Invited Commentary: Le Mystère de Montréal

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This issue of the *Journal* features the publication of one of the more controversial studies regarding that most contested of human immunodeficiency virus (HIV) prevention interventions, needle exchange programs (NEPs) (1). The Montreal study, long a focus of speculation by researchers and of misrepresentation by the opponents of NEPs, even as it had remained unpublished, will now rise or fall on its own merits. In my view, the study raises no substantial concerns about the effectiveness of NEPs but does point the way to improving the programs.

Some historical background is essential if the place of the present study in the body of needle exchange research is to be fully appreciated. In the fall of 1993, the US Centers for Disease Control and Prevention completed a review of NEP effectiveness and concluded that NEPs are likely to reduce the incidence of HIV among injection drug users (IDUs) and do not appear to be associated with an increase in drug use rates, the two criteria that must be met for the US federal ban on NEP funding to be lifted. Realizing the political implications of a document in which senior federal scientists recommended that the federal funding ban be lifted, a course seemingly at odds with the government "zero tolerance" policy on drugs, the administration chose to suppress the troublesome document (2). This strategy stifled the debate until the *Washington Post* obtained the documents in February 1995. This is where the Montreal study became a pawn in the US debate over needle exchange. Forced to justify how the government had ignored its own scientists' recommendations, Assistant Secretary for Health Philip R. Lee defended the ban by citing three unpublished studies, including the Montreal study, which he said had raised doubts in his mind about the effectiveness of NEPs (3).

At the time Dr. Lee made these comments, the National Academy of Sciences was completing a congressionally mandated report on needle exchange. The nearly final report also recommended that the ban on federal funding be lifted. Believing that to not address the studies cited by the administration to justify maintaining the ban would limit the usefulness of its work, the National Academy of Sciences put its report on hold and convened a special session at which the authors of the three studies presented their research. The product was an appendix to the National Academy of Sciences report that raised serious methodological and interpretational questions about the studies. Despite the additional session, the central recommendation of the National Academy of Sciences report remained unchanged. Like all other federally funded reviews of NEP effectiveness before or since, the September 1995 report concluded that the two criteria necessary for lifting the federal NEP funding ban had been met (4). Almost 3 years since the unpublished studies were first used by the administration to justify its inaction, the ban remains in place, the first of the three controversial studies still has not been published, and the second has been reanalyzed and now suggests potential benefits for NEPs (5). The third appears in this edition of the *Journal* (1).

In that third study, Bruneau et al. enrolled 1,599 in-and out-of-treatment IDUs in Montreal and then prospectively followed 974 who were HIV seronegative at baseline. After adjusting for empirical confounders, IDUs who attended the NEP at baseline were 2.2 times as likely to be HIV positive at baseline (95 percent confidence interval (CI) 1.5–3.2) and 1.7 times as likely to seroconvert (95 percent CI 1.0–2.7) during a median of 15 months of follow-up. In a nested case-control analysis, exclusive NEP use was positively associated with seroconversion, although the confidence interval was wide (adjusted odds ratio = 6.5, 95 percent CI 1.8–23.8).

Do these results demonstrate that NEPs, far from preventing HIV transmission, actually cause an increase in transmission as some NEP opponents have
claimed? And do the results mandate the abandonment of HIV prevention policies for IDUs based on the provision of sterile syringes? The simple answer to both of these questions is “no.”

As the authors themselves point out, “This cohort is an observational study and was not designed to study or evaluate NEPs” (1, p. 995). The investigators suggest that their findings may result from the NEP facilitating the formation of social networks that increased HIV transmission. In the absence of any supportive data, this must be regarded as highly speculative. The more likely explanation is that powerful selection forces attracted the most risky IDUs in Montreal to the NEP. Indeed, on a wide array of measures, the authors’ data confirm this; NEP participants were much less likely to be in drug treatment and much more likely to inject frequently, borrow injection equipment, frequent shooting galleries, and share injection equipment with an HIV-positive IDU. As noted, the baseline prevalence data are consistent with these behavioral data (16 percent among NEP attenders vs. 6 percent among nonattenders). Not surprisingly, as other studies have found, high HIV prevalence in a community predicts high HIV incidence (6).

As the National Academy of Sciences stated in its review of the Montreal study, “It is clear that some selectivity processes are at work. Something is attracting high-risk injectors to the exchange program. Without a more detailed understanding of the characteristics that distinguish [NEP] nonusers from users, we cannot ascribe the differences in seroprevalence and seroincidence rates to the needle exchange program” (4, pp. 292–3).

Why would such selection forces exist? For most of the study period, the major Montreal NEP, CACTUS, was open only from 9:00 p.m. to 4:00 a.m. and was exchanging fewer than 200,000 syringes per year, a rather limited number for a city so large. In addition, public health officials in Montreal have, appropriately, sought to expand sterile syringe availability by involving pharmacists in the provision of syringes (7), an initiative that is only now beginning in the United States. Finally, CACTUS is located in a part of Montreal notable for high levels of commercial sex work. Thus, the NEP was likely to be disproportionately utilized by IDUs who were out in the streets in the very early hours of the morning and who had difficulty obtaining or affording purchase of syringes through pharmacies. It is not surprising that these individuals would be at greater risk for HIV.

