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Methodological Issues in Epidemiological, Prevention, and Treatment Research on Drug-Exposed Women and Their Children

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Preface

Prenatal exposure to drugs of abuse has become a major public health concern of national importance. It has adversely affected the lives of hundreds of thousands of babies born each year in the United States to drug-dependent mothers, The cost of providing intensive care to drug-exposed infants can be enormous. The care and treatment of one infant could run to more than $100,000 depending on the severity of sickness, Many of the infants born to drug-abusing mothers do not remain with the parents, which produces an excessive burden on the resources of foster care provider agencies, The National Institute on Drug Abuse (NIDA) has assumed a lead role in supporting research on identifying prenatal effects of drugs of abuse on the behavioral, intellectual, and physical development of these infants and on determining their effects on reproductive outcomes in the addicted mother. Moreover, NIDA is placing an increased emphasis on research related to the prevention and treatment of developmental anomalies induced by drugs of abuse. This research will be helpful in reducing suffering in the lives of babies, families, and society at large.

Methodological difficulties and confounding variables have been impeding progress toward the research goals identified above. It is clear that, in dealing with the special problems of drug dependence, interaction and collaboration among different disciplines should be encouraged-interaction between those who have studied human development for many years and those who are experienced in dealing with the problems associated with drug dependence. Therefore, NIDA sponsored two research technical reviews that focused on the experimental design issues inherent in research into the effects of prenatal exposure to drugs of abuse. The purpose of these technical reviews was to bring together panels of eminent researchers to consider how meaningful data can best be obtained and to identify the kinds of research questions that can be addressed given current technological limitations.

The proceedings of the first technical review, published in another NIDA monograph, were related to the conduct of controlled studies on the effects of prenatal exposure to drugs of abuse.

This monograph represents the proceedings of the second technical review on epidemiological, prevention, and treatment research on the effects of prenatal drug exposure on women and children. The following NIDA staff members participated in its planning and served as associate editors of this monograph: M. Marlyne Kilbey, Ph.D., cochair (Dr. Kilbey also served as science adviser to the Director of NIDA during 1989); Khursheed Asghar, Ph.D., cochair; Coryl L. Jones, Ph.D.; Jag H. Khalsa, Ph.D.; Elizabeth Ft. Rahdert, Ph.D.; Beatrice A. Rouse, Ph.D.; and Vincent Smeriglio, Ph.D.

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Methodological Issues in Prevention Research on Drug Use and Pregnancy

Lewayne D. Gilchrlst and Mary *Rogers Gillmore*

INTRODUCTION

This chapter examines conceptual and methodological issues relevant for future approaches to planning and conducting research to prevent drug-related problems in women and children. It begins with a brief historic overview of prevention strategies and then identifies critical issues in conceptualizing research on prevention of drug-related problems in women and children and the methodological challenges that accompany these conceptual issues.

CURRENT THEORIES AND MODELS OF PREVENTION

A review of drug prevention efforts in this century suggests that the field is following (albeit slowly) developments in heart disease and cancer prevention by moving toward approaches that recognize the complexity of human behavior and the limitations of unidimensional or single-focus strategies for achieving lasting behavior change. During the past 40 years, several different models of prevention have been in use. Virtually all these models emphasize one aspect of human functioning, but none can be said to be based on a realistically holistic view of human behavior (Jones 1990). Prior to 1960, prevention programers assumed that lack of information was the fundamental reason why individuals engaged in health-compromising or -damaging behavior. However, it became clear that providing clear information about consequences was not sufficiently powerful as an intervention to achieve marked or widespread changes in behavior. The next model, called the individual deficiencies model, assumed that some personality deficit (e.g., lack of self-esteem or positive self-image, lack of good values, or the inability to make good decisions) led individuals to engage in behavior harmful to themselves, Empirical tests of preventive interventions focused solely on building self-esteem, and values clarification also suggested that this intervention is not powerful enough to achieve widespread changes in behavior.

