibody to HIV were obtained from 117 Africans (40 AIDS patients, 40 AIDS-related-complex (ARC) patients and 37 symptomless subjects) from Burundi, Central Africa. For comparison, sera positive for antibody to HIV were obtained from 80 French citizens (21 AIDS patients, 13 ARC patients and 36 symptomless subjects). Specific antibody to HIV-core antigens (HIV-core Ab) were detected with a competitive enzyme immunoassay in which a recombinant-DNA-produced HIV core protein is used as antigen (Envacore, Abbott). The entire major core protein p24 is present in this recombinant antigen.

Ninety per cent of AIDS patients (36/40) and ARC patients (36/40) and 97% (36/37) of symptomless seropositive individuals were positive for antibody to HIV-core antigen in the African group. But in the French group, HIV-core Ab was detected in only 24% (5/21) of AIDS patients, 74% (17/23) of ARC patients and 86% (31/36) of symptomless seropositive individuals. The prevalences of HIV-core Ab observed in African AIDS patients and in French AIDS patients were highly different ($p<10^{-6}$). Similar observations have already been obtained using a radioimmunoprecipitation technique (P. Kanki *et al. International Symposium of African AIDS*, Brussels, November 1985).

The clinical signs and the incidence of AIDS in Central Africa are very similar to those observed in the United States and Europe[8,9], but the fact that African AIDS patients do not have a significant decrease or loss of antibody to HIV-core proteins is contrary to the hypothesis that the immune response to p24 plays a role in protection against the development of AIDS.

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Protein binding to DNA

SIR—In a recent discussion of protein–DNA interaction, Richmond[1] suggested that a synthetic homologue of the normal *Eco*RI restriction endonuclease recognition sequence could test the hypothesis that the sequence itself might determine the unwinding that allows the specific interaction with the protein. He proposed a sequence in which 2,6-diaminopurines replaced the central adenines in the recognition sequence GAATTC. This analogue would have the normal array of hydrogen bonding donors and acceptors in the major groove and added amino groups in the minor groove.

We have, in fact, synthesized such an analogue as an octadeoxyribonucleotide and tested it as a substrate with the *Eco*RI endonuclease[2] and the modification methylase[3]. In addition, we synthesized an analogue with 2-aminopurines at these same positions; this has the added amino groups in the minor grooves but lacks the 6-amino groups in the major groove that have been shown to be hydrogen bond donors to glutamic acid side-chains of the *Eco*RI endonuclease in the enzyme–oligodeoxyribonucleotide structure determined by McClarin *et al.*[4].

Our experiments indicate that the primary effects on the steady state kinetics of the hydrolysis reaction are due to the introduction of the amino groups into the minor groove, where there is no protein in the crystal structure[4], and not their removal from the major groove. The relative specificity constant (k_{cat}/K_M) for the analogue with the 2,6-diaminopurine substitutions is 0.11, whereas it is 0.09 for the 2-aminopurine substitutions. These results support the contention that the addition of an amino group to the minor groove of the central A–T base pairs of the recognition sequence interferes with the activity of the enzyme by preventing the DNA from attaining a conformation required for binding or catalysis. The addition of a methyl group to the 3-position of this same adenine in an alkylation-interference experiment prevented binding of the endonuclease to the recognition sequence[5]. The presence of the 2-amino or 3-methyl groups in the minor groove may prevent the unwinding of the DNA helix to form the Type I neokink[4] that is necessary to open the major groove to allow the protein access to the otherwise cryptic recognition determinants. Sequence-dependent conformational constraints in the DNA may play an important role in determining the specificity of interaction between proteins and DNA.

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Reversible evolution?

SIR— Harvey and Partridge (*Nature* **326**, 128; 1987) state that most ". . . biologists view adaptive evolutionary change as reversible." Nowhere in the report is an attempt made to clarify the ambiguity inherent in their concept of reversibility. It would be unfortunate if the non-biologist readers of this journal now hold the misconception that adaptive evolution is reversible in a literal sense.

Reversibility denotes, *sensu stricto*, the capacity to retrogress to an ancestral state, duplicating all intermediate states, seriatum. Although Dollo's law (which embraces a concept of irreversibility) is interpreted variously, it remains the common view among biologists and historians alike that, even if intermediate steps are ignored, independently evolved phenomena are rarely indistinguishable. Although point mutations are reversible, as evolving systems become more polygenic (that is, as trends involve ever greater numbers of genes), the probability of returning to a given ancestral state becomes vanishingly small, because this quantity is the product of the probabilities of reversion of each involved gene. In the context of morphological or behavioural change over hundreds of thousands of generations, the occasional isolated reversion of such microscopic events are lost in the manifold trends of organismal evolution. Or they at least find themselves cast against a novel genetic background.

In an effort to provide a basis for reversibility, the authors offer the familiar example of industrial melanism in the peppered moth, *Biston betularia*. The frequency of melanic forms first increased as pollution from the industrial revolution took hold and then decreased as smoke control measures were enforced, as a function of their visibility to predators. It has been argued that this vignette of adaptive evolution in action is oversimplified. Observed allelic frequencies do not conform to a simple model of predation selection, and differential fitness unrelated to crypsis is likely a complicating factor (Jones, J.S. *Nature* **300**, 109; 1982).

Harvey and Partridge then cite an interesting case of behavioural irreversibility in a hymenopteran genus, and adumbrate that such examples are relatively rare. Evidence of evolutionary irreversibility is, *a fortiori*, ubiquitous. A