December 19, 1996

Deborah Carle
Grants Management Branch
National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Carle:

Subject: RO1 DA10181-01A1

Enclosed please find copies of both first year direct costs and entire budget direct costs for the proposed supplement to cover the costs of offering "vouchers to cover the costs of purchase of Hepatitis B Virus (HBV) vaccine for those subjects not eligible for provision of the vaccine through Medicaid, the Indian Health Service, or private health insurance." We are presenting you with two options.

Option 1 makes the following five assumptions. 1. Ten percent of each group will be Alaska Natives and eligible for provision of the vaccine through the Indian Health Service. 2. Ten percent of the non-Alaska Natives will be receiving Medicaid. 3. There will be three injections provided in each year. 4. Participants may be eligible in all three years of the study and may need to repeat the vaccination series for a variety of reasons. 5. We will not know antibody status so that is not taken into account.

In addition to the two budget sheets, I am also providing a copy of the letter from the Municipality of Anchorage Department of Health and Human Services that gives the price of $36 for each vaccine administration and also gives the estimate of 10% of the population in their experience as receiving Medicaid.

The total first year direct costs requested are $96,495. The Indirect rate is 32.9% and the first year Indirect amount is $31,747. The total entire project period direct costs requested are $301,219 and the entire period indirect costs requested are $99,101. This makes an overall total of $400,320.

Option 2 makes the following assumptions. 1. Ten percent of each group will be Alaska Natives and eligible for provision of the vaccine through the Indian Health Service. 2. Ten percent of the non-Alaska Natives will be receiving Medicaid. 3. There will be a maximum of three injections provided in total. 4. Participants may be

eligible in any year of the study, but may only receive the vaccination series only once no matter what the timing between vaccine administrations is. 5. We will not know the antibody status and will not take that into consideration. 6. Whether or not a participant develops detectable antibody titers after the three administration series will not be taken into account. For option 2 the direct costs are $96,495 and the indirect costs are $31,747. The overall total costs for option 2 are $128,242.

Of course these calculations assumes agreement with our assumptions. If NIDA wishes to change any of the assumptions we will, of course, defer to NIDA's greater wisdom. Thank you for all of your assistance and support during these trying times.

Sincerely,

Dennis G. Fisher, Ph.D.
Principal Investigator

Susan K. Harper
Grants & Contracts Manager

Cc: Janett Trubatch
Peter Hartsock
Richard Needle
Rosellen Rosich

Enclosures: 3

The Alaska Needle Exchange Trial: Lessons in Design and Politics

Presented April 3, 1998

Johns Hopkins University, Center for Clinical Trials

March 14 1996--received priority score of 112, top .05 percent of proposals funded that cycle

June 1996—Submitted proposal to Alaska Science and Technology Foundation for needles and syringes

July 1996—Reports start coming in from Municipality of Anchorage Health Department that someone from California is calling around town "digging up dirt"; ASTF reviews proposal and reveals that two outside reviewers declare the proposed research is unethical. They decide to fund $32,000 for purchase of needles and syringes despite reviewers' comments.

August 1996—First funds received from ASTF by AAAA.

September 1996—Notice of Award received to start work on Interventions grant; personal attorney speaks with Peter Lurie, assures me that Lurie accepts that he is in danger of committing tort by wrongfully interfering in the right conduct of my affairs. Attorney assures me that "you won't have any more problems."

October 17, 1996—National Public Radio leaves voice mail message wanting to know how I "respond to the allegations." I do not know what they are talking about; I receive a copy of the letter from Peter Lurie and Sidney Wolfe (Public Citizen) to Harold Varmus (Director of NIH), demanding that he stop the research grant.

November 1996—I write 15 page letter refuting all of Lurie's criticisms and send it to Harold Varmus. North American Syringe Exchange Network (NASEN) ships 10,000 needles and syringes to Anchorage and starts activist group who set up competing needle exchange. Peter Lurie flies activists to Anchorage to conduct "mini research" on pharmacy sales to refute me. Harold Varmus puts together blue ribbon panel to review grant; I attend panel meeting and am interrogated by panel about the proposal and a letter that was faxed to the panel, without my knowledge, that morning from Peter Lurie that includes the "results" of his secret study; while I am in Washington DC and NYC, activists attempt to get AAAA Board of Directors to pull out of needle exchange project.

December 1996—NIH panel presents their findings and recommendation to move forward with research to Harold Varmus's advisory council; Peter Lurie blasts decision as result of NIH "insiders." While I am in Washington DC, NASEN brings David Purchase to Anchorage from Tacoma needle exchange for publicity campaign to promote NEII. Varmus writes letter to Alan Leshner,

Director of NIDA, to direct me to go ahead with study and to provide me with additional funds to provide hepatitis B vaccine for those not IHS or MEDICAID.

January 1997—I receive permission from Alan Leshner, Director of NIDA, to proceed with research, but permission letter includes provision to provide Hepatitis B vaccine. Immediately after permission is given (on a Friday) it is revoked (the following Monday).

March 1997—Grant is scheduled to be reviewed by sub-committee of House of Representatives, led by Rep. Christopher Shays of Connecticut. Leshner deletes former injectors from study as too controversial but keeps sample size requirements the same. Several weeks I talk to NIDA everyday, one week I am ordered to telephone them every half-hour from 6:00 a.m. to 6:00 p.m. Alaska time, to provide them with information as they prepare for House hearings.

April 1997—original hearing date is postponed until May 8. I still have not been able to begin recruitment. Lurie makes attack on Johns Hopkins researchers over "unethical" AZT clinical trial in Africa.

May 1997—Subcommittee hearings held. Transcripts of hearing forwarded to me. FDA is central target of committee hearings. My own brother attends the hearings and is persuaded by Lurie that my study is evil. I am able to begin recruitment. NEII sends confederate into study to steal copy of Informed Consent Form. AAAA writes letter demanding changes to informed consent form specified by NEII and Peter Lurie.