The next paradigm to emerge, the social influences model, has wide currency at the present time. Tests of this model dominated prevention research in the 1980s. This model assumes that individuals act in accordance with social pressures and that they can be taught to recognize these pressures and can learn skills to resist these influences. Tests of this model applied to smoking prevention and cardiovascular disease prevention have shown some positive results (Pentz et al. 1989a). Resistance to the social influences model has broadened in recent years to a more inclusive life skills training approach that recognizes that many individuals have not had enough experience to handle complex social or interpersonal situations well. Thus, skills training focuses on a host of issues beyond substance use and abuse. Studies of these skills-building programs show some positive results. However, most tests of these models have occurred in schools and, thus, do not capture the most at-risk individuals, It also appears true that the initially positive effects from skills-building interventions decay rapidly for many individuals once the formal intervention program is over.

A more realistically complex prevention paradigm is emerging in comprehensive, multilevel community development approaches aimed at simultaneously modifying-in mutually reinforcing ways-both individuals and the environments in which they are embedded through coordination of multiple program elements, including mass media; teacher, parent, and student training; and involvement of a spectrum of community leaders in social planning, social action, and advocacy activities (Blackburn et al. 1984; Bracht 1990; Farquhar et al. 1984; Flay 1986; Hawkins et al. 1991; Lasater et al. 1984; Pentz 1986). A variety of principles from communication and social marketing theory, social learning theory, diffusion of innovations theory, and community organization theory are employed in these drug abuse prevention efforts. Current research suggests that there is a generalizable set of procedures for initiating and sustaining effective prevention activities in communities (Bracht 1990). This set of procedures appears applicable across a range of communities, including minority communities. To date, the most complete tests of the community development approach to drug abuse prevention are still in progress. In the past 5 years, the work of Pentz and associates (Pentz et al. 1989a, 1989b, 1989c) and of Hawkins and colleagues (1991) has shown positive results from multiple-element, community-based efforts targeting adolescents and focused specifically on drug abuse prevention.

What the nascent science of prevention still lacks is an integrated theory of change that will encompass individuals and their environmental contexts, Review of the progression of prevention strategies in this century reveals a tension between two philosophies and, indeed, two lines of prevention-relevant investigation: (1) the public health philosophy directed at increasing population-

wide knowledge through mass communication aimed at the largest possible target audience and (2) the clinical-developmental philosophy directed at assessing "where the client is" and then starting an intervention based on that and on understanding the sometimes unique psychological and situational factors that shape individual behavior (Bibace and Walsh 1990). With the public health approach, entire population subgroups are the target audience (e.g., adolescents, women, minorities). Planners rely on broad demographic categorizations to determine program content, and there is an implicit assumption that motivations to use drugs are similar for all members of a targeted demographic group. The clinical-developmental approach, in contrast, assumes that motivation for initial and continued drug use varies substantially "as a function of interindividual and intraindividual differences" (Jones 1990, p. 259). This philosophy assumes the possibility of large differences in motivation and receptivity to intervention even among demographically similar individuals. Researchers and planners with this philosophy place great emphasis on sensitivity to social, psychological, environmental, cultural, and developmental factors that influence individuals' behavior (Baumrind and Moselle 1985). Because the clinical-developmental philosophy seems to call for individualized, time-consuming, and, thus, expensive interventions, this philosophy has not been well employed in drug prevention program development, even though the limited effectiveness of generic public health philosophy strategies is widely recognized.

It is no longer feasible to think in single-cause/single-remedy terms about prevention of drug abuse. With regard to preventive interventions to reduce drug-related problems during and after pregnancy, it seems highly desirable to develop programs that integrate the sensitivity and specificity of clinical-developmental approaches with the efficiency and generalizability of public health approaches. The next section examines potential new directions for integrating these approaches to increase the scope and efficacy of preventive interventions to reduce drug-related damage to women and children.

CONCEPTUAL ISSUES IN PREVENTION RESEARCH

The evolution of specific interventions to prevent drug-produced damage to a developing fetus has barely begun. To better address the goal of reducing drug use before, during, and after pregnancy in women of childbearing age, prevention researchers will need to expand their conceptual horizons in at least three areas. First, there is a need to develop a deeper common understanding of the concept of prevention. Second, clinical-developmental models and theories are needed to better ground prevention program messages and methods in empirically based understanding of the belief and value structures of individuals (women and men) in various population subgroups. Third, if

preventive interventions are to have any lasting effects, better account has to be taken of the broader environments in which target audiences live, and environmental factors in preventive efforts must be enlisted and accounted for rather than ignored.

