Factors To Consider When Using Hair as a Cocaine-Exposure Measure for Mothers or Newborns

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INTRODUCTION

Historical information about drug exposure is available from an analysis of hair. But is hair testing good enough to reliably determine *degree of exposure* and help judge the specific contribution of cocaine to infant risk? Furthermore, is hair testing a worthwhile outcome measure for tracking maternal progress in remediation programs?

Pregnant women who are identified as occasional users of illegal drugs such as cocaine often are lumped together with seriously dependent women into an undifferentiated category of "maternal drug abuser." This occurs even though the teratologic consequences of cocaine use appear to follow the same general pattern found for legal drugs such as alcohol and tobacco. That is, the nature and degree of infant risk appear to bear some relationship to dose level, time of fetal exposure, and general maternal health and nutrition (Kopp and Kaler 1989). Risk factors are interactive; mothers often use multiple drugs; and the relative importance of different risk factors is often difficult to specify in human studies, particularly without *reliable* exposure information (Zuckerman 1991, pp. 352-362; Suomi and Higley 1991, pp. 291-302; Sokol et al. 1986). Despite such uncertainties, some service providers adopt the simplistic assumption that any degree of gestational cocaine exposure will produce defective children and accordingly find justification for heroic early intervention, a practice earlier decried by Coles (1992, pp. 248-258), Coles and Platzman (1993), and others. A similar sense of urgency rarely follows when a woman reports occasional use of alcohol or tobacco while pregnant.

A child exposed to large doses of drugs during early gestation and later raised in an environment of significant stress is thought to be at greatest risk for postnatal problems (Kosofsky 1991, pp. 128-143; Kopp and Kaler 1989). Realistic estimates of environmental stresses can sometimes be made by providers and outreach workers, but knowledge of the degree of gestational exposure is more problematic. Because maternal hair testing allows the possibility of a quantitative and historical estimate of degree of fetal cocaine exposure, it could serve as an objective screen for gauging the degree of alarm warranted on delivery. Estimates based on the ponderal index and infant head circumference suggest that intrauterine growth retardation (IUGR) occurs in association with cocaine early in gestation (Frank et al. 1990), at a time that antedates postnatal detection through either urine or meconium sampling.

Analysis of a pregnant woman's hair, segmented by trimester, could aid in honing the presumption of drug-related risk and serve as a useful correlate of postnatal outcomes such as IUGR; however, infant cocaine hair levels probably would not be as good a diagnostic of teratologic effects as maternal hair. Callahan and colleagues (1992) segmented maternal hair samples that were presumed to represent 9 months into three trimester segments. They found the maternal cocaine hair levels of only the last trimester to significantly correlate with the infant hair cocaine levels, which confirms the conventional wisdom that cocaine found in *infant hair* reflects only the last months of gestation. However, that mothers' and infants' hair cocaine levels cross-correlate helps support the argument that the technique is reliable, a finding supported by Marques and colleagues (1993). Therefore, maternal hair, not infant hair, becomes the key specimen for assessing the degree of fetal exposure during the first trimester when drugs can retard growth or impair normal organogenesis.

In a separate domain, adult drug treatment programs often have to choose between the costs and inconveniences of frequent urine screening or the legendary inaccuracy of self-report as a means of documenting change in drug use status during long-term followup. Here, too, hair analysis holds promise for helping to objectify these estimates. However, few studies report cocaine in the hair as a repeated measures outcome variable to document program effectiveness. If the hair of the mother has a reliable record of exposure and if the technique is valid, then hair testing can prove to be more than just a surveillance tool: It can be a diagnostic tool and an outcome variable of considerable value to clinicians and researchers.

Nevertheless, before any health-related uses of hair testing can be fully realized, more rigorously analyzed information is needed to help document the factors that influence hair testing results.

