immunotherapy (PIT) in AIDS patients, some of them double-blind control studies showing significant clinical benefits to the recipients[5–8]. 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 cells[9]. 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.

ABRAHAM KARPAS
Department of Haematology, Cambridge University Clinical School, MRC Centre, Hills Road, Cambridge, CB2 2QH UK

STEPHEN ASH
Ealing Hospital, London, UB1 3HW UK

DOUGLAS BAINBRIDGE
Royal London Hospital, London, UK

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 elsewhere[2]. Second, studies relying on clinical benefit[6,7] 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 levels[12]. 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 individuals[13]. 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 responses[14]. 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.

PAUL W.H.I. PARREN[1],
QUENTIN J. SATTENAU[2] &
DENNIS R. BURTON[1]
[1]*The Scripps Research Institute, Departments of Immunology and Molecular Biology 10550 North Torrey Pines Road (IMM2) La Jolla CA 92037, USA*
Email: burton@scripps.edu
[2]*Centre d'Immunologie de Marseille Luminy Case 906, 13288 Marseille, France*

1. Parren, P.W.H.I., Burton, D.R. & Sattenau, Q.J. HIV-1 antibody — debris or virion? *Nature Med.* **3**, 366 (1997).
2. Karpas, A. *et al.* Lytic infection by British AIDS virus and the development of rapid cell test for antiviral antibodies. *Lancet* **ii**, 695–697 (1985).
3. Karpas, A. *et al.* Effect of passive immunization in patients with acquired immunodeficiency syndrome –– related complex and acquired immunodeficiency syndrome. *Proc. Natl. Acad. Sci. USA* **85**, 9234–9237 (1988).
4. Karpas, A. *et al.* Polymerase chain reaction evidence for immunodeficiency virus-1 neutralization by passive immunization in patients with AIDS and AIDS-related complex. *Proc. Natl. Acad. Sci. USA* **87**, 1195–1199 (1990).
5. Vittecoq, D. *et al.* Passive immunotherapy in AIDS: a randomized trial of serial human immunodeficiency virus-positive transfusions of plasma rich in p24 antibodies versus transfusions of seronegative plasma. *J. Inf. Diseases* **265**, 364–368 (1992).
6. Levy, J. *et al.* Passive hyperimmune therapy in the treatment of AIDS: Results of a multicenter double-blind controlled trial. *Blood* **84**, 2130–2135 (1994).
7. Vittecoq, D. *et al.* Passive immunotherapy in AIDS. A double-blind randomized study based on transfusions of plasma rich in anti human immunodeficiency virus 1 antibodies versus transfusions of seronegative plasma. Proc. *Natl. Acad. Sci. USA* **92**, 1195–1199 (1995).
8. Blick, G. *et al.* Passive immunotherapy in advanced HIV infection and therapeutic plasmaphoresis in asymptomatic HIV-positive individuals: A four-year clinical experience. Biother. (in the press).
9. Cao, Y. *et al.* Virologic and immunologic characterization of long term survivors of human immunodeficiency virus type 1 infection. *N. Engl. J. Med.* **332**, 201–208 (1995).
10. Pantaleo, G. *et al.* studies in subjects with long term non-progressive human immunodeficiency virus infection. *N. Engl. J. Med.* **332**, 209–216 (1995).
11. Jacobson, J.M. *et al.* Passive Immunotherapy in treatment of advanced human immunodeficiency virus infection - Reply. *J. Infect. Dis.* **170**, 743–744 (1994).
12. Lambert, J.S. *et al.* Safety and pharmacokinetics of hyperimmune anti-human immunodeficiency virus (HIV) immunoglobulin administered to HIV-infected pregnant women and their newborns. *J. Infect. Dis.* **175**, 283–291 (1997).
13. Montefiori, D.C. *et al.* Neutralizing and infection-enhancing antibody responses to human immunodeficiency virus type 1 in long term non-progressors. *J. Infect. Dis.* **173**, 60–67 (1996).
14. Harrer, T. *et al.* Strong cytotoxic T cell and weak neutralizing antibody responses in a subset of persons with stable nonprogressing HIV type 1 infection. *AIDS Res. Hum. Retroviruses* **12**, 585–592 (1996).

ERRATUM

Editorial changes made in the Letter by Parren *et al.* (*Nature Medicine* **3**, 366–377 (1997)) after proofreading 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).