

immunotherapy (PIT) in AIDS patients, some of them double-blind control studies showing significant clinical benefits to the recipients⁵⁻⁶. Also, in studies of long term survivors of HIV infection, all survivors have been found to have high levels of neutralizing antibodies^{9,10} sometimes without significant cellular immunity against HIV-infected cells⁹. We also have evidence to suggest that passive immunotherapy given in the early stages of the diseases, induces long-term clinical remission: we have been monitoring an HIV-positive child in whom PIT was initiated at the age of 3.5 years and who has been receiving plasma at monthly intervals (since August 1993) as the only anti-HIV-1 treatment. The child has normal physical and mental development.

We hope this may convince Parren *et al.* that HIV-1 neutralizing antibodies, far from being unusual, are a normal response in the early stages of infection and that they correlate with and perhaps explain the unusually long (nine years on average) AIDS-free period. The reason that they eventually fail to win the war against the infection is unknown but may be due to: continued viral integration, reproduction and infection of new cells in lymphoid sites inaccessible to antibodies; cell-to-cell transmission of infection; the emergence of neutralizing-resistant mutant viral strains; or infection and destruction of CD4 T-cells, removing the helpers for antibody-producing cells, so depleting and eventually ablating the protective response.

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Parren et al. reply — Dr. Karpas and colleagues question our conclusion that the antibody response in HIV-1 infection is elicited by viral debris rather than the virus by quoting examples of the supposed efficacy of antibody in controlling HIV-1 infection. They state that our argument is based on the inability of antibody to clear HIV-1 infection. It is not. It is based on the general observation that anti-HIV antibodies from seropositive

donors display high affinities for viral debris (unprocessed gp160 in particular) and poor affinities for native viral envelope oligomer. As a consequence of this, typical anti-HIV antibodies may be rather inefficient against the virus.

The evidence that Karpas *et al.* put forward for the efficacy of antibodies in controlling HIV-1 infection is unconvincing. First, some of Karpas' methodology may be flawed as has been critically appraised elsewhere². Second, studies relying on clinical benefit^{5,7} may measure the effects of passively transferred immunoglobulin specific for opportunistic pathogens. Changes in HIV-1 viral loads furthermore were not addressed, but a recent study with a comparable immune globulin preparation indicated no significant effects on viral levels¹². Moreover, hyperimmune globulin trials in mother-child transmission have recently been discontinued in the US because of lack of clear evidence of efficacy.

Neutralizing antibody responses in long-term non-progressors (LTNP) are somewhat broader and more potent compared with other HIV-1 infected individuals¹³. Although statistically significant, this relationship is not absolute as suggested by Karpas *et al.*, and LTNP are heterogeneous as a group with respect to the magnitude of the viral load and antiviral activity of both cellular and humoral immune responses¹⁴. The analyses therefore do not immediately imply a causal relationship between the presence of these antibodies and survival. Broader neutralization, for example, could also be the result of the long-term exposure to a greater variety of quasispecies within a constantly changing viral population. A conclusion that can be drawn however is that even in LTNP, except for very few exceptional cases, primary isolate neutralizing antibody serum titers are poor.

Re-examination of the data from passive immunization trials and antibodies in LTNP therefore demonstrate an agreement between *in vivo* and *in vitro* studies and indicate a general inefficiency of anti-HIV-1 antibodies against the virus. Finally, we emphatically do not discount that antibodies, either passively introduced or from vaccination, could be effective against HIV-1. Our argument is rather that the quality of these antibodies is a critical factor. Natural infection and subunit vaccination appear to produce very few antibodies of useful anti-viral potency.

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ERRATUM

Editorial changes made in the Letter by Parren *et al.* (*Nature Medicine* **3**, 366-377 (1997)) after proof-reading resulted in a series of references becoming misnumbered. The corrected version of the Letter can be obtained from Dennis Burton via e-mail (burton@scripps.edu).