Health Consequences of Rural Illicit Drug Use: Questions Without Answers

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Previous chapters in this monograph have noted a general lack of epidemiological data concerning illicit drug use in rural America, a lack that extends to the health consequences of substance misuse behaviors among rural dwellers. Urban population studies indicate that the major health risks associated with illicit drug use are hepatitis (users are 12 times as likely as nonusers to contract hepatitis C), tuberculosis, sexually transmitted diseases, various other bacterial infections, and human immunodeficiency virus (HIV) infection.

Suppression of the immune system, inadequate nutrition, and other lifestyle factors are typically cited as the reasons for these health outcomes. However, characteristics of the individual's environment may also play a role. For example, health care facilities and personnel are typically less available in rural than in urban areas. Rates of substance misuse-related health conditions may vary with both availability of health care and with the rate of substance misuse in the community. What few rural data are available indicate that geographic region may also influence disease rates, although the reasons for this variation are unclear.

This chapter presents an overview of health problems related to illicit drug use in rural areas. Findings from research conducted in the Anchorage, Alaska area are compared with national data and, where possible, with U.S. rural data. The relationships between drug abuse and HIV infection, hepatitis, and pulmonary problems, and evidence of a possible network of disease transmission are discussed with special emphasis being placed on the implications for rural dwellers. Methodological problems and recommendations for future research are also presented.

ANCHORAGE, ALASKA

Alaska presents special problems for the study of drug use. Alaska has the reputation of high rates of alcohol use, but many people are unaware of the very high rates of drug use (Fisher and Booker 1990).

One reason for the lack of information about drug use in Alaska is that Alaska is excluded from the major national surveys of drug use such as the National Household Survey on Drug Abuse (Research Triangle Institute 1991). Moreover, the State is not listed in the National Drug Abuse Treatment Unit Survey (NDATUS). This dearth of information exists even though Alaska spends more per capita on narcotic law enforcement than any other State in the Nation.

Anchorage, the major city in Alaska, has a combined city-borough form of government known as the Municipality of Anchorage (MOA), an area of 1,958 square miles with a population density of 132 persons per square mile. The 1995 population of Alaska is 615,900; 41.9 percent of the State's population (257,780) lives in Anchorage (MOA 1995).

Despite its urban characteristics, Anchorage differs from other seemingly similar cities in the contiguous United States in several respects. First, it is the major city in a State that is 2.18 times larger than Texas. The next largest city in Alaska is Fairbanks, with a population of 84,380. Thus, Anchorage is, by far, the largest city in a State characterized by vast unpopulated areas. Nonetheless, compared to the major cities of other States, Anchorage is relatively small in population. Second, Anchorage has grown rapidly in the past 20 years. Census data for 1970, 1980, and 1990 put the population of Anchorage at 126,385, 174,431, and 226,338, respectively. While much of this growth can be attributed to in-migration from other States and countries, a substantial amount is migration from rural areas of Alaska. Third, the Matanuska-Susitna Borough, which is the next population center near Anchorage, has a population of 50,601, making Anchorage the focus of retail, health care, and other human services for a huge rural area. Finally, for Native Alaskans and others who have been disenfranchised by their home communities due to substance abuse, the availability of free shelter and food in Anchorage makes it a desirable site for relocation. Thus, although the population of Anchorage is not rural, it does include many individuals who come from rural areas.

ANCHORAGE, ALASKA SAMPLE

The data presented in this chapter come from research funded by the National Institute on Drug Abuse (NIDA) under a cooperative agreement for acquired immunodeficiency syndrome (AIDS) community-based outreach/intervention research. The grant, titled "IVDUs (intravenous drug users) Not in Treatment in Alaska," is the first NIDA research grant in Alaskan history. Data collection began in 1991. To be eligible for inclusion, a subject had to: (a) be 18 years of age or older, (b) have not been in substance abuse treatment for at least 30 days before intake, (c) test positive for cocaine metabolites, morphine, or amphetamine on a urine test, and/or have visible track marks.

