cine may therefore be looked on as an added safety feature.

It is not known which specific immune responses are required for therapeutic benefit, so we have proceeded cautiously. More than 1,100 HIV-positive patients are enrolled in five independent phase I trials and three independent phase II trials with gp160 with up to 4 years of follow-up. The phase I studies have shown evidence of stable CD4 cell counts, stimulation of cytotoxic T cells and the suggestion of restoration of immune function. Some of these results have also been confirmed in phase II studies.

On the basis of these and other clinical results, MicroGeneSys gp160 was chosen by scientists at the Karolinska Institute, the National Bacteriological Laboratory and South Hospital in Sweden for the first phase III vaccine therapy studies.

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SIR — Differences in opinion may exist as to whether the principles of therapeutic vaccines have been solidly established. It is clear, however, that the immune response in preventive and therapeutic vaccines differs in fundamental ways. Preventive vaccines are introduced into an immunologically naive system, whereas therapeutic vaccines encounter a system already immunologically primed. In the present discussion on the gp160 protein from MicroGeneSys[1] this fact has been largely ignored. The concept of 'original antigenic sin' was first shown by studies on the antibody response against influenza virus. A first encounter with a particular virus strain led subsequent contacts with other influenza strains to induce antibody responses strongly biased against the first 'original' strain. Subsequent research has documented that this effect occurs at the B- and T-cell levels.

The fact that gp160 expressed in baculovirus with the sequence of HIV strain IIIB (LAI) will induce different immune responses when used *de novo* in previously unimmunized individuals as compared to already infected individuals is thus highly logical. Whereas non-infected individuals respond with largely type-specific responses, infected individuals respond with a profile distinctly different from the normal individual. A broad antibody response, including not only IIIB but MN and even autologous isolates with regard to neutralization, is thus induced by vaccinating the infected individual. Similarly, there is significant enhancement of T-cell responses against HIV–*env*–protein-derived peptides.

Our extensive placebo double-blind study of HIV-1-infected individuals from the Nordic countries and Switzerland that is now starting has two basic aims: (1) To verify or disprove that therapeutic vaccines can induce an anti-HIV immune response of such a kind that it has clinical, positive consequences; and (2) to carry out a double-blind trial that could lead to clinical use of the product.

It has been shown that a broadened serological response occurs after immunization of HIV-infected individuals and that T-cell responses increase drastically[2]. Further, increased affinity to unrelated crossreactive MN HIV peptides increases after immunization with rgp160 of the LAI strain (B. W. *et al.*, unpublished results). These observations suggest that an anamnestic response to the patient's own virus might become reactivated by the foreign, but still related, protein. Certainly other candidates may also induce such reactivities. Both CD4 and CD8 cytotoxic T lymphocytes have, perhaps unexpectedly, been shown specifically to increase during a series of six immunizations of previously HIV-infected subjects[4].

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MOORE *ET AL.* REPLY — Volvovitz and Smith claim that MicroGeneSys, Inc. has "designed" its gp160 to be denatured. Oral presentations by company scientists indicate that the design feature involves extraction of gp160 from insect cells in the presence of urea, followed by enrichment of the glycoprotein fraction on lentil lectin columns. The conversion of MicroGeneSys to the virtues of denatured immunogens is one of Damascene proportions. Can this be the same company whose scientists's opinion was only 2 years ago that ". . . native structure is required for an HIV-1 envelope glycoprotein to be a successful vaccine antigen"[12]? This was at a time when the same gp160 product was being vigorously touted by MicroGeneSys as a prophylactic vaccine candidate; a time when, as now, being able to mimic as closely as possible the natural viral antigens was held to be important for such a vaccine. It is significant that MicroGeneSys gp160 has been excluded from recent trials of prophylactic vaccines[13]. Is it cynical to suppose that, far from "designing" its gp160 to be denatured, MicroGeneSys has rewritten history and grasped the concept of vaccine immunotherapy as a way to exploit their denatured product? *Post hoc ergo propter hoc.*

A rationale for using denatured gp160 as a therapeutic agent in HIV-infected people is to boost the immune response by raising antibodies against novel gp160 epitopes, as Volvovitz and Smith, and Wahren *et al.*, describe above. This concept, originally promoted by Redfield and Birx[3], is not entirely devoid of merit. We believe, however, that to achieve a relevant alteration of the immune response will require an immunogen substantially more sophisticated than the MicroGeneSys gp160. It would be a shame if a superficially reasonable idea was destroyed by a premature focus on poorly designed reagents. Wahren *et al.* also justify the use of MicroGeneSys gp160 as a recall antigen, which boosts the production of antibodies raised originally against native viral antigens earlier in infection. But it is precisely those antibodies which Volvovitz and Smith dismiss so cavalierly as unimportant for prevention of progression of HIV disease! Which view prevails?

Volvovitz and Smith cite reports that binding of gp120 to CD4 *in vitro* can perturb immune cell functions. To date, however, there is no evidence from clinical trials that native gp120 vaccines harm the immune systems of naive or HIV-infected recipients *in vivo*. But Volvovitz and Smith fail to point out that the region of retroviral envelope glycoproteins (including HIV-1) most commonly found to have immunosuppressive effects *in vitro* is located in the ectodomain of gp41 (ref. 14), and is therefore present in MicroGeneSys gp160 but absent from gp120. Furthermore, gp160 has the potential for raising unwanted autoimmune responses because of a region similar to MHC class II present in the gp41 moiety[15] but not in gp120. Perhaps these features should also have been "designed" out by MicroGeneSys? The importance under *in vivo* conditions of any of these *in vitro* observations[5–11,14,15] remains to be determined.

Wahren *et al.* advertize that they are testing MicroGeneSys gp160 in a large-scale clinical trial in Sweden. Data from controlled phase II trials of MicroGeneSys gp160 by the US Army should be available later this year. These will reveal whether or not Wahren *et al.* were wise to expand the scope of their experiment before knowing the results of previous ones. We did not suggest in our previous Scientific Correspondence[1] that such trials should not take place; indeed one of us (J. R.) will soon be involved in a clinical trial of MicroGeneSys gp160 in pregnant women. We restricted our comments to the design of pending trials in the United States that are a matter of considerable debate, and suggested that such trials should be comparative precisely because, as Volvovitz and Smith say, "it is not known which specific