June 1997—NIDA site visit. We are told that the only possible important result of our study is to demonstrate how to get IDUs to receive vaccinations.

August 1997 – Data Safety and Monitoring Board meeting. Board wants to have a member who is biostatistician.

November 1997—We start $10 incentive for participants who comply with vaccination protocol.

March 1997 – Receive telephone call from NIDA who wants answers to all of their questions faxed to them by close of business EST. We had just closed down for a week of data entry so that we would be ready for March DSMB meeting. We manage to get NIDA their answers by c.o.b. EST. NIDA faxes letter that they want telephone calls every two weeks to keep track of project. DSMB meeting includes Lloyd Fisher from University of Washington, chair of biostatistics department. DSMB revises specific aims, approves randomization and masking scheme, moves to invite NIDA representative to August 1998 meeting, and approves changes to NEP. NIDA telephone call during which they decide they will come out for the next DSMB meeting before I can tell them that

DSMB has voted to invite them. Second NEP site opens at Alaska Native Medical Center (ANMC).

November 12, 1996

Harold Varmus, MD
Director
National Institutes of Health
Building 1, Room 126
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Dr. Varmus:

I am writing to you in response to a letter sent to you by Drs. Peter Lurie and Sidney M. Wolfe dated October 17, 1996. I am asking that a copy of this letter be placed into the official record concerning the grant titled "Interventions to Reduce HBV, HCV, & HIV in IDUs." I feel it necessary to comment on many of their statements. Many of their comments are inaccurate. I will *italicize* their statements.

I would also like to inform you that I will be close (by Alaska standards) to the Washington DC area in November and would be willing to go to Bethesda or wherever the panel is meeting to answer any questions or to assist in your effort in any way. My secretary will be keeping track of my itinerary and you can reach her at 907-786-1801.

We are writing to urge you to immediately cancel the National Institutes of Health (NIH) funding of a research project in Anchorage, Alaska that would randomize people who are injection drug users (IDUs) to receive or not receive syringes from needle exchange programs (NEPs).

This is a distortion of the research design. It implies that this is a clinical trial in which a treatment group is compared to a no-treatment control. This is not the case. In our design there will be two different methods of trying to deliver syringes to participants in the study. One method is a needle exchange program (NEP); the other method is through legal pharmacy sales. There is no state law prohibiting needle/syringe sales in Alaska. This is documented in the appendix to the proposal. The other issue that Lurie and Wolfe do not mention is the mechanism of secondary or indirect exchanging. This is when someone in the NEP condition exchanges syringes for someone in the pharmacy sales

condition. This is perfectly permissible in our design; we only intend to measure the extent to which it takes place.

If one agrees to participate in the study, one stands a 50% chance of being permitted to attend the NEP.

Lurie and Wolfe are not aware that we removed a condition analogous to a "compassionate arm" condition, termed a "declared crossover," from the proposal at the last revision because of the concern by the Initial Review Group (IRG) at the National Institute on Drug Abuse (NIDA) about excessive crossover. As participation is voluntary, I believe this condition is a necessity. In fact, I have had conversations with the Community Research Branch chief about putting the declared crossover condition back in, at least temporarily, until the Data Safety and Monitoring Board can examine the issue and make a final decision.

The remaining 50% of study subjects (300 people) will be turned away from the NEP (subjects will be issued a bar-coded identification card which can generate an image on the research project's computer) and will instead be given information about purchasing syringes from pharmacies, information many or most will already have.

There are actually two different groups who will be randomized into the two different conditions. There will be 600 current injectors (defined as having visible signs of injection, "track marks," and reporting drug injection in the 30 days prior to intake) and 500 former injectors (defined as having visible signs of injection and reporting that they injected at least once in their life but did not inject in the 30 days prior to intake). That means that there will be 300 current and 250 former injectors in each condition.

As far as most of the participants having information about purchasing syringes from pharmacies, this is not as certain as Lurie and Wolfe claim. Anchorage was a participant in the Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research (CA) program at NIDA. Of the 22 sites in the CA, Anchorage had the second highest rate of needle sharing among its IDUs. Our pharmacy sales intervention will instruct individuals about: (a) which pharmacies to patronize and which not to patronize, (b) what the hours of operation of each of the recommended pharmacies are, (c) what the bus routes to each of the recommended pharmacies are, (d) what to say to the pharmacist, (e) what to ask for, (f) any specials on syringes that may be in effect at any of the pharmacies, (g) verbal and nonverbal cues that the pharmacist may be aware of that may bias selling syringes to them (including dress). We have surveyed and attempted

syringe purchase at all of the pharmacies within the Municipality of Anchorage, so we actually know which ones to avoid. Of the IDUs in the Anchorage CA study only 55% had purchased syringes at pharmacies. It may be that with the kind of pharmacy sales intervention proposed, more IDUs will be successful in their pharmacy purchase. This may itself be an effective intervention that may reduce needle sharing.

In fact, there was already evidence that NEPs decrease the risk of acquiring hepatitis by the time Dr. Fisher submitted his grant proposal to the NIH in December 1995. An article in the American Journal of Public Health in November 1995 describes a case-control study that demonstrated a six-fold reduction in the odds of acquiring hepatitis B and a seven-fold reduction in the odds of acquiring hepatitis C among IDUs who had ever attended an NEP in comparison to IDUs who had never attended a NEP.

I am well aware of the referenced study (Hagen, Des Jarlais, Friedman, Purchase, & Alter, 1995). In fact, the first author of the study in question helped write the description of her study for my proposal. Even though this study was a major contribution to the field, there are several limitations with this study. First of all, there were only 28 IDUs with hepatitis B and 20 with hepatitis C, who were compared to 38 and 26 respectively controls. These kinds of small numbers (total n=112) can produce statistical artifacts, and adjusted confidence intervals were large, ranging from 1.5 to 32.8. Non-randomized studies with small numbers such as these should not be used for establishing national policy.