The Risk Behavior Assessment (RBA) was the data-collection instrument used at intake. The RBA has been demonstrated to have good test-retest reliability (Dowling-Guyer et al. 1994; Fisher et al. 1993*b*; Needle et al., in press; Weatherby et al. 1994). Phlebotomy for HIV testing and other lab tests were also performed.

Sampling was conducted according to a targeted sampling plan guided by the Watters and Biernacki (1989) model. Approximately 30 to 35 new subjects were recruited each month, starting in November 1991. New subject recruitment is ongoing. Not all analyses used all subjects. The sample design provided for an overrepresentation of blacks and Alaska Natives and an underrepresentation of whites and Asians (see figure 1).

Men comprise 68.6 percent of the sample and the median age is 34 years. This compares with 51.4 percent male and a median age of 29.8 years for the MOA. Figure 2 compares the educational attainment of the sample with that of the MOA population and indicates that a higher proportion of the sample falls into the less than high school, general equivalency diploma (GED), and high school graduate categories, whereas lower proportions fall into the some college and college graduate categories.

HIV INFECTION

Several reports on HIV infection and risk behaviors among rural residents have appeared in the recent research literature. A synthesis of these

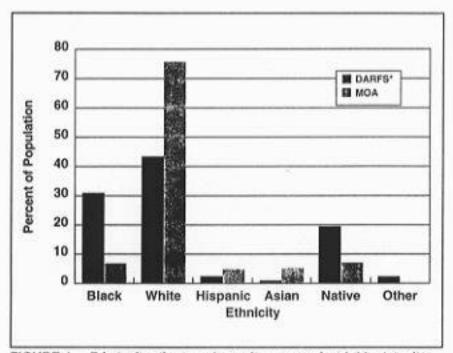


FIGURE 1. Ethnic distribution of sample compared with Municipality of Anchorage (MOA).

KEY: * = Drug Abuse Research Field Station.

findings points to some interesting regional differences. For example, data from the southern region indicates that compared to other women tested for HIV, those who were infected had a greater number of sex partners, had used smokable cocaine (Ellerbrock et al. 1991), and were likely to be African-Americans (Bartlett et al. 1993). In fact, the rate of AIDS cases associated with injection drug use was 19 times higher among African-American than among white women (Whyte and Carr 1992). Interestingly, rural HIV positive women were likely to have acquired the disease while living in AIDS epicenters and to have then moved to rural areas (Cohn et al. 1991). Reports comparing urban Miami, Florida to rural Georgia found urban and rural crack using women were similar on their risk for HIV infection (Forney et al. 1992). A review article on HIV infection in rural areas of the country concluded that HIV infection among women who trade sex for drugs or money is more evident in the southeast portion of the country (Berry 1993).

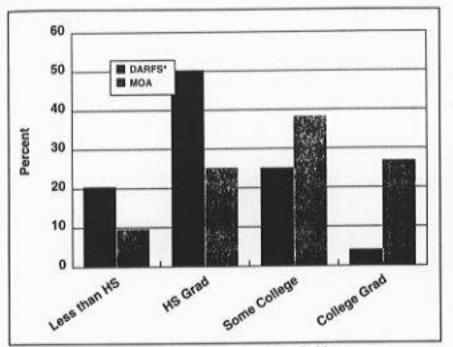


FIGURE 2. Educational attainment-age 25 and older.

KEY: * = Drug Abuse Research Field Station.

In contrast, women in the Western region have shown a somewhat different pattern. Araba-Owoyele and colleagues (1993) found that AIDS cases among heterosexual injection drug users in rural areas of California are more likely to be white or Hispanic rather than black. Tucker and colleagues (1991) found that rural western areas of the country are increasingly affected by HIV; transportation and housing are major difficulties.

