

The False-Positive Polymerase Chain Reaction and the Ostrich

To the Editor—Gerberding [1] reported that 1 of 327 health care workers exposed by needlestick to human immunodeficiency virus (HIV) seroconverted within 4 weeks of exposure. She also reported that 4 of the 327 had "one or more positive" polymerase chain reaction (PCR) tests. An additional 7 persons had "an indeterminate PCR test result on the initial specimen" (>6 months after exposure). Later samples for all 11 were negative, "and none seroconverted or developed p24 antigenemia." These data led to the conclusion that "false-positive results [of PCR] occur even under the most stringent test conditions." How false is false?

In view of the growing body of information on virus-positive yet seronegative individuals, care should be exercised as to which measure we use for true and false infection.

Exposure to and infection with HIV without subsequent seroconversion has been repeatedly reported. Some investigators claim that all positive PCR results (negative PCR is never, for some reason, considered to be false-negative) that are not matched by positive ELISA serology are false-positive. But what should we do with virus (isolation)-positive cases that remain seronegative [1-4] (unpublished data)?

On the basis of studies that have shown that HIV resides in the latent period (at least initially) mainly in lymph nodes [5] and not in peripheral blood mononuclear cells (PBMC), we should be more suspicious of reports of false-negative PCR. (Looking for HIV in PBMC is similar to searching for it under the lamppost.)

How can we deal with conflicting results in two different test systems? One way would be to use an epidemiologic approach in which a large number of low-risk persons would be tested and monitored by a reliable laboratory to determine the rate of false-positive HIV PCR results among these persons. The results could then be compared with those reported by Gerberding [1]. An immunologic approach would examine other HIV-specific responses

that would develop only if a true exposure to HIV occurred. Such markers might include T cell proliferation in response to HIV-specific peptides [6] and in vitro antibody production after mitogen activation. If such HIV-specific immune responses are detected, then the PCR results are probably not false-positive, but the serologic results are false-negative. Such contradictory findings would support the view that serology by ELISA should not be used as a reference standard for detection of HIV infection. If many PCR-positive seronegative samples are not false, it is possible that positive ELISA serology delineates a selected skewed population of HIV-infected persons—those who seroconverted and who will likely develop AIDS. Closer examination of PCR-positive yet seronegative persons could shed light on little (or not) known modes of immunologic responses to the virus, modes that may not lead to development of AIDS.

HIV investigators cannot afford to bury their heads in sand, like the ostrich, believing that what is not seen by serology does not exist. Nor can they be forever mired in the endless sand of false-positive results.

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Reply

To the Editor—Dr. Jehuda-Cohen [1] questions my assertion that positive polymerase chain reaction (PCR) results reported from seronegative health care providers are false-positives. In this case, the answer does not lie in what is buried in the sand, but rather in what is buried in the freezer. Additional aliquots of the initial and follow-up lymphocyte DNA samples from subjects with one or more positive PCR results were subsequently tested in the original laboratory and also in a second reference laboratory. In addition, a whole blood specimen obtained 2 months after the second positive PCR from the subject with two consecutive positive results was sent via express to the reference laboratory for immediate DNA testing. No human immunodeficiency virus (HIV) DNA was detectable in any of these samples. Thus, the most likely explanation for positive PCR results observed in this cohort is that sample contamination occurred during the aliquoting, processing, or shipping of the large number of samples (including positive controls) to the reference laboratory.

The "simple numeric data" presented by Jehuda-Cohen do accurately represent the findings of my study. As described in [1], 3 of 133 tested subjects with a documented parenteral HIV exposure to HIV had a positive PCR result and 1 of 91 tested subjects who lacked a documented exposure had a positive PCR result. The difference in these proportions is not significant, the expected finding if cross-contamination and not occupational trans-

mission was the cause of the positive results. Furthermore, the fact that all of the subjects remain healthy and none has seroconverted suggests that these PCR test results were not predictive of clinical outcome. In my view, isolated positive PCR test results should not be used to establish a diagnosis of HIV in the absence of additional clinical, serologic, or virologic evidence of infection, at least in a population such as health care providers with a low pretest probability of infection.

The biology of transcutaneous HIV exposure and infection is not established. Lymphocytes from seronegative health care providers who sustained parenteral exposures to HIV respond to HIV antigens *in vitro*, suggesting a role for the cellular immune system in preventing or aborting infection [3]. Jehuda-Cohen's speculation that silent HIV infection, detected only by PCR, represents an important stage in the immune response to infection is intriguing, but must be confirmed. In the meantime, we do a great disservice to health care providers by suggesting that seronegative infection, if it occurs at all, is anything but an extremely rare outcome after occupational exposure.

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