There are, however, more important problems inherent in not only this case-control study, but in all studies that have not employed randomization. Campbell and Stanley (1963) pointed out many years ago problems with different research designs. They termed these problems "Factors jeopardizing internal and external validity." Two of their factors are especially relevant to consideration of needle exchange research. One of these factors is known as selection bias and the other is history. Selection bias refers to the problem that when there are two groups of individuals who differ on one variable, those same individuals may also differ on other variables. These other variables may be correlated to the one putative variable of interest, but it is these other variables that may account for the effect that is attributed (perhaps erroneously) to the variable of interest. For instance, let us say that we did a hypothetical case control study in which children in the 1950s who swam at public swimming pools were significantly more likely to come down with polio than children who did not use public swimming pools. Are we justified in concluding that swimming pools cause polio? The

answer is no. We have only shown an association between swimming pools and polio. It may be that when the children get together and play at the swimming pools, they also exchange viruses and more children become infected in this way. The children who go to public swimming pools may also differ in many ways from children who do not. It is some of these other differences that may account for the polio and not the use of swimming pools.

So too in the case of needle exchange, it may be that IDUs who use needle exchanges are different from IDUs who do not. In fact, a study titled "Montreal needle exchange attenders versus non-attenders: What's the difference?" compared IDUs who attended the NEP in Montreal to IDUs who did not attend the NEP in Montreal (Hankins, Gendron, & Tran, 1994). They found that the HIV prevalence is more than double in those IDUs who attended the NEP as compared to those who did not. They explain this result with "Montreal's needle exchange appears to be attracting a clientele at higher risk than other IDU." In other words, they attribute the increase in prevalence to a selection bias. If selection bias can be used to explain an increase in prevalence as in Montreal, then it may be possible that it can also explain a decrease as in Tacoma (Hagen, Des Jarlais, Friedman, Purchase, & Alter, 1995).

Another study that had as its objective to distinguish between NEP attenders versus non-attenders also found some important differences (Junge, et al., 1996). They found that "the Baltimore NEP attracted high-frequency and cocaine injectors." We have reported that the log transform of the number of injections is a very good predictor for needle sharing in Anchorage (Fisher, Cagle, Queen, & Hosmer, 1994). The finding of high frequency injectors seems to be quite consistent with the Montreal data. A study in the Netherlands found that "The relatively more marginalised idu's obtain their syringes and needles from nep's" (DeJong, 1991). This is another report of a selection effect with NEPs. The important point is that non-randomized studies are subject to selection bias. This is a point that Lurie himself has made, "...the need for large sample sizes and the inability to randomize idus to NEPs preclude direct demonstration of reduced HIV incidence" (Lurie, et al., 1994)

So far, I have discussed the problem of selection bias, but have not touched on the problem of history which Campbell and Stanley define as "the specific events occurring between the first and second measurement in addition to the experimental variable (p. 5)." If there is a series of measurements that are taken on only one group, for example only the group that uses the NEP, then there is no way of knowing what changes may be occurring at the same point in time among similar individuals who are not using the NEP

because no measurements were taken. This effect is manipulated quite regularly by county sheriffs who want to show that a traffic safety program has produced great decreases in traffic deaths. It turns out that traffic deaths go up and down in regular cycles and the sheriff merely times the onset of his traffic safety program with the onset of the predicted low traffic death season. Again, the problem is that there is no randomized comparison group.

The researchers somehow believe that referrals for the pharmacy purchase of syringes represents an ethical alternative to the NEP condition for those not randomized to the NEP. Abundant data suggests otherwise. First, all the non-randomized controlled studies on the effect of NEPs on IDUs' risk behaviors implicitly compare syringe availability through NEPs with syringe availability through pharmacies and diverted sources. In all studies, the reduction in the rate of syringe sharing, the behavior that transmits HIV infection, was as great or greater in the NEP group (Lurie & Reingold, 1993). Thus, the control group proposed by the researchers has already been demonstrated to be inferior.

Lurie and Wolfe are misinformed on several points. First of all, not all states have legal needle purchase through pharmacies. In fact, only 38 states have no ordinance prohibiting the over-the-counter sale of sterile syringes (Compton, Cottler, Decker, Mager, & Stringfellow, 1992). Second, the pharmacy sales condition in our study is an enhanced condition in which a whole training procedure will be performed by the intervention counselors as outlined above. We are also finding that needle sharing has a strong seasonal component to it in Alaska in that even controlling for the number of injections, people share more in the winter than they do in the summer (Fenaughty, Choudhury, Reynolds, & Fisher, 1996). It is our feeling that the reason for the increased winter sharing is the problems of dealing with the weather, that is, having to put on more clothes, winter boots, gloves, hats, dealing with cars that do not start, dealing with roads that are not snowplowed, or that are icy, parking lots that are not plowed, etc. It may be that the closer that a source of needles is to the IDU, the more likely the IDU is to obtain needles from that source in the winter. This would actually argue in favor of pharmacies as compared to needle exchanges because there are 29 pharmacies in the Municipality of Anchorage, but there will be only 2 needle exchanges.

A study of the legalization of pharmacy sales in Connecticut would seem to support this notion as they observed that "the success of the nonprescription sale of sterile needles and syringes is attributed to accessibility and convenience" (Anonymous, 1995). Comerford, Chitwood, McKay,

Anderson, and Page (1990) report that a majority of IDUs felt that over the counter purchase of syringes in pharmacies would be more effective than a needle exchange in reducing sharing. Similarly, Blystad, Skjaervold, Evjen, and Hustad (1989) conclude that "an exchange scheme based on community pharmacies were favored by IVDA to specialised clinics" in a 10 month trial in Trondheim, Norway.