Berry (1993) found that the epidemic among gay or bisexual men is strongly evident in rural areas of the country. For example, gay men in North Carolina were likely to have been infected while residing in North Carolina rather than in AIDS epicenters (Cohn et al. 1991). This is consistent with the Alaskan data. Among drug users, it was found that those who are gay were significantly more likely to be HIV positive (5/13 = 38 percent) than were heterosexual (11/1,176 = 0.01percent) drug users (z = 11.68, p < 0.01), and the same held true for drug users who are bisexual (6/58 = 10 percent, z = 6.00, p < 0.01). Conway and colleagues (1992) compared American Indian/Alaska Native (AI/AN) serum specimens from 58 prenatal and sexually transmitted disease (STD) clinics and found that while the rate of HIV infection among pregnant women was similar for urban versus rural clinics, the STD clinic specimens showed significantly higher rates for the urban than the rural clinics. Metler and colleagues (1991) have shown that the rate of increase among the AI/AN group is extremely high and that this group has high rates of STDs and drug abuse.

The alkyl nitrites (a group that includes amyl nitrites, butyl nitrites, and isopropyl nitrites) is a class of drugs that is highly associated with HIV infection. These drugs, sometimes known as "poppers," have been used since the 1960s and are associated with high-risk sexual behaviors (Haverkos 1988) and self-perception of being at risk for AIDS (Fisher et al. 1992). Sales of alkyl nitrites are illegal according to Federal law; however they are still widely sold at adult bookstores in several States, including Alaska (Fisher 1993). Alkyl nitrites may be more available in rural States because of a lack of Federal regulatory presence. Additional studies are needed to determine the extent of this form of drug abuse in rural areas. Nitrites may need to be included in prevalence surveys conducted in rural areas, and physicians treating people with AIDS may need to assess the extent of nitrite use and make a determination of the likelihood of Kaposi's sarcoma (Haverkos 1988).

HEPATITIS B

Hepatitis B virus (HBV) is a public health problem in Alaska, the rest of the United States, and throughout the world. The U.S. experiences 30,000 new infections each year, and 300 million chronically infected persons are believed to exist internationally (Shapiro and Margolis 1990). Parenteral drug use is one of the most frequently reported methods of transmission for HBV; a 42 percent increase of HBV associated with drug use has been reported since 1984 (Metropolitan Insurance Companies 1990). Methamphetamine and cocaine have been reported as the two drugs of choice for IVDUs infected with HBV (Centers for Disease Control 1988, 1992). Zeldis and colleagues (1992), however, found heroin to be highly associated with HBV prevalence. Injection drug users (IDUs) who are not in treatment warrant attention because they comprise the majority of IDUs nationwide (Lampinen et al. 1989), and engage in more high-risk behavior than those in treatment, at clinics, or who are incarcerated (McCusker et al. 1990).

Hepatitis B risk profiles based on self-report data from Anchorage, Alaska were compared with profiles obtained from 15 additional U.S. sites. The prevalence of HBV among the Alaska participants was 14 percent (101/714). Two-thirds of those positive for HBV were white men, white women, and Alaska Native women. The risk profile for Alaska men (N = 483) included: (a) using needles to inject drugs in the past 30 days (OR = 2.6), (b) a greater number of injection episodes involving heroin or nonprescription methadone in the past 30 days (OR = 1.6), and (c) ever having used other opiates (OR = 5.2) such as hydromorphone. The risk profile for Alaska women (N = 226) included: (a) ever trading sex for drugs (OR = 2.4) or money (OR = 1.6), (b) using needles to inject drugs in the past 30 days (OR = 3.0), (c) total number of injection episodes involving any drug in the past 30 days (OR = 1.1), and (d) num-ber of sex partners who had injected drugs in the past 30 days (OR = 1.4).

The HBV prevalence in the national sample was 16 percent (1,236/7,695), with a range of 8 percent to 25 percent among the sites. The risk profile for men nationally (N = 4,821) included: (a) ever using heroin (OR = 2.0), amphetamines (OR = 1.9), or nonprescription methadone (OR = 1.4); (b) using needles to inject drugs in the past 30 days (OR = 1.8); (c) ever being told they had AIDS/HIV (OR = 1.8); (d) ever being in drug treatment or detoxification (OR = 1.6); (e) years of life spent in jail (OR = 1.03); and (f) number of times they were told they had gonorrhea (OR = 1.04). The risk profile for women nationally (N = 2,121) included: (a) ever using heroin (OR = 1.7) or amphetamines (OR = 1.5), (b) ever being in drug treatment or detoxification (OR = 1.8), (c) using needles to inject drugs in the past 30 days (OR = 1.7), and (d) ever being in methadone maintenance (OR = 1.6).