ISSUES OF VALIDITY AND RELIABILITY

Some drug researchers are troubled by the technology of hair analysis for drugs of abuse because there are unanswered questions about variables that affect drug sequestration in hair, the comparability or validity of results based on different drug extraction techniques, and the degree of reliability and quantifiability of the procedure (Keegan 1991-92; Taylor 1990; Holden 1990). Such expressions of caution, articulated in the scientific literature, are partly scientific and partly derivative of ethical concerns over the many inappropriate ways this technology could be used to exclude or punish people who disobey the law. It first should be determined that there will be a health-related benefit from hair analysis. Such concern is especially valid in view of racial differences in hair composition, differences that could well be reflected in hair's affinity for drug uptake. For example, the ratio of fibrous protein to matrix substance in hair across three major racial groups can vary by a factor of 2.5, where Asian > Caucasian > African (Dekio and Jidoi 1990). Thus, hair is not a homogeneous substrate, and until more is known about the variables that affect drug uptake and levels found in hair, it is premature to assume comparable exposure based on comparable levels in hair. This latter problem is not at issue when studying repeated measures within subjects and evaluating change over time.

Uptake of cocaine and its metabolites into hair is *not* a strict function of blood concentration. Several different research teams, including Henderson and colleagues (1992) and Möller and colleagues (1992), using the hair of South American coca chewers, and Nakahara and coworkers (1992), using rat hair, have reported that the ratio of cocaine metabolites to cocaine is different in hair from that in blood. The parent compound, untransformed cocaine, is found in much higher concentrations (4 to 9 times higher) in hair than are its main metabolites, benzoylecgonine (BZE) and ecgonine methyl ester, despite the higher blood concentrations and longer circulating half-lives of the metabolites. Therefore, although levels of cocaine and its products found in hair may reflect the amount consumed by an individual, there are factors influencing uptake or measurement that reverse the blood concentration ratios of these compounds. Reasons for these differences are not clear, but such findings render confident quantitative comparisons across individuals still slightly beyond reach at this time.

Even so, it should be acknowledged that such uncertainties are inevitable in a young technology, and they warrant caution in, but not dismissal of, the technique. Because of the uncertainties, health researchers who use hair testing results should avoid blurring the boundary between the health implications and the legal implications of cocaine use. It is neither wise nor unusual for a pregnant woman to consume alcohol or tobacco; the same holds for cocaine. But just as there is no defensible health motive to recommend drug treatment intervention for the occasional pregnant alcohol user, there is no health basis for advocating treatment of the occasional cocaine user. If the aggregated research record can show hair to have *quantitatively* valid and reliable exposure information—gleaned either from the mother's or the newborn's hair—then it may help to target therapeutic interventions prenatally or postnatally on the mothers and infants at highest risk. By contrast, law enforcement, which is enjoying somewhat of a romance with hair testing, is less concerned with exposure levels than it is with evidence of illicit activity, an inherently more dichotomous problem and one that is less dependent on the quantitation that is critical to the health sciences.

Broadly speaking, science appears to be midway through a two-part examination of the validity and reliability of hair testing. Two criteria that should be satisfied are (1) dichotomous or qualitative accuracy of hair testing—Does it detect drugs of abuse in hair?—and (2) quantitative accuracy of hair testing—Does the level of a drug found in the hair of an individual reflect the amount consumed over time? There is general agreement that the question about qualitative accuracy has been answered in the affirmative through research conducted over the past decade. Hair does provide a record of drug exposure of adults and newborns (Cone 1990; Cone et al. 1991; Graham et al. 1989; Welch et al. 1993; Forman et al. 1992; Marques et al. 1993; Callahan et al. 1992; Baumgartner et al. 1989). Moreover, research groups that have compared hair, meconium, urine, and self-report have found hair to be the most sensitive (e.g., maximum true positives and minimum false negatives) at detecting the presence of cocaine in newborn infants (Ostrea 1992, pp. 61-79; Callahan et al. 1992). However, there is still some concern that despite the sensitivity of detection via hair, the specificity (minimum false positives and maximum true negatives) of maternal hair (not necessarily infant hair) may be low in some circumstances. This concern grows from the debate among researchers about whether drugs carried by smoke, and which then adhere to hair, can be fully washed off the surface during sample preparation. Cone and colleagues (1991) report that intentional high-dosage environmental exposure with cocaine produces false positives that cannot be fully washed out in the laboratory. The implications of this are important for both legal and health actions, because if there are to be sanctions imposed on someone (or an exposure risk assumed) when drugs are found, it is important to know that drugs found in hair have arrived there from the circulation of blood internally and not from the circulation of air externally. This is obviously not a problem when sampling hair from a newborn infant, but it becomes progressively more of a concern as the infant grows older and is exposed to crack cocaine smoke in the air.