Second, the researchers argue that the study is ethical because Alaska has no requirement for a medical prescription in order to purchase a syringe. Again the data, conveniently excluded from their research proposal, do not support them. For example, in St. Louis, Missouri (a state without a syringe prescription law), an African American and a white research assistant each requested ten syringes from 33 pharmacies. Eighteen percent of the pharmacies stated that small quantities of syringes were not available (IDUs tend to purchase small numbers of syringes at a time), an additional 12% refused to sell to either research assistant and an additional 12% refused to sell to the African American only (Compton, Cottler, Decker, Mager, & Stringfellow, 1992). Thus, African Americans were prevented from purchasing syringes in 42% of the pharmacies. In New Orleans, Louisiana, also a state without a prescription law, only 14.5% of pharmacists said they sold syringes to anyone, and many required a prescription (Lawrence, Lawrence, Atkinson, Risi, & Lauro, 1991).

It is unfortunate that Lurie and Wolfe imply that these referenced data were "conveniently excluded" from our research proposal. The St. Louis data are interesting and we not only were aware of the study, but we have already mapped the policies of all 29 pharmacies within the Municipality of Anchorage. Our intervention counselors have personally been to all pharmacies and have each either made or attempted purchases at all pharmacies. Having this knowledge, along with designing a monitoring system so that we will be kept informed of changes in policies, enables us to tell our participants in the pharmacy sales condition which pharmacies to go to and which to avoid. It seems like a fairly simple solution and we are unsure why Lurie and Wolfe feel it is an insurmountable problem. Contrary to the St. Louis data, we have not been able to detect any ethnic bias to needle selling by pharmacists in Anchorage. In fact, our African American intervention counselor has been the most successful at purchasing syringes at pharmacies.

We have actually done our own needle procurement study among our CA participants who were IDUs (Cagle, Fisher, Queen,

& Des Jarlais, 1994). We had no ethnic or sex differences in purchasing syringes at pharmacies.

All of this assumes that the IDU has the money to purchase the syringes.

A ten pack of syringes in Anchorage is reported to cost $2.81 (SD=$0.54, R=$2.09 - $3.99) not on sale. The on sale price has been as low as $1.89. None of our IDU participants has ever reported (upon questioning) that the cost of syringes has been the obstacle to syringe purchase in Anchorage.

From a public health perspective, it would be ideal for IDUs to have access to both NEPs and pharmacies. Individual IDUs prefer different sources of syringes and maximizing the IDUs' choices is likely to be the most effective HIV prevention strategy.

The reason for our research on this question is to test whether needle exchange decreases disease transmission and does not increase drug use, which the evidence to date indicates. The question of whether NEPs are more effective than pharmacy sales is an additional important aspect to our design. There are many states in which NEPs are never going to be legal. It is also for those states or municipalities, that this study is particularly germane. It may be very important to know what the effect of NEP is in comparison to legal pharmacy sales because in some states NEPs may never happen, but pharmacy sales might be a possibility.

For the researchers, however, this creates the problem of "crossover": IDUs assigned to the NEP may want to attend the pharmacy or vice versa.

We have plans to ask permission to reinstate the "declared crossover" condition on a trial basis and let the Data Safety and Monitoring Board make a decision on whether to keep it or not. The declared crossover condition is analogous to what is called a "compassionate arm" in most clinical trials, that is, it is a way for current injector participants who are assigned to the pharmacy sales condition, but who have an extreme need to be in the NEP condition to crossover and be allowed to use the NEP. We would intend to analyze the data both as a crossover and as an intention to treat (i.e., we would analyze the data both ways).

We state several times in our proposal that any individual in either condition who wants to purchase syringes at a pharmacy in no way is violating any "rules" of the study. It is perfectly acceptable. We just want to know about it so we can measure it. In a similar vein (no pun intended),

anyone in the NEP condition can exchange syringes for anyone in the pharmacy sales condition. Here too, we just want to know about it so we can measure it.

Thus, the researchers go out of their way to prevent "crossover," going so far as to have the NEP open only when the pharmacy that accounts for most sales of syringes to IDUs is also open. This stands public health common sense on its head and places people who are IDUs at risk for fatal infections. NEPs should complement alternative syringe sources, not compete with them. In this sense, the study is not even a reasonable test of the public health question it should be investigating.

The proposed hours of operation of the needle exchanges are: Monday through Friday 9:00 a.m. - 9:00 p.m., Saturday 9:00 a.m. - 6:00 p.m., and Sunday 10:00 a.m. - 6:00 p.m. We are not aware of any needle exchange program in the world that is open more hours than this.

Both groups will have increased access to needles, not decreased. Lurie and Wolfe's accusation that somehow the study will increase the risk for infection is simply not true. In fact, the opposite is true. It is only because of this study that the Alaskan AIDS Assistance Association (AAAA) was awarded a $32,000 grant from the Alaska Science and Technology Foundation (ASTF) for syringe purchase. This grant has allowed AAAA to greatly expand its needle exchange program that, if Lurie and Wolfe are correct in their views of NEP, should result in a tremendous decrease of risk rather than an increase as they state.

The research is, therefore, unethical for at least three reasons:

1. If an IDU does not enroll in the study, he or she cannot use the NEP at all, thus coercing subjects to enroll;

2. For IDUs who enroll in the study, only 50% will be permitted to attend the NEP; the others will be turned away;

It is common for needle exchange programs to be established so that the funding is contingent upon an evaluation being performed. This particular NEP is being funded by ASTF and it was only funded as a public health knowledge project. There is an additional letter that has been submitted from the ASTF about their funding.

Before and during the time that we were writing the various revisions of this proposal, we conducted focus groups of our CA IDU participants. We asked them about participating in such a study even though they only had half a chance to be in the NEP group. Interestingly, all of the subjects felt that the study was important enough that they were willing to

participate in such a study. They also felt that the pharmacy sales condition was a good alternative. It is the consensus of opinion of those of us in Anchorage, that this is the only way to have a needle exchange start out on a large scale and be able to survive. If we did not have this kind of a strict research design, then we would not be able to have the Anchorage needle exchange program survive.