The Anchorage and national prevalences of HBV were quite similar. The risk profiles for men and women in both the Anchorage and the national sample indicated that using needles in the 30 days before intake was a primary risk factor for a positive HBV history. For Alaska women, three out of five risk factors were associated with sexual behavior, whereas the national data for the other women indicated only drug use variables as risk factors. The only risk factor for men suggesting sexual transmission was how many times men in the national sample had been told they had gonorrhea.

HEPATITIS C

Hepatitis C virus (HCV) is responsible for the majority of non-A, non-B (NANB) hepatitis in the United States. Approximately 50 percent of people with hepatitis C develop chronic liver disease. Symptoms may include nausea, vomiting, anorexia, abdominal discomfort, and jaundice (Schloss and Beller 1994).

This virus is usually transmitted through injection drug use (including blood transfusions and dialysis), although sexual transmission has also been documented. Data from 297 members of the Alaska sample tested for HCV found that 42 percent were infected and that the major risk factor was injection drug use. For every time participants injected drugs within the past 30 days they were 12.8 times more likely to be anti-HCV positive (Orr et al. 1994). An additional correlate was ever having been in drug treatment.

RESPIRATORY AILMENTS

A variety of respiratory problems have been reported in the literature as being associated with cocaine smoking (Laposata and Mayo 1993; Meisels and Loke 1993); these include respiratory symptoms, pulmonary hemorrhage, pulmonary edema, asthma, pulmonary barotrauma, thermal airway injury, hypersensitivity reactions, and interstitial lung disease. However, it is likely that these problems are multifactorial or idiosyncratic. Even though the collective literature fails to reveal a clear picture of the symptoms diagnostic of cocaine use, it is predicted that the spectrum of cocaine-induced pulmonary disease will increase as the use of cocaine increases. For example, Kline and Hirasuna (1990) reported a case study of pulmonary edema that, after excluding the effect of adulterants, appeared to be due exclusively to the cocaine itself. Crane and colleagues (1991) reported an outbreak of tuberculosis among crack cocaine users for whom transmission was, in part, blamed on the conditions under which the drug was smoked. That is, cocaine smokers often close off ventilation at the smoking site to avoid detection. Having a group of people inhaling and exhaling hot smoke in close proximity to one another may facilitate transmission of a multitude of airborne diseases, including tuberculosis.

Klinger and associates (1992) reported a case of a woman who had large amounts of carbonaceous material in her lungs after cocaine smoking. Her other symptoms included cough and fever, and pulmonary infiltrates were found. The results from another research group may illuminate some of these findings. After controlling for the smoking of other substances, Tashkin and colleagues (1992) concluded that cocaine smoking produces: (a) cough, black sputum, and chest pain; (b) obstructive ventilatory abnormalities in the large airways; and (c) impairment in the diffusing capacity of the lung. Moreover, these effects can be attributed to the inhaled cocaine itself, rather than to the characteristics of the smoking (Khalsa et al. 1992).

METHODOLOGICAL ISSUES

Several methodological issues warrant special consideration when undertaking substance abuse and health research. Two of the most important are understanding local drug terminology and the validity of self-reports. A rural-relevant discussion of these issues is presented.