False Negatives

When a pregnant or postpartum woman's hair is found to contain cocaine, it is useful to know how much meaning this has for the degree of exposure of her infant or for her own treatment needs. Although infant hair analysis for cocaine should have high specificity, infant hair has no direct information about first trimester exposure. Therefore, the best estimate of early gestational exposure of infants depends on the valid and reliable analysis of maternal hair. Without full confidence in the specificity of maternal hair analysis, it cannot be assumed that levels in a mother's hair reflect consumption. Therefore, it is worthwhile identifying circumstances under which levels found in maternal hair *can* be believed. Currently, the question of fetal exposure turns more on maternal self-report and whether drugs have been found at delivery than on any historical objective basis.

Because the circulatory half-lives of cocaine and its metabolites are short and because mothers at highest risk often are not available for testing earlier than at delivery (because they receive little prenatal care), the commonly employed estimate of infant exposure based on urine samples is only an indirect approximation of infant risk and reflects only the mother's use within days of delivery. Such reliance on urine is known to have a high false-negative rate. Ostrea (1992, pp. 61-79) cites estimates of the false-negative rates that range from 32 to 63 percent of cases when relying only on urine collected at delivery. These estimates match well with the author's false-negative results based on a known sample of 136 cocaine-using women. Using maternal hair as an index criterion for a woman who is cocaine-positive, the rates of false negatives are 72 percent for urine cocaine and 27 percent for urine BZE (when both hair and new urine samples were taken on the same day an average of 2 months after delivery). Fully 98 percent of all mothers in the project sample were cocaine positive in the hair. Among all infants of hair-cocaine-positive mothers who were measured, 95 percent were hair cocaine positive.

Pair Correlations

One difficulty of doing good validational studies of hair analysis in humans is dosage control. There have been few (if any) laboratory studies of controlled, long-term, high-dosage drug use that compared hair analysis with known consumption. Such studies are difficult because dosing subjects as frequently and as lavishly as addicts dose themselves poses both ethical and liability risks that most research centers cannot take. Conversely, the purity and amount of a drug voluntarily self-administered in the field are difficult to determine from interviews; therefore, comparing hair levels with real consumption over time is loaded with uncontrollable error. Long-term frequent urine sampling over many months of self-administered use by street addicts would likely be the most accurate way to establish quantitative accuracy of hair testing in humans.

One alternative method for *estimating* reliability is to determine the degree of concordance between mother-infant pairs. This is a reasonable estimate because mother and fetus are exposed to shared blood products. Earlier data from the author's studies (Marques et al. 1993) that compared mother and infant based on the first 62 pairs showed that a large proportion (more than 50 percent) of all maternal hair was reported by laboratory technicians to be in poor condition; such damaged hair weakens the strength of the overall correlation between mother and infant. Correlations that select on the basis of only good condition maternal hair had explained 40 percent of the variability found in infant hair cocaine (correlation coefficient [*r*]=0.63, number of cases [n]=38, probability [*p*]<0.0005) (Marques et al. 1993). Cases added since that earlier report have raised the total bivariate sample correlation (unselected for hair condition) to *r*=0.52 for 111 pairs (94 percent African-American), representing a strong degree of concordance between mothers and infants. The scatter plots with regression line and 95-percent confidence intervals are shown in figure 1. The values are normalized through square root transformations because the distribution of raw values was highly skewed. A large proportion of these hair samples were reported to be in poor condition by the laboratory, presumably because of the use of hair treatments. Washing and preparing damaged maternal hair may result in finding less cocaine in the sample (relative to infant), which causes the overall regression line for all paired cases to intersect the Y axis at a positive point. If separate confidence