Lurie and Wolfe continually try to portray this study as a clinical trial with a no treatment control group. Nothing could be further from the truth. I have pointed out continually in this letter and in the proposal that this design compares two different means of getting clean needles to IDUs. In a clinical trial in which there are two treatments being compared, for example, treatment A and treatment B, Lurie and Wolfe are describing treatment A as the absence of treatment B. This is like the old Jewish mother joke in which the Jewish mother gives her son two shirts for his birthday. When she next visits him and he is wearing one of the shirts, she looks at him with very sad eyes and says "So...the other one you didn't like?"

We have two different conditions, both of which are ways of trying to reduce risk of infection in IDUs. Neither condition is a no treatment control and Lurie and Wolfe are grossly misrepresenting the study when they try to portray the pharmacy sales condition as a no treatment control.

3. It is highly inappropriate to stand by and watch IDUs in both research groups contracting potentially fatal hepatitis B infections when an extremely effective vaccine for hepatitis B exists. It is difficult for us to imagine an analogous study in which babies were monitored for the occurrence of tetanus, while not being provided with the existing vaccine.

The Indian Health Service will provide vaccination to all Alaska Native referrals from this research project (J. Williams, personal communication, October 31, 1996; also see letter of agreement). This is what we did for our CA study for five years and the IHS was very cooperative with our project. In fact, Mr. Jim Williams, Director of the Viral Hepatitis Program of the IHS helped to design our pre and post-test hepatitis counseling procedures and presented these procedures to the CA steering committee at NIDA. The vaccine is discussed in our intervention by the intervention counselors and is included in the appendices to the grant proposal on cards I.8b, I.9, II.N2b, and II.P1b. In Anchorage, most of the current IDUs are either white or Alaska Native, so referring the Alaska Native participants to the IHS Viral Hepatitis Program is how we intend to deal with the issue of providing hepatitis B vaccination for the Alaska

Native participants. We are not, as Lurie and Wolfe wrongly allege, "withholding" the hepatitis B vaccine. The non-Alaska Native participants will be referred to the Municipality of Anchorage (MOA) Department of Health and Social Services Sexually Transmitted Disease (STD) clinic for administration of the vaccine. We will provide a coupon that our participants can present to the STD clinic to have the nurses at the STD clinic administer the vaccine. Participants who are Medicaid eligible can have Medicaid pay for the vaccine that the participants can take to the STD clinic for administration.

The counseling for the hepatitis vaccine is documented in the appendices to the grant proposal for session I (cards I.8b and I.9), session II for those who test negative (card II.N2b), and session II for those who test positive (card II.P1b). When we do the counseling is when we do the referrals for those individuals who want to be vaccinated. The coupons for the MOA STD clinic are documented in the Informed Consent Form.

The risk of dying from hepatitis B is very low with a case fatality of 1% (Hoofnagle, & Schafer, 1986). The rate of HIV infection in Alaska is also very low. As of December 31, 1995, 590 (0.7%) of 87,564 individuals tested through the Section of Laboratories, Division of Public Health, State of Alaska, are positive for HIV infection (State of Alaska, 1996). Even in our CA cohort, we only had approximately 2% HIV positive. The major risk factor among our drug users was men who have sex with men and not injection drug use.

The analogy between hepatitis B and tetanus is not very good. Acute Hepatitis B infection has a case fatality rate of 1% (Hoofnagle, & Schafer, 1986). Tetanus, on the other hand, has a case-fatality rate of 65% (Magnussen, 1986). In fact, in heroin addicts, tetanus has been reported to be almost always fatal (Levinson, Marske, & Shein, 1955). The difference between 1% and 65% is over a complete order of magnitude.

The second problem with the analogy between tetanus and hepatitis B is that tetanus immunization only requires a single administration, whereas hepatitis B immunization requires three separate dose administrations to induce antibody in 85% of recipients (Francis et al., 1982). This was demonstrated in a randomized, double-blind, vaccine/placebo trial of hepatitis B vaccine among 1402 homosexual men in five American cities even though there had already been trials done in French hemodialysis centers, Senagalese village children and homosexual men in New York.

Those of us who have worked with injection drug users know how difficult it is to get IDUs to return for follow-up, let alone three separate visits on a fairly strict time schedule. This is especially true when large monetary

incentives are not provided (Reynolds, Fisher, & Cagle, 1996). Loue, Lurie, and Lloyd (1995) have made arguments similar to what Lurie and Wolfe are making in their letter to you. They minimize the difficulties of getting IDUs to comply with a vaccination protocol by stating that "it has been demonstrated that IDUs can show high compliance with the complex vaccination schedule." To support their contention they cite an Italian study in which the investigators approached 190 IDUs and were able to finally administer all three doses to 99 IDUs for a rate of 52% of those initially approached (Lugoboni, Mezzelani, Venturini, Fibbia & Des Jarlais, 1992). This is in stark contrast to a study done at a sexually transmitted disease clinic in San Francisco in which 135 or 9.74% of the 1386 initially approached received all three administrations (Weinstock, Bolan, Moran, Peterman, Polish, & Reingold, 1995).

In Alaska, the Indian Health Service has been vaccinating Alaska Natives against hepatitis B since 1981 (K. Wainwright, personal communication October 31, 1996). A massive immunization program was begun in 1985 and major attempts were made to immunize all Alaska Natives. Even though the IHS has been engaging in this massive effort, when we tested our Alaska Native subjects for evidence of vaccination, we only found 13.51% of the Alaska Natives testing positive for indications of vaccination (Fisher, Kuhrt-Hunstiger, Orr, & Davis, 1996). When we asked the IHS why we obtained these findings, we were told that it was the drug users among the Alaska Natives who were the least likely to comply with the vaccination protocol.

The parallels here to the Tuskegee Syphilis Study, in which African-American men were denied penicillin treatment for syphilis for about three decades, are clear. Although in the Tuskegee, study known effective treatment for a life-threatening disease was withheld, in this human experiment, two known effective means of prevention--hepatitis B vaccine and the provision at no cost of sterile needles and syringes--are being withheld.