Defining Prevention In the Context of Pregnancy

One of the thorniest issues related to documenting the impact of preventive interventions relates to establishing common agreement about what constitutes "success." In planning the best approach to prevention, what is the optimal outcome for which one should strive? Should one strive to prevent the onset of drug use among women of childbearing age or focus on the more circumscribed goal of complete abstinence of all drugs during pregnancy? Is merely reducing drug use (as opposed to attaining complete abstinence) during pregnancy a sufficient gain to conclude that a prevention program should be continued or is worth the cost? Is a prevention program a success if, following childbirth, women relapse rapidly to drug use? Program goals are unclear in many current prevention demonstration programs. Goals are stated in general terms-often as general as "some intervention is better than none," and improvement on any of dozens of variables is counted as success. Intervention methods are proposed but not linked to desired outcomes or specific goals. Finally, certain outcome variables are measured, but their relationship to the originally articulated program goal is not identified.

Case management should not be the only preventive intervention relevant to reducing drug-related damage to women and children. If the bottom line is to reduce the number of drug-damaged children born each year, numerous strategies can be used. Efforts can be made to decrease drug use before, during, and after pregnancy in women of childbearing age; to reduce the incidence of pregnancy in drug-using or potentially drug-using sexually active groups; and to reduce drug use during and after pregnancy to minimize (but not eliminate) drug exposure. Therapy programs can be developed to normalize the development (that is, prevent the onset of problems) in drug-exposed children. These various prevention foci or goals reflect the classic nosology of primary, secondary, and tertiary prevention activities.

Prevention program planners could benefit from clearer and more flexible understanding of these different levels and types of prevention. Primary prevention is preventing initial occurrence of any problem; in the present case, this means preventing onset of drug use in women of childbearing age or at least preventing drug use before conception and pregnancy. This primary prevention goal is not addressed in much current programing for women and children. The vast majority of extant studies related to drug use and women

and children take place in health care settings that require that a woman be pregnant to be eligible for study enrollment. At this point, it is too late for primary prevention.

Secondary prevention is the minimization of problems given the existence of the risk factor-use of substances by a woman who is pregnant. Programs designed to reduce or eliminate drug use after conception fall into the secondary prevention category. This category contains the bulk of the studies to date.

Tertiary prevention in classic terminology covers efforts to reduce the impact or disabling consequences of drug exposure on infants. Few empirical studies to date relate to this tertiary prevention goal. In current conceptualizations of preventive interventions, these distinctions among the levels of prevention seem blurred, and this blurriness reduces researchers' effectiveness-first, in isolating important issues for empirical study and, second, in reporting the results from prevention studies in ways that are maximally useful to policymakers and to community-based clinicians and practitioners. Without clarity at this fundamental conceptual level, research on preventive interventions will continue to be seen as fragmented and equivocal, and results from multiple studies will not be meaningfully aggregated. In short, prevention will not advance as a coherent science.

Understanding the Audiences' Beliefs and Values

A second area that needs broader understanding and conceptual clarity is the integration of clinical/developmental knowledge into the planning of preventive interventions. Successful prevention programing rests on accurate understanding of the lives and concerns of targeted program recipients. Numerous studies demonstrate that information alone-that is, providing individuals and communities with facts-has only a small impact on problem behavior. As the advertising industry has shown, understanding the psychological processes involved in individuals' perceptions of events and behavior is central to selecting persuasion techniques that will influence motivation and actual behavior. Without understanding audience beliefs and values, messages and methods intended to persuade individuals to engage in more healthy behavior can be dismissed easily by the intended audience as irrelevant or, worse, as offensive. Three factors appear to strongly influence beliefs and values and, thus, the receipt of potential preventive interventions: gender and gender role socialization, culture and ethnicity, and developmental maturity.