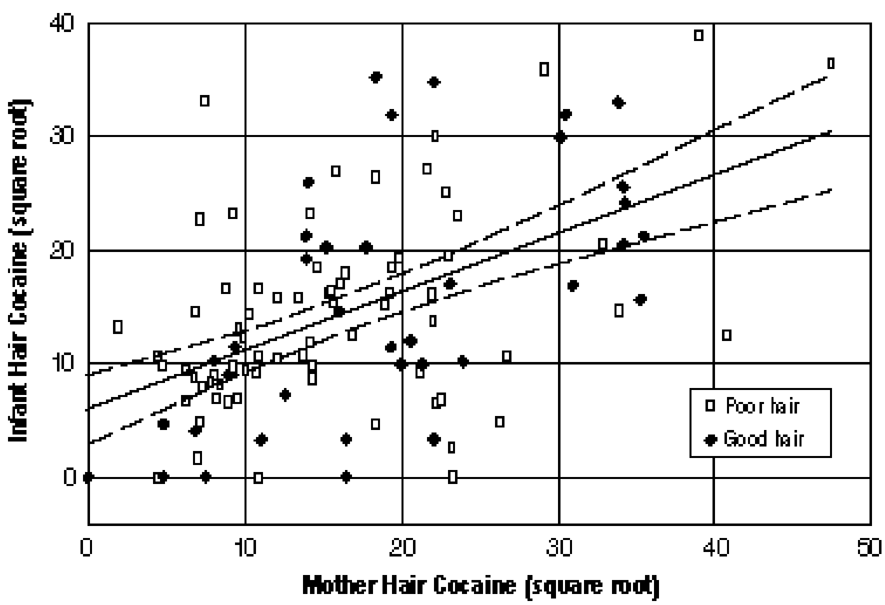

FIGURE 1. Infant/mother pairs (n=111) cocaine in hair

NOTE: r (correlation coefficient)=0.52; t (t statistic)=6.33; p (probability)<0.001. Solid line indicates regression; broken lines indicates ±95-percent confidence intervals.

SOURCE: National Public Services Research Institute intervals and regression line for only the good maternal hair (black circles in figure 1) were plotted (not shown here), then the 0,0 point origin of the plot would be captured within the confidence intervals.

Callahan and colleagues (1992), with a sample of 82 percent Caucasian women, report an even stronger correlation between mothers and infants (r=0.72, n=52). A big difference in the Callahan data set and the author's is the proportion of (0,0) pairs (40 percent of all Callahan's cases were [0,0] pairs). The inclusion of unexposed cases is completely valid and appropriate, but it tends to constrain the regression line through the origin and raise the correlation. The data shown in figure 1 were more uniformly exposed, containing only one (0,0) pair. Artificially adding 40 percent null (0,0) pairs to the author's data (artificially raising n to 155) raises the full-scale correlation from 0.52 to 0.78, a correlation more in line with Callahan's; a similar adjustment to the cases selected for good condition maternal hair raises the correlation to 0.85. These two studies are among the first to report full-scale correlations between mothers and infants. Taken together, they lend some measure of credence to the quantitative accuracy of hair testing as a reflection of circulating blood levels of cocaine.