As I have already amply documented, this study does not withhold hepatitis B vaccine. Secondly, sterile needles and syringes are not being withheld from either group. Were it not for this research project, there would be no needle exchange program on this scale in Anchorage, Alaska. Both groups will be better off for participating in this project, not worse off as Lurie and Wolfe state.

The parallels to the Tuskegee Syphilis Study are totally inaccurate and inappropriate. While the Tuskegee Syphilis Study had no protocol or any supervision by an independent review board, the "Interventions to Reduce HBV, HCV, & HIV in

IDUs" (Interventions) study has had a full review by the University of Alaska Anchorage (UAA) Institutional Review Board (IRB). Being a university without a Multiple Assurance of Compliance Number, the UAA IRB was subject to more scrutiny by the Office of Protection from Research Risks (OPRR), not less, in that UAA needed to obtain a Single Project Assurance. This means that this specific IRB for this specific review of this proposal had to be specifically approved by OPRR. OPRR, in fact, did issue the SPA.

The Tuskegee study followed individuals who (at least in one group) all had syphilis. They were purposely not treated for an existing disease so that researchers could answer the question of whether blacks with syphilis were more likely to get neurological manifestations of the disease as compared to whites who were thought to be more likely to get cardiovascular manifestations. The syphilis infections were always followed by considerable morbidity and mortality. In the Interventions study, the participants do not have a disease already. If they acquire hepatitis B, they will be referred for treatment, and 99% of people with acute hepatitis B recover from the disease (Hoofnagle, & Schafer, 1986).

In the Tuskegee study, the men were actively prevented from obtaining treatment from other sources. We have neither the intention, the desire, nor the ability to do this.

The Tuskegee study did not have a Data Safety and Monitoring Board (DSMB). The Interventions study has such a board that is designed to meet every six months. The procedures for the DSMB are described in the application on pages 69-70. If the DSMB finds that the NEP condition significantly reduces disease transmission, then they can open both arms of the study to the NEP. If, however, the DSMB finds that the NEP condition is associated with a significant increase in injection drug use or a significant relapse to injection drug use by former injectors, then the DSMB can shut the entire project down. The Tuskegee study had no such mechanism of oversight.

In the Tuskegee study, no information was given to the subjects about the true nature of the study, and thus informed consent was not obtained. In the Interventions project, informed consent using an Informed Consent Form approved by the UAA IRB and also approved by OPRR will be used and documented and a copy given to every single participant in the study. Having Lurie and Wolfe use the Tuskegee study to besmirch the Interventions study, trivializes the suffering of those unfortunate victims of the Tuskegee study.

In summary, this study should not be funded unless:
1. All IDUs in the study are provided with hepatitis B vaccine; and
2. All IDUs are permitted to attend the NEP; and

3. The research project design is overhauled so that no IDUs are denied access to needle exchange services.

The procedures for dealing with referrals for hepatitis B vaccination have already been discussed. The Interventions grant is not the only needle exchange grant that is testing for hepatitis B. There are several other grants that are also testing for hepatitis B. The Interventions grant is actually doing more, not less, to get the participants in this study vaccinated than the other projects are with their participants.

If the criteria that Lurie and Wolfe are using to attack this proposal were applied to other studies, then no phase III clinical trial would have ever taken place. The classic clinical trial of the hepatitis B vaccine carried out by Donald Francis et al. (1982) was done after "randomized efficacy trails of HBV vaccine have been done among staff members of French hemodialysis centers, Senagalese village children, and homosexual men in New York." They still carried out a randomized double-blind, vaccine/placebo trial of the hepatitis B vaccine among 1402 homosexual men. If Lurie and Wolfe had been allowed to politically censor the Francis study and other studies like it, and to stop any study they want in the future, then no randomized clinical trials will be able to take place and science will not be able to progress.

The fact that this clinical trial design has been immediately politicized and tried in the news media is antithetical to the scientific search for truth. I petition you to reaffirm the peer review process, for it is only by protecting the scientific process from political attack that the search for truth can proceed.

Sincerely,

Dennis G. Fisher, Ph.D.
Principal Investigator and Professor

cc. Dr. Alan Leshner
Dr. Richard Needle
Dr. Peter Hartsock
Sister Andrea Nenzel
Jim Williams
Dr. Janett Trubatch
Congressman Henry Waxman
Senator Edward Kennedy
Senator Ted Stevens

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RE: "INVITED COMMENTARY: LE MYSTERE DE MONTREAL"

Editor
American Journal of Epidemiology
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Dear Editor,

In his invited commentary, Lurie (1) speaks out on the uncertain benefits and harms associated with needle exchange programs (NEP). The setting is the apparently unexpected findings of Bruneau et al. (2) who observed statistically significant increased HIV prevalence and incidence associated with needle exchange attendance in Montreal. In Lurie's view, "diverse studies generate a picture that overwhelmingly supports the effectiveness of NEP's" (1, page 1005 para 2). The theses in his commentary are: 1) that the findings of Bruneau et al. (2) are the artifacts of selection bias and inadequate control for confounding; 2) that our randomized trial of needle exchange currently underway in Anchorage, Alaska is unethical and methodologically flawed, and; 3) that, in Montreal, "what is needed to reduce the terrible toll of HIV among Montreal IDU's is not less needle exchange but more" (1, page 1005, para 2).

The explicit dismissal of Bruneau et al.'s (2) findings as the result of selection bias in Lurie's advocation of more needle exchange misses a critical public health obligation, to identify the behaviors of this group of injectors in Montreal and similar populations elsewhere. Granting Lurie's view that, with adequate access, needle exchange is effective in reducing HIV incidence, what constitutes adequate access is not well understood. It is likely a complex interplay of availability, knowledge, attitudes, readiness for change, and finally, behavior. Thus, it is premature and possibly incorrect to presume that the Montreal cohort, for whom needle exchange participation has been shown to be associated with increased risk of HIV infection, is necessarily best served by still more needle exchange. Rather, we should be looking to the unique database of Bruneau et al. (2) for clues to the complexities of unsafe injection practices and HIV transmission.