One response to this criticism is that the authors used multivariate statistical techniques to correct for behavioral characteristics, and the incidence differential persisted. In what appears to be part of a growing but regrettable trend in epidemiology, the authors present the results of their statistical models without providing other crucial data. What were the measures of association for variables other than NEP use? Did the statistical properties of the variables meet the requirements of the models? Might unmeasured confounders explain the findings? (The fact that in all analyses, the measures of NEP effect move consistently toward the null as more confounders are added to the models suggests that some uncontrolled confounding may remain.) In the absence of this information, the models cannot be interpreted with great confidence. Many epidemiologists have found multivariate associations that appear and disappear with relatively minor changes in a statistical model.

Furthermore, the use of overly simple measures of NEP use (e.g., use/nonuse; exclusive use/nonexclusive use/nonuse) results in the loss of much of the information that could be contained in richer measures of NEP use, such as the number or proportion of syringes obtained from the NEP. (In fairness to the authors, this is true for many other NEP studies.) This leads to loss of precision and, potentially, to systematic bias. The same is true for the measurement of potential confounders. Finally, in the absence of seroconversion rates predating the NEP, one cannot know whether the NEP participants (or nonparticipants) might have seroconverted at a rate still higher than that observed here if the NEP had not opened.

However, if the Montreal study is to be faulted for selection bias and its observational nature, the same general criticisms can be leveled at observational studies that show lower HIV seroconversion rates among NEP participants. One should not criticize the Montreal study while touting other recent data from New York City, which demonstrate a 70 percent reduction in HIV incidence for NEP users (8), or new data from Baltimore, Maryland—not yet published in the medical literature—which reportedly show a 40 percent reduction (9, 10). As Bruneaux et al. rightly point out, the impact of an NEP is likely to depend significantly on the local context. Although other studies have described NEPs that attract IDUs who inject more frequently (11, 12), unusual local conditions in Montreal appear to have attracted particularly high-risk IDUs to the NEP, bringing with them higher seroconversion rates. The opposite could be the case in other localities. To the extent that NEPs will be most efficient if they provide services to the highest risk IDUs, the attractiveness of the Montreal NEP to high-risk IDUs should be viewed as a sign of success, not failure.
National Institute on Drug Abuse to take place in Anchorage, Alaska. In the study, IDUs will be randomized either to obtaining free syringes from an NEP or to obtaining information about how to purchase syringes at pharmacies—information all or most will already have. IDUs who do not enroll in the study or who are randomized to the comparison condition will be turned away from the NEP if they attempt to procure syringes there (13). Given the numerous reviews that have concluded that NEPs are effective in reducing the incidence of HIV and that have recommended both NEPs and pharmacy-based syringe availability, this study appears to be in violation of principle five of the Nuremberg Code, which requires that “No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur...” (14). In addition, crossover of individuals from the NEP group to the pharmacies and of needles in both directions is likely to undermine the randomization and to produce an uninterpretable study.

If observational studies are subject to criticism and if randomized, controlled trials of NEPs are logistically impossible and unethical, how is one to determine whether NEPs are effective? Certainly no one study, on its own, should be used to declare the programs effective or otherwise. Rather, it is by examining multiple lines of evidence from studies of differing designs to discern consistent patterns in the data—what the National Academy of Sciences report referred to as “patterns of evidence”—that we can best reach reliable conclusions. The first of these is the biological plausibility of the intervention: that in accordance with basic infectious disease principles (15), eliminating an inanimate object (in this case the syringe) that transmits infection from person to person can reduce the incidence of infection. The second line of evidence is behavioral: There is clear evidence from more than a dozen studies that IDUs attending NEPs reduce their syringe-sharing rates and do so more than IDUs not attending NEPs (16). Third, a case-control study from Tacoma, Washington, demonstrated a six- and sevenfold reduction in the odds of acquiring hepatitis B and C among those who had ever attended an NEP compared with those who had never attended one (17). Fourth, mathematical models of a variety of designs have calculated decreases in HIV incidence ranging from 15 to 70 percent for those attending NEPs (16, 18); one study also included empirical data demonstrating a sharp reduction in the prevalence of HIV in the needles returned by IDUs attending the NEP, consistent with the presumed mechanism of NEP effectiveness (19). Fifth, international ecological data suggest that NEPs are associated with stable HIV seroprevalences in the cities that have implemented them (20). In another ecological analysis, HIV seroprevalence increased 5.9 percent per year in cities without NEPs but declined 5.8 percent per year in cities with NEPs (21). Finally, to the extent that the thousands of IDUs who have been referred to drug treatment from NEPs reduce their rate of drug injection, drug-related HIV risk is diminished or eliminated (16).

Together these diverse studies generate a picture that overwhelmingly supports the effectiveness of NEPs. It is worth recalling that there is not a single behavioral HIV prevention intervention that has been proven effective in reducing HIV incidence in a randomized, controlled trial. To simply criticize all studies for their shortcomings compared with the randomized trial “gold standard” and to defer public health action on those grounds is to surrender the science of epidemiology to thoughtless empiricism and to endanger the lives of thousands of IDUs, their sex partners, and their children (22).

The Montreal study has three principal lessons for us. First, it is an illustration of how research findings can be manipulated by politicians, even before publication, to justify policy agendas quite opposite from those the authors would support. Second, if NEPs are attracting the highest risk IDUs, they would seem to be ideal locations to provide and evaluate more intensive risk-reduction interventions. Finally, the major conclusion from the Montreal study is precisely the one the authors drew when the limit on the number of syringes that could be exchanged was revoked: What is needed to reduce the terrible toll of HIV among Montreal IDUs is not less needle exchange but more.

REFERENCES