Correlation With Other Measures

Another reason for confidence in the quantitative accuracy of hair cocaine analysis is its correlation with other analytic methods. In the author's studies, the correlation between BZE levels in maternal urine (point-in-time sampling) and maternal hair was found to be significant for all cases (r=0.32, n=136, p<0.0005) and more strongly correlated when selecting only for hair in good condition (r=0.45, n=45, p<0.001); maternal urine BZE also was correlated with infant hair (r=0.35, n=108, p<0.0005). Even the short circulatory half-life of the parent compound cocaine was significantly correlated with hair but less strongly so (r=0.23 for both maternal and infant hair; p<0.003, n=136 and p<0.008, n=108, respectively). Although the window of time reflected by each measure is different (urine—short term, at best a few days; hair—long term, earliest detection at 1 week), just finding the relationship (and the correlation between mothers and infants) strengthens the basis for believing that hair can be quantitatively reliable. This is so because, over a large sample of users, those who use the most cocaine in the long term are also likely to show the greatest use in the short term. This principle of human nature, not overlapping windows of detectability, is the likely basis for the correlation. The presence of a correlation is more telling than the absence of one would be, especially because these are different matrices measured by different laboratories using different analytic techniques (gas chromatography/mass spectrometry and radioimmunoassay [RIA]).

Therefore, if two analytic procedures are well correlated, it would be helpful if the self-reported cocaine use also were correlated. However, the correlations found here between self-report and urine or hair endorse the position taken by McLellan and colleagues (1992) on the Addiction Severity Index (ASI), who limit questions about historical use on the ASI to the past 30 days because they have found longer term retrospective reporting of drug use to be unreliable. Of three self-report measures studied in this study's data set, only self-report in the past 30 days was correlated with analytic measures of use/exposure; both maternal urine cocaine metabolite (r=0.27, n=131, p<0.001) and maternal hair cocaine (r=0.17, n=136, p=0.022) showed weak positive correlations with 30-day self-report. Table 1 shows the cross-correlation matrix of cocaine measures relative to mother's use.

USING HAIR TESTING

If all the cautions about the analysis of drugs in hair can be accommodated or controlled to the satisfaction of the researcher, then hair testing has many advantages. From a pragmatic angle, the primary advantages are the savings of project time spent in sample handling and the potential reduction of laboratory costs (one sample every 3 or 4 months instead of twice-a-week samples). From a scientific angle, hair testing may permit the establishment of more specific relationships between exposure and outcome (mother treatment or infant health). Hair testing also brings a much less demeaning collection procedure for the client. On the down side, it is a new violation of privacy that warrants serious concern. Some women are resolutely opposed to hair sampling; some women maintain short hair; and an occasional client may be suspicious (e.g., the author's Caribbean subject who suspected that samples of her hair would be used in a clandestine Santeria ritual). Overall, about 8 percent of women have refused to provide hair for the author's study; approximately 12 percent have refused to allow their infants to be sampled.

Mothers

The greatest value of maternal hair testing may be that it allows the researcher or program evaluator to collect an integrated pool of drug-use outcome measures that represent an extended posttreatment period. Several types of drugs can be measured in a sample via a screening RIA, some (e.g., cocaine) far more accurately than others (e.g., marijuana). An example for cocaine, based on cases with repeated measures at three time points, is shown in figure 2. The ordinate is scaled in raw (untransformed) hair cocaine values; the left group shows all cases, and the right group is selected for the cases with hair judged to be in better condition. The figure

TABLE 1. *Correlation coefficients among cocaine-exposure estimates*

	Infant Hair Cocaine			Mother Urine Cocaine			Mother Urine Metabolite			Self-Report 30-Day			Self-Report History		
Drug-Exposure Measures	*r*	n	*p*	*r*	n	*p*	*r*	n	*p*	*r*	n	*p*	*r*	n	*p*
Mother hair cocaine	.52	111	.000	.24	136	.003	.32	136	.000	.17	136	.022	–.14	125	.065
Infant hair cocaine				.23	108	.008	.35	108	.000	.14	110	.069	–.14	102	.084
Mother urine cocaine							.59	136	.000	.21	131	.001	.04	120	.370
Mother urine metabolite										.27	131	.001	–.13	120	.078
Self-report 30-day													–.03	125	.359
Self-report history															