Similarly, Lurie's (1) additional dismissal of our randomized trial of needle exchange versus legal pharmacy sales (3) is also inappropriate. Briefly, our trial seeks to compare the efficacies of two methods for delivering clean injection paraphernalia to drug injectors, needle exchange versus legal pharmacy sales. The following corrections to Lurie's commentary are indicated: 1) individuals randomized to the needle exchange condition are not barred from obtaining syringes by any other means, including through pharmacy sales; 2) secondary exchange, that is, having a participant in the needle exchange condition exchange syringes for a participant in the pharmacy sales condition, is

not prohibited; and 3) the pharmacy sales condition is an intervention that includes training in the purchase of syringes from a pharmacist. The significance of our experimental paradigm is a comparison of the effects of two plans of delivering clean injection paraphernalia. In its formulation, we sought to inform decision making in the real world conditions faced by public health practitioners concerned with reducing HIV risk. Thus, understanding the relative successes of the two plans is among our primary aims and the phenomenon of crossover, far from being an analytical nightmare, is an outcome of special interest. Specifically, participants randomized to the needle exchange condition who elect to obtain clean works from a pharmacy offer insights into the limitations of the needle exchange approach, and vice versa. Among our secondary analyses will be an exploration of 1) the predictors of choosing to obtain clean works, and 2) the choice of method of access to clean injection paraphernalia, needle exchange or pharmacy sales. We also wish to clarify that in defining our two study arms (needle exchange, pharmacy sales), we sought to compare two delivery methods, each under optimal conditions. Accordingly, randomization to pharmacy sales is actually to an enhanced pharmacy sale intervention. In addition to being informed of sympathetic pharmacy locations, these randomizees are taught effective methods of purchasing syringes, including what to say, how to behave, etc. Finally, because of state law, we reiterate that all drug injectors in Anchorage are free to obtain clean syringes by whatever means they choose, whether or not they are study participants.

As well, we dispute strongly the charge that our trial violates principle five of the Nuremberg code which states that no experiment should be conducted where there is a priori reason to believe that death or disabling injury will occur. This accusation presumes that needle exchange is always associated with a lower disease rate. This is an assumption that is untenable in light of the data from both Vancouver (4) and Montreal (2). Moreover, the design of this trial includes several measures to benefit all drug users in Anchorage, Alaska, independent of their participation in our trial. Our team has researched local pharmacies and has identified which are favorably inclined towards the sale of syringes. Thus, for participants and non-participants alike, it will be easier to obtain sterile syringes as a result of this trial. As well, we offer free hepatitis B vaccination to all participants, including free taxicab rides to the clinic. External oversight of its ethical merit is also assured, through the appointment of a Data Safety and Monitoring Board that meets every six months. To date, no ethical concerns have been voiced.

Too often, the need for policy decision making cannot wait for results of research. Nevertheless, it is our view that this particular commentary, "Le Mystere de Montreal" (1), is a policy interpretation of a research finding. As such, its contribution to our understanding of the benefits and harms associated with needle exchange is limited. We are reminded of several important studies demonstrating the benefits of needle exchange but are then asked to dismiss, first, the unique opportunities that present themselves in the

rich data base of Bruneau et al. (2) and, second, a unique randomized trial of two feasible approaches to delivering clean injection paraphernalia, needle exchange versus legal pharmacy sales. We caution against the dismissal of the Bruneau et al (2) study and our own as a potentially dangerous setback to our understanding of the needle exchange and HIV infection in drug injectors.

Dennis G. Fisher
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Carol Bigelow
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#1407

NEEDLE EXCHANGE PROGRAMS

Public Citizen

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

November 18, 1996

Harold Varmus, MD
Director
National Institutes of Health
Building 1, Room 126
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Dear Dr. Varmus:

Because of our ongoing concern about the NIH-funded research project to randomize people who are injection drug users (IDUs) to receive or not receive sterile syringes from needle exchange programs (NEPs), we have completed a study to determine the actual availability of syringes through pharmacies in Anchorage, Alaska for those people who, through the process of randomization, are excluded from using the NEP. The results give lie to the claim of the study's Principal Investigator, Dennis Fisher, that the pharmacy condition represents an ethical alternative to NEPs because syringes are easily available through pharmacies in Anchorage. Even though the state has no requirement for a doctor's prescription in order to purchase syringes in pharmacies, our results demonstrate that only 14% of pharmacies in Anchorage consistently sell sterile syringes to people who may be IDUs in an unencumbered fashion. It is of particular concern that an African American woman was denied syringes at all five pharmacies she surveyed, including two that had sold syringes to non-African Americans the previous day. These data further demonstrate the unethical nature of the proposed research and underscore the need for it to be canceled immediately before the lives of IDUs are endangered.

Methods

Our study method was similar to that utilized in a previous study of syringe availability in St. Louis, Missouri (Compton W, Cottler L, Decker S, Mager D, Stringfellow R. Legal needle buying in St. Louis. American Journal of Public Health 1992; 82:595-6.), in which research assistants were sent in to pharmacies and attempted to purchase syringes. We used the list of

29 pharmacies attached to Dr. Fisher's NIH proposal. Two pharmacies in Eagle River, about 25 miles from Anchorage, and one hospital pharmacy were excluded from the study. Four independent pharmacies were closed on the weekend the study was conducted and an additional pharmacy on Dr. Fisher's list could not be located. This left 21 pharmacies for study.

Three volunteers (one white male, one African American female and one female of mixed white and Alaskan native descent, all in their mid-40s) were trained to participate in the study. Each was assigned pharmacies to visit and trained to approach the pharmacist or clerk and say verbatim: "I need a pack of ten 28-gauge, 100-unit insulin syringes, please." If the pharmacist or clerk refused to sell syringes, the volunteers were instructed to engage in casual conversation to determine why they could not purchase the syringes. The volunteers, none of whom are active IDUs, were dressed casually. They did not carry the survey instrument (questionnaire) into the pharmacy, but filled it out immediately upon leaving the pharmacy. The instrument also included questions addressing whether the pharmacist or clerk asked for a prescription for the syringes, whether they inquired about the volunteer's medical condition and whether the volunteer was required to sign a list of people purchasing syringes, all of which represent obstacles to syringe purchase. The volunteers also obtained receipts from those pharmacies willing to sell syringes. Pharmacies were visited once, except for two pharmacies that were visited twice.