Drug Terminology

The use of a smokable form of cocaine was popularized by drug users in large urban areas in the 1980s. The mass media used the term crack to describe this highly detrimental and instantly addictive drug. For many drug users, especially those in rural areas, these messages actually preceded the introduction and use of smokable cocaine and may have precipitated a change in terminology for it (Ouellet 1993). Cocaine smokers not only call the substance crack, but also rock, ready-rock, or freebase (Cagle et al. 1993; Ouellet 1993; Ratner 1993). This plurality of terms suggests, that prior to conducting surveys and interpreting data, it is important to understand the language, including local terminology, associated with drug use (Fullilove and Fullilove 1993). Failure to consider drug nomenclature can result in underestimates of use. For instance, terminology may be very specific to a location or ethnic group, and one may, therefore, see great variability in rural areas where there are both diversity between communities and isolation from other communities.

For example, the drug history section of the RBA elicits information about past and current (in the past 30 days) drug use. The RBA asks (a) "Have you ever used crack (smokable cocaine)?" and (b) "Have you ever used cocaine by itself (other than crack) that you injected or snorted?" When asked the first question, respondents usually commented that crack is a synthetic drug unlike the cocaine they were smoking and that there was no crack in Alaska because it was all in New York or California. In a number of cases, respondents said "no" to crack use and "yes" to injecting or snorting, but when asked, "How many days in the last 30 days have you used [snorted and/or injected] cocaine by itself?" they indicated zero. At this point, knowing that the respondents had tested positive for cocaine metabolites, interviewers probed respondents by reminding them that they had tested positive to cocaine and asking "How did you use the cocaine?" Usually the response was that they had smoked it; consequently, interviewers now ask "Have you ever used smokable cocaine?" This generic term seems to be better understood and more acceptable to the respondent.

Self-Report

Self-report is a convenient method of collecting data when resources are limited, as they are in rural areas. However, the extent to which self-report provides a valid measure when sampling from a drug-using population is regularly challenged. Many studies have focused on truthfulness and have demonstrated a rather high degree among addicts (Ball 1967; Bonito et al. 1976; Stephens 1972). However, threats to respondent validity, when subjects are unable to remember or never knew answers to administered questions, have been largely ignored. (Harrell 1985). This may result in fallacious inferences made by researchers and health care practitioners, as in the case of health histories of asymptomatic disease. The accuracy of self-reported health history in high-risk populations may not be sufficient to use as measures of infection prevalence. For example, several studies of high-risk populations have suggested large discrepancies between HBV infection based upon self-report and serological evidence of HBV infection (Comfort and Wu 1989; Hart et al. 1993; Kleyn et al. 1993). Such discrepancies may underestimate HBV prevalence and relative risk (Joe et al. 1990; Kuhrt-Hunstiger and Fisher 1994; NIDA 1989a, 1989b; Simpson et al. 1993) and have important implications for investigations of HIV.

To ascertain the validity of the Anchorage data, agreement between self- reported and serological-based HBV infection rates among drug users were compared. Data were collected between February and August, 1993. Of the 124 men and 68 women in this sample, ethnic distribution was as follows: black, 46 percent; white, 32 percent; Alaska Native/American Indian, 16 percent; Hispanic, 3 percent; and Asian/Pacific, 1 percent. Current needle users comprised 27 percent of subjects. All participants were tested for HBV seromarkers by enzyme immunoassay for HBV surface antigen (HBsAg), core antibody (anti-HBc), and surface antibody (anti-HBs). A subgroup (N = 100) of this sample was also serotested for alanine aminotransferase (ALT) and hepatitis C infection (anti-HCV). Additionally, all subjects were asked the RBA question, "How many times have you been told by a doctor or a nurse that you had hepatitis B?"

Presence of anti-HBc or HBsAg was used as the standard for a history of HBV infection. Self-reported prevalence of HBV was 15 percent, whereas the serological testing prevalence was 36 percent. Of the 123 subjects testing negative for HBV (64 percent), 119 responded that they have never been told they were infected with HBV (specificity = 96.75 percent). Moreover, the majority of subjects testing positive for HBV responded that they had never been told they were infected with HBV (65.22 percent), yielding a low sensitivity of 34.78 percent. When anti-HBs was compared to selfreport, specificity was 92.42 percent and sensitivity was 31.58 percent. Non-HBV seromarkers also provided relatively low sensitivity for HBV self-report. ALT levels above 48 international units per liter (IU/L) were considered elevated. Sensitivity and specificity of HBV self-report compared to elevated ALT were 31.58 percent and 87.67 percent, respectively. HBV self-report sensitivity and specificity associated with anti-HCV were 26.92 percent and 95.83 percent.