KEY: *r*=correlation coefficient; n=number of cases; *p*=probability (of chance occurrence)

SOURCE: Adapted and reprinted from Marques, P.R.; Tippetts, A.S.; and Branch, D.G., *American Journal of Drug and Alcohol Abuse*, 19(2), 1993, pp. 159-175, by courtesy of Marcel Dekker, Inc.

makes clear the possible *group* outcome monitoring that is possible with repeated hair samples.

Having access to a quantifiable index of exposure allows the researcher to ask at least two different categories of questions about the mother:
(1) What are the baseline characteristics of higher vs. lower users (knowing that hair type is a possible but unproven confounder)? and
(2) Which maternal characteristics are associated with reduced use from baseline over the duration of the project period?

Baseline Characteristics

None of the correlations between baseline hair cocaine levels and mother characteristics were found to be particularly strong, despite a broad variety of measures. However, among the strongest, most elements of the Caldwell HOME (Home Observation for Measurement of the Environment) scale (Caldwell and Bradley 1978) were negatively correlated with cocaine, especially the maternal involvement scale (r=-0.29, n=96, p<0.004); when 36 cases of "good hair" were selected, the correlation between maternal involvement and hair cocaine was -0.40. The Nursing Child Assessment Satellite Training (NCAST) feeding scale (Barnard 1980) also was strongly negatively correlated with good condition hair for cocaine (r=-0.50, n=42, p<0.0005), but using all 107 cases, the correlation was less interesting at r=-0.17, albeit still significant. In addition, the educational level of 142 cases was positively and significantly (but weakly) correlated to the

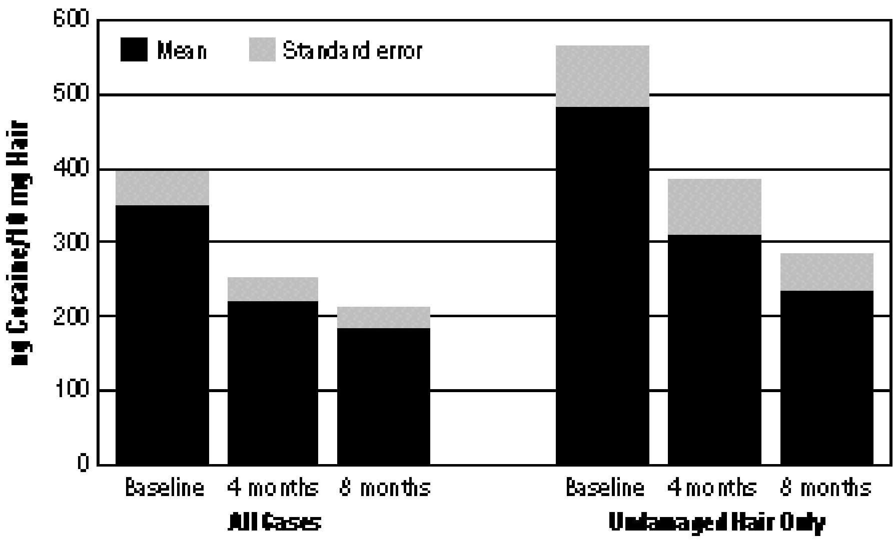

FIGURE 2. Measurement of hair cocaine in mothers (change from baseline to 4 and 8 months)

level of cocaine: The higher the educational level (within this sample of women having an average of 11 years of education), the more cocaine was found at baseline.

