

HIV infection. T cell suppression was not universally observed either: some (9), but not all (5), groups have reported GvH disease instead.

Lusso *et al.* urge a "note of caution concerning biosafety measures" as a result of the direct demonstration that pseudotypes can form between X-MuLV and HIV. They suggest that the pseudotypes could be "more pathogenic" than HIV itself. HIV is a formidable pathogen in its own right. Like other retroviruses (including pseudotyped retroviruses), it is not spread by the aerosol route and, at low titer, should be handled under Biosafety Level 2 conditions. Nonetheless, all of our experiments with HIV-infected SCID-hu mice have been conducted under more stringent Biosafety Level 3 (BSL3) precautions. In the case of HIV-transgenic mice (10), BSL4 has been used. This level of biocontainment is designed to eliminate the possibility of aerosol spread of HIV. If a pseudotyped HIV were to form, it would also be contained.

Lusso *et al.* show that pseudotypes can form between HIV and X-MuLV. Such phenotypic mixing (between, for example, HIV and HTLV-1, VSV, and herpesviruses) might well be an important component of HIV-induced pathogenesis in humans, and any experiment dealing with HIV in vivo or in vitro should be designed to control for the possibility of pseudotype formation. Yet the body of data already gathered and published about HIV-infected SCID-hu mice speaks for itself. These animals can be used in a safe and productive fashion to study the efficacy of antiviral compounds against HIV in vivo.

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Response: We are grateful to Mc Cune *et al.* for their remarks, which provide an opportunity for a more detailed discussion of some issues raised by our report (1) describing the interactions between human immunodeficiency virus type-1 (HIV-1) and xenotropic murine leukemia virus (MuLV). While it is clear that phenotypic mixing is a well-documented interaction between enveloped viruses, our results provided the first evidence that such a phenomenon can involve HIV-1, the causative agent of the acquired immunodeficiency syndrome (AIDS). Similar data have been subsequently reported by other investigators (2). The issue of phenotypic mixing has not been previously addressed, to our knowledge, in any publication concerning animal models for HIV infection, including the reports by Mc Cune *et al.* (3) and other investigators studying the SCID mouse models.

Although our results may be particularly relevant to the SCID models for HIV infection, our attention was not solely directed to the work of Mc Cune *et al.* We believe the issue of endogenous retroviruses may be of far more general relevance and may also involve other animal models used for the study of human physiology or pathology. The persistent and productive infection with a retrovirus like MuLV may indeed represent an undesired additional variable in the experimental picture. Nonetheless, we have not "suggested" that "data gathered from HIV-infected mice [be] irrelevant." On the contrary, we are thoroughly convinced that the SCID mouse models for HIV infection may provide valuable information for the study of human AIDS.

Mc Cune *et al.* state that a single human cell line that we explanted from immunodeficient mice had acquired xenotropic MuLV. However, as clearly documented in table 1 of our paper (1), several human hematopoietic cell types (six out of six tested) became persistently infected with xenotropic MuLV after heterotransplantation into mice. In addition, although Mc Cune *et al.* focus their attention on the question of "pseudotypes," phenotypic mixing was not the only interaction between HIV-1 and MuLV described in our report: MuLV also dramatically accelerated the time course of HIV-1 expression and cytopathicity in coinfecting human T cells (1).

We are glad to learn that the preliminary investigation mentioned by Mc Cune *et al.*

found no signs of phenotypic mixing between HIV-1 and MuLV in the SCIDhu/HIV-1 model. However, we believe that technical difficulties may hamper the identification of phenotypic mixing in vivo, unless specific experiments are designed to verify this occurrence, and highly sensitive techniques are used. In addition, in their preliminary observations, Mc Cune *et al.* rule out the formation of pseudotypes between HIV-1 and amphotropic MuLV. However, amphotropic MuLV has not been detected in the *Mus* germ line (4). Therefore, phenotypic mixing involving amphotropic MuLV is unlikely to occur in laboratory strains of mice.

The question of whether "low-frequency" phenotypic mixing can constitute a problem for the use of murine models for AIDS is difficult to address before the testing of specific therapeutic regimens in vivo. We agree with Mc Cune *et al.* that "the formation of pseudotypes between HIV and X-MuLV should have no impact on the conclusions of [the] study [on the suppressive effect of AZT on HIV-1 infection in SCIDhu mice]." However, in this instance, AZT would be effective against the replicative cycles of both murine retroviruses and HIV-1 (5). By contrast, the efficacy of some therapeutic-prophylactic approaches selectively targeted to HIV-1, for example, soluble CD4 therapy, could become questionable.

Concerning the decrease of circulating immunoglobulins in HIV-infected SCID mice, we regret the confusion arising from our report about the various designations used for SCID mouse models engrafted with human cells. This observation was made exclusively for the so-called "hu-PBL-SCID" model (the one described by the group headed by D. Mosier), but not for the "SCIDhu" model (the one described by Mc Cune). Although Mc Cune *et al.* state that these data are still unpublished, they have been repeatedly presented at international meetings and have recently been published (6). Unfortunately, this important topic has not been addressed in reports concerning HIV-1-infected "SCIDhu" mice (Mc Cune's model).

It is obviously not news to us that "HIV is a formidable pathogen" per se, as our laboratory has contributed significantly to the initial definition of its pathogenic role and routes of transmission. However, the pathogenicity of HIV could become even more formidable if hypothetical variants emerge, making it transmissible by means of non-parenteral routes. This notwithstanding, we stress that we did not attempt to demonstrate or to suggest that phenotypically mixed HIV-1 could be transmitted through

the aerosol route.

We reaffirm that the principle aim of our study was to make researchers aware of the possible interactions between HIV and endogenous retroviruses and, more in general, to the remarkable frequency of infection with xenotropic MuLV observed in human cells heterotransplanted into mice. We believe that such awareness could be important for the correct design and interpretation of some experimental models in vivo.

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"For heaven's sake George, if it's fire they want, let them take it!"