Among those testing positive for HBV, ethnic minority (black and American Indian/Alaska Native) groups were least likely to self-report infection. Of the 32 white subjects who were HBV positive, 22 (62.5 percent) self-reported HBV infection, whereas only 5 of 29 positive blacks (17.2 percent), 4 of 10 (40 percent) positive Alaska Native/American Indian, and 1 of 7 (14.3 percent) other ethnicity self-reported HBV. The ethnic distribution of individuals selfreporting HBV infection differs considerably from the ethnic distribution of those sero-testing positive, as is demonstrated in figure 3.

Self-report of hepatitis B infection prevalence in the current sample provided a biased estimate when compared to sero-confirmed tests. When drug users reported that they had been told they were infected with HBV, they did so very accurately. This supports other findings that suggest accuracy and truthfulness in self-report among drug users. However, an alarming number of subjects had never been or did not remember being told of their HBV infection history.

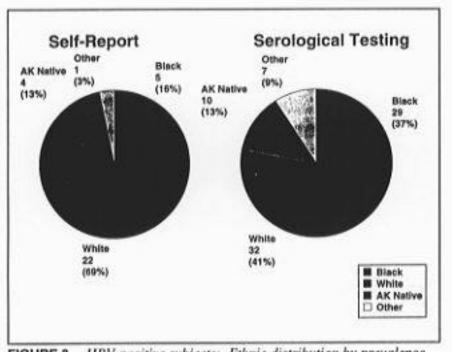


FIGURE 3. HBV-positive subjects: Ethnic distribution by prevalence measure.

Further investigation is needed to explain factors contributing to low HBV treatment and self-report. However, there are several possible explanations. First, hepatitis symptoms frequently are either not present or they resemble flu symptoms. Persons with these types of symptoms may not seek health care. Second, HBV infection attributed to illegal drug use may deter drug users from seeking treatment for an infection that is essentially untreatable. Third, the cost of laboratory tests may prevent drug users, especially low-income users, from being tested. This may also explain the ethnic differences in self-report versus serological test results.

Each of these three possible reasons for low self-report and treatment may have particular importance for rural health. First, rural areas typically have fewer health care facilities and providers, and this is particularly true in Alaska. Under such circumstances, individuals who are experiencing symptoms of a minor illness would not be likely to seek out a health care professional.

Second, in rural communities, the possibility of anonymous testing for diseases with a link to substance abuse may be impossible because

everyone knows everyone else. Thus, users may be particularly sensitive to scrutiny and detection by health care providers who know them and their family. Clients may, therefore, forego testing and treatment when, in reality, anonymity does not exist.

Finally, those in rural areas often work in seasonal occupations such as seafood, timber, and farming where they have lower access to health insurance. For these individuals, the cost of laboratory tests may be prohibitive, causing them to treat the symptoms and ignore the cause. For these, and possibly other, reasons one would expect that morbidity among rural residents, especially that based on selfreport, would be underreported.

Obtaining Sex Partner Information

Earlier work (Fisher et al. 1993*b*) suggested that obtaining information about the sex partners of subjects, especially from Alaska Native female drug users, might help in establishing high-risk routes and networks of disease transmission. A study was initiated in which participants were asked about their (up to five) most recent sex partners, specifically the partner's ethnicity, age, gender, drug use history (if known), condom use at this encounter, whether anything (drugs or money) was traded either way for the sex, and relationship.

Data were analyzed using a multidimensional unfolding analysis (Coombs 1964; SAS Institute 1992). Results displayed in figure 4 are a joint-space representation of the distance between points. The threeletter point labels refer first to gender, second to ethnicity, and third to whether the point refers to the respondent him/herself or to a sex partner of the respondent. Dimensions are arbitrarily located; therefore, it is not as important to interpret the dimensions of the space as it is to interpret the relative locations of the points in the space. Points reflect patterns in the data.