Results

Seventeen of the 21 pharmacies were visited by the volunteers. Of these, only six (35%) agreed to sell syringes. However, two of these six refused to sell syringes to the African American woman the next day. (The African American woman was refused syringes at all five pharmacies she visited.) Of the six that agreed to sell syringes, three required the volunteers to sign a list of syringe purchasers, and one of these inquired into the medical need for purchasing syringes. A fourth pharmacy was located in a membership store (Costco) and required membership identification, which the volunteer happened to have. Thus, only two pharmacies, both from the Fred Meyers chain, provided unrestricted syringe sales. A call to corporate headquarters confirmed that this was corporate policy and so the third Fred Meyers in Anchorage was not visited and was counted as having syringes available. The average price for 10 syringes at the six pharmacies was $3.38, almost double what Dennis Fisher has publicly stated.

Six of the 11 pharmacies that refused syringe sales asked for a physician's prescription, even though Alaska has no prescription law. In addition, four

of the 17 pharmacies required the volunteer to sign a list of syringe purchasers and eight asked questions about the volunteer's medical condition. After being refused syringes at five Carr's pharmacies, a call to Carr's corporate headquarters confirmed that it was corporate policy not to sell syringes and thus three additional Carr's were not visited. Thus, including the four pharmacies that were not visited, only seven of 21 pharmacies (33%) sold syringes under any circumstances, two of which subsequently refused the African American volunteer and four of which had additional obstacles to syringe purchase. Therefore, in only the three Fred Meyers pharmacies (14% of the 21 pharmacies studied) is there consistent and unencumbered syringe access.

Discussion

These data underline the difficulty of obtaining sterile syringes in Anchorage (explaining in part the high hepatitis B and C prevalences there), and make the pharmacy condition in the University of Alaska randomized trial an unacceptable alternative to the NEP.

Three observations are in order. First, it should be noted that Anchorage is one of the few cities in the United States that has a municipal paraphernalia law (most states, although not Alaska, have state paraphernalia laws), which effectively gives the pharmacist the responsibility of determining whether the syringe will be used for a legitimate medical purpose. This in part explains the reluctance of pharmacies to sell syringes to IDUs. And, despite Dr. Fisher's claim that those assigned to the pharmacy condition will be given vouchers for free syringes in pharmacies (Beswick T. NIH freezes needle exchange study: UCSF researcher requests ethics review. Bay Area Reporter, October 24, 1996, p. 23), there is no mention of vouchers (for either syringes in pharmacies or for hepatitis B vaccination) in his NIH protocol.

Second, despite Dr. Fisher's claim that IDUs are not willing to take the three-injection hepatitis B vaccine, those who have made a real effort to accomplish this have met with notable success. For example, in Italy 91% of IDUs recruited and retained in an hepatitis B vaccination program completed all three injections (Lugoboni F, Mezzelani P, Venturini L, Fibbia GC, Des Jarlais DC. An HBV vaccination program from street injecting drug users: implications for testing an HIV vaccine. Presented at VIIIth International Conference on AIDS, Amsterdam, 1992 (PoC 4796)). The difficulty of vaccinating IDUs is therefore a self-serving excuse by Dr. Fisher to avoid obliterating hepatitis B as a study endpoint in his study.

Third, IDUs prevented from attending the NEP will be losing more than free access to sterile syringes. They will also be losing access to the following additional free services that, according to Dr. Fisher's protocol,

are to be provided by the Anchorage NEP, but are not available at pharmacies: condoms, bleach for the disinfection of injecting equipment, alcohol wipes, sterile water and HIV prevention literature.

Interestingly, the question of conducting a randomized controlled trial of NEPs was considered by the National Academy of Sciences panel in its landmark review of the efficacy of NEPs. The panel's report did not even discuss the possibility of randomizing by individual, the method proposed by Dr. Fisher, presumably because the National Academy of Sciences panel believed that community randomization is a preferable method for assessing community-based interventions like NEPs. The report stated: "Furthermore, given the results of two recent government-sponsored reports that concluded that these programs have positive effects and do not appear to have negative effects [the same conclusion ultimately reached by the National Academy of Sciences in its report], it may not be ethical to withhold treatment from communities willing to initiate such programs ... The panel recommends adopting strong observational epidemiologic designs rather than attempting to conduct large-scale randomized experiments to evaluate needle exchange and bleach distribution programs" (Normand J, Vlahov D, Moses LE. Preventing HIV Transmission: The Role of Sterile Needles and Bleach. National Academy Press, Washington, DC, 1995).

Our data from Anchorage document the multiple obstacles to syringe purchase in pharmacies and demonstrate the inadequacy of pharmacy syringe sales as an alternative to NEPs. Indeed, to follow the researchers' logic, if existing pharmacy sales practices in states without prescription laws were indeed an ethical alternative to NEPs, there would be no need for NEPs in any state without a prescription law. Not one of the six federally funded reviews referred to in our previous letter to you (or any other study to our knowledge) made the recommendation that NEPs are only necessary in states with prescription laws; instead most endorsed the combination of pharmacies and NEPs as the optimal national approach to providing sterile syringes to IDUs. As has been demonstrated throughout the world, given access to both NEPs and pharmacies, some IDUs will choose to use NEPs, some will choose pharmacies, and a significant proportion will use both. It is precisely that choice that IDUs who are enrolled in the Anchorage study will be denied. It is time for the NIH to admit its error and put an end to this highly unethical and exploitative study.

Sincerely,

Peter Lurie, MD, MPH
Research Associate

Sidney M. Wolfe, M.D.
Director