Gender and Gender Role Socialization. Emerging research on the psychology of women and on gender role socialization so far has not been well used to develop new perspectives on tailoring preventive interventions for preventing drug-related harm to women and children. Gilligan and colleagues (Gilligan 1982; Gilligan et al. 1988) present evidence for gender-specific differences in ethics, psychological and interpersonal priorities, and sense of morality. Blechman (1980, 1984), Gilchrist and colleagues (1989), Miller (1986), Beschner and colleagues (1984), and many others present evidence that the method and the content of interventions intended to affect women's behavior should be tailored specifically for women. Prevention program planners need deeper understanding of the beliefs, values, attitudes, feelings, fears, and intentions that shape women's behavior in the realms of sexual activity and drug use. Luker's classic work (Luker 1975) on women's cost-benefit thinking regarding becoming pregnant and carrying a pregnancy to term illustrates the utility of examining decisions and behavior that initially appear irrational or self-destructive from the perspective of individual women's personal values and belief structures.

Culture and Ethnicity. With regard to the importance for prevention programing of understanding culture- and ethnic-specific beliefs and values, Marin's work in analyzing aspects of Hispanic culture that have relevance for acquired immunodeficiency syndrome prevention programing serves as **a** model (Marin 1990; Marin, in press; Marin and Marin 1990). Marin analyzes central aspects of Hispanic culture and how this culture differs from the individualistic-oriented culture of mainstream American society. Examining such cultural values as allocentrism (i.e., other-oriented or collectivistic orientation) and familialism (i.e., the tendency for family members to seek help from each other rather than from outsiders), she concludes that the most effective strategies for preventing drug initiation and reducing current drug use among Hispanics would be those directed toward and involving whole families and communities rather than those focused solely on individuals. Similar cultural analyses have begun with regard to black women's beliefs and values (Flaskerud and Rush 1989; Mays and Cochran 1988). Mays and Cochran recommend health messages for black communities that appeal to a sense of responsibility to others in the community and to ensuring a good future for the other blacks. In most racial subgroups there exists pride in being a member of the group. Can this pride be used to foster healthy babies? There are norms in many minority subcultures that highly prize fertility and childbearing. Can these norms be harnessed in some way to create social censure for parents when infants are born damaged by drugs and to foster community and especially masculine pride in producing drug-free, healthy babies?

Developmental Maturity. With regard to developmental maturity, the work of Biblace and Walsh (1990), Baumrind (1985, 1987), Jordan and O'Grady (1982), and others provides interesting information about the ways in which children and adults fail to understand or fail to make use of widely available educational efforts aimed at improving their own health and well-being. Appreciating the concept of prevention requires a fairly high level of cognitive maturity. Pursuing a developmental approach to prevention program development is not limited to programing aimed at children (Bibace and Walsh 1990). As health psychologists frequently show, many adults commonly rely on immature thinking with respect to the probable harmful consequences of their own cigarette smoking, alcohol consumption, and lifestyle (Stoeckle and Barsky 1980). How do women justify to themselves and to others continued drug use and unprotected intercourse in the face of health promotive information? What techniques can practitioners use to break down these false justifications?

Sensitive understanding of the kinds of personal differences sketched above seems central to improving the acceptability and efficacy of current and potential preventive interventions, There is so little solid information available in these areas that is directly applicable to designing preventive interventions that it is hard to know what questions are relevant,

Understanding Environmental Contexts

The third area requiring conceptual broadening and clarity relates to understanding environmental contexts in which behavior occurs. Environments are important to prevention programers for two reasons. First, interventions, both preventive and remedial, are delivered in the context of environmental institutions and organizational systems, and these systems can become units of interventions. Thus far, the health care system has had most of the responsibility for preventive interventions related to drug use during (but not before or after) pregnancy. There is a need to examine other institutional and organizational opportunities for achieving drug prevention goals (Gilchrist 1990).

Second, environments in the form of systems and social networks exert exceedingly powerful direct and indirect influences on the recipients of a prevention program. There is abundant evidence that individuals have a strong tendency to behave in ways that fit the norms of their social networks (Fisher 1988). When an individual attempts to behave in ways that appear inconsistent with social network values, the networks resist such change and often exert strong antichange influences (Schachter 1951). As prevention programers become more adept at analyzing environments and environmental/situational supports, it may be possible to conclude that it is more effective to address preventive intervention efforts toward people in the target individuals'

environment rather than to address target individuals (in this case, women) directly. Prevention program developers need to ask such questions as: How might parents, peers, and sexual partners of women at risk for drug involvement before, during, and after pregnancy be enlisted as assistants for ensuring infants' health by creating expectations that will keep young women drug free?