The point at 0.22, 0.91 represents male white respondents (MWR) and female white partners (FWP). The fact that these two are identical in location indicates a strong preference among male white respondents for female white sex partners. (As used here, the term "preference" means self-reported experience and does not imply preference in the more general sense.) Similarly, female white respondents show a preference

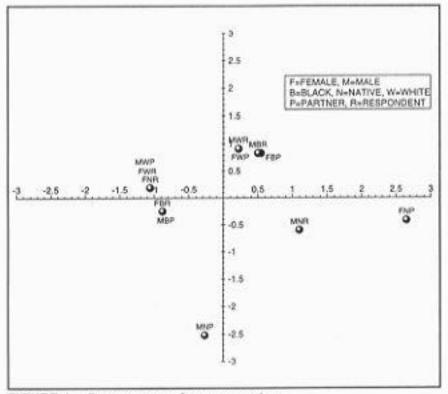


FIGURE 4. Sex partner preference mapping.

for white males. The points that represent male black respondents (MBR) show that these respondents had a preference for female black sex partners (FBP), but also a fairly strong preference for female white sex partners (FWP). Similarly, female black respondents (FBR) show a preference for male black partners (MBP). Thus, among blacks and whites there was a tendency toward having sex with racially similar partners.

However, this pattern did not hold for the Alaska Natives. First, male Alaska Native respondents (MNR) (located at 1.1, -0.6) do not show a strong preference for any specific type of sex partner. This is a reflection of their generally low self-report of having any sex partners at all. Second, female Alaska Native respondents (FNR) show a strong preference for male white partners (MWP). Thus, they are unique in showing a preference across ethnic groups. This point suggests a potential disease vector, the only one that crosses ethnicities, between Alaska Native female drug users and white men. In addition, these men are also likely to be injection drug users. The authors' earlier research demonstrated that the Alaska Native female subjects have a much higher proportion of sex partners who are needle users than any other sex/race combination (Fisher et al. 1993*a*). Moreover, white men and women and Alaska Native women are the sex/race groups that are most likely to be needle users.

Hamilton and Seyfrit (1994) have demonstrated a higher rate of female outmigration from the rural areas of Alaska to the urban area of Anchorage. In fact, "Bush villages tend to have more young Native men than women, whereas larger cities have more young Native women than men" (p. 1). The relationship between this circumstance and the preference for white sex partners is unclear.

RECOMMENDATIONS FOR FURTHER RESEARCH

There are several major problems with doing research in rural areas. One is that confidentiality can be difficult to maintain in a setting where everyone knows everyone else. Another is that, traditionally, national studies have overlooked rural areas. A third is the lack of an infra-structure for conducting complex studies in rural areas, which is enmeshed in a cycle that includes a lack of literature to cite in writing grant proposals to establish the infrastructure, to do the research, and to create the literature.

Larger urban areas are part of Federal efforts such as the Drug Use Forecasting (DUF) and the Drug Abuse Warning Network (DAWN) systems that provide data at the national level and to local and State entities. A similar system of data collection and screening is needed for rural areas. The creation of local infrastructures should be systematically supported so that local researchers can collect community-level data. Historically, researchers from major universities have obtained Federal grant money to conduct rural area studies with little or no input from local populations. This pattern has generated opposition on the part of local populations to all research, even that proposed by local researchers attempting to do local studies. Funding organizations should recognize that local researchers have a stake in their community as well as respect for local values and norms. These aspects of the social milieu are often missed by nonlocal researchers.

Steel and colleagues (1993, p. 287) have stated that "a clear need exists for research attention to injection drug use as a risk factor for HIV disease in small cities and nonmetropolitan areas. To formulate

effective HIV prevention strategies in these areas, systematic studies about the nature and extent of risk behaviors of injection drug users in less-populated areas are called for." One would only need to generalize their statements for needed studies to include all drug use as risk factors for disease in general.

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