Subject Characteristics Associated With Decreased Use During the Intervention

Women who showed a trend toward reduced use during the project period had entry characteristics different from those who showed little decrease in cocaine use as measured by hair testing. Those who stayed in the sample (65 percent of all clients were still accessible after the first year and 50 percent after the second year) appeared to temper their drug use over time. This can be seen in figure 2, which shows cocaine levels in the hair of the women across 8 months. The decrease is significant as a linear effect and is even more accurately modeled by a second-order polynomial regression that accounts for the slowing of the magnitude of change.

The variables correlated with reduction in use over an 8-month period differ depending on how change is calculated (as a log-change-ratio score, a percent-change score, or an absolute difference; see Tippetts and Marques [this volume] for further information). There are no good rules for deciding how to calculate change. However, across the different potential change variables, the most persistent correlates of reduction in hair cocaine levels over time, for this sample, were reduction in Beck Depression Inventory scores (Beck 1978) and increased Rosenberg self-esteem scale scores (Rosenberg 1965). Those highest on the Millon passive-aggressive scale (Millon 1987) and antisocial personality scales (Millon 1987) were more apt to show an increase in hair cocaine levels across the 8-month period ($p<0.001$). These findings are preliminary and are cited only as examples of the use to which hair measures can be put in treatment outcome research.

In summary, the advantages of hair testing to researchers and clinicians come both from the convenience and the potential for greater accuracy. The risks are both scientific and societal and can derive from premature advocacy of an incompletely validated technology. These factors should be weighed by anyone planning to use hair testing in clinical research.

COMMENTS AND QUESTIONS

Many critics of hair analysis seem to believe that its value should be judged relative to the proven accuracy of urine testing, and for forensic purposes that is true. However, health outcome research has different needs. Hair testing may answer questions about long-term exposure where serial urine sampling is not a practical alternative because of its cost and inconvenience. The arena in which hair testing should be evaluated is relative to other historical exposure estimates, such as meconium analysis and self-report. Behavioral researchers long ago learned to live with measurement error and for that reason require much larger sample sizes before confidence in a finding is warranted. In pharmacological studies a higher standard of accuracy is expected, and sample sizes are typically much smaller. Nevertheless, all researchers require better answers to some of the large questions of hair analysis that still need clarification. One is the effect of passive crack-smoke exposure on cocaine levels found in hair, and there are other important questions as well.

Hair testing advocates presume that hair grows at a rate of 1.3 cm per month (Baumgartner et al. 1989). The variables influencing hair growth rate are not clear, and it strains credibility to assume that growth is uniform across sexes, races, ages, hair types and compositions, and nutritional states. The effects of these factors should be easy questions to answer, but they do not appear to have been reported yet. Also, given those subject variables, what effect do such variables have on drug uptake and sequestration, and why is there a discrepancy between the ratio of metabolites to cocaine in hair relative to blood? Furthermore, is someone who takes more showers or sweats or swims more apt to lose drug from the hair? It is always good practice to take hair samples from the approximate same site in repeated measurements, but to what extent are there differences in regions of the head in measured drug concentration? Also, if there are differences, what should be made of them? Would it be better to sample and select hair from different regions of the head to get a truer estimate of exposure? Is the issue of hair damage important? How important is it? How old must an infant be before the correlation between mother and child falls apart?

If it can be assumed that up to half the statistical variability in the hair cocaine levels found among a group of mothers is reflected in the hair cocaine found in their infants, what accounts for the other half? How much of the unaccounted variance is analytic error as opposed to experimental error? That is, what contribution to error is made by the use of RIA as opposed to more precise techniques? Is linear regression necessarily the best way to model the relationship between exposure levels in mothers and infants? Also, given the large amount of error, what responsibility does the research community have to prevent unintended advocacy or promotion of this potentially intrusive technology? Hair analysis seems useful at the group-outcome level for researchers, but the careless use of the procedure could compromise civil liberties if hair drug levels are mistakenly believed to accurately reflect a particular individual’s use.

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