RESEARCH METHODOLOGY AND DESIGN ISSUES

The above outline of conceptual issues suggests that there are four types of methodological challenges for prevention researchers: (1) those relevant for carefully defining prevention program goals and outcomes, (2) those relevant for developing valid and feasible assessment tools for collecting critical clinical-developmental information for more productively focusing preventive interventions, (3) those relevant for documenting environmental contexts affecting individual behavior and prevention program implementation, and (4) those relevant for shoring up criticisms that undermine the persuasiveness of current prevention study designs.

Defining Prevention Program Goals and Outcomes

Understanding of the various levels of prevention-primary, secondary, or tertiary-should undergird selection and reporting of specific outcomes. Reporting that a prevention program worked or did not work is less important than carefully documenting how it worked and for whom. In the past, prevention researchers have assumed that the ultimate good to come from their research was **a** treatment manual filled with empirically validated treatment procedures. These manuals-often as specific as scripts-are widely disseminated (or are intended to be so). However, the assumption that a treatment manual is the most valuable result from prevention research needs to be reexamined. Given the gender, cultural, maturational, and community influences that shape human behavior in different ways, what may be most useful to disseminate is an empirically identified process for developing a preventive intervention that when undertaken will produce the most sensitively tailored and most powerful program possible. Such a blueprint for action must contain valid tools or models for assessing key elements at the individual and the community levels. More importantly, this blueprint would outline what to do with each type and level of information to plan the most effective preventive approach.

This view of the best ultimate product for prevention research suggests that much more emphasis than is now the case be placed on analyzing the process of prevention program development and on identifying positive and negative influences on prevention program implementation. Such analyses necessarily will have to deal in detail with political and "climate" issues and sensitive

identification of factors that affect optimal program delivery. Finding solutions to important process problems (such as systematic investigation of methods for keeping clients enrolled in a specific intervention effort) may need to become the legitimate central focus for some prevention research studies.
If researchers take seriously the need to address environmental issues that influence women's behavior, they will have to grapple with how to enroll members of women's social networks in intervention studies. Many women have steady sexual partners, although they may not be legally married to them. Sampling and enrolling couples, families, and possibly extended family networks in prevention-related studies, rather than continually focusing only on individual women, will require creativity, perseverance, and focused study but should be amply rewarding in terms of yielding new knowledge.

Prevention researchers should be encouraged to collect and report process-related data so that eventually meta-analyses might be conducted across studies on process factors similar to the analyses now done on treatment outcomes (Tobler 1986). Methodological challenges involved in documenting program processes also should include dealing with the cost of launching and sustaining programs in given communities. Typically, a cost-benefit analysis is not undertaken when testing an intervention, although such information is central for informing policy decisions. Prevention researchers need to think through how much of a reduction in drug exposure or other targeted outcomes warrants continuation and replication of a given program.

Collecting Relevant Clinical-Developmental Information

Prevention researchers need to develop the conceptual frameworks and, above all, the assessment procedures capable of capturing gender, cultural, maturational, and community organization issues that have high relevance for selecting the most powerful persuasion and intervention strategies. Existing cross-sectional survey techniques may have limited utility for this task. Coordinated ethnographic studies involving multiple investigators, locales, and common goals may be useful in developing an empirically validated understanding of belief and value structures relevant for building persuasive prevention techniques for specifically targeted audiences.

The Theory of Reasoned Action (Fishbein and Ajzen 1975; Ajzen and Fishbein 1980) and the related Theory of Planned Behavior (Ajzen 1985) can be employed as frameworks for analyzing beliefs and values and the patterns in the relationship of these behavioral influences on decisions and behavior (Baker 1988; Davidson and Morrison 1983). The Theory of Reasoned Action considers the affective response to performing a behavior and the perceived social norms about the behavior. This theory has proven useful in

understanding decisions related to sexual behavior but has not been applied often to understanding drug use, particularly among women. The integration of recent advances in social learning theory (e.g., Bandura's concept of self-efficacy) into the Theory of Reasoned Action appears promising. Relevant questions to pursue include the following: What are the values underlying reported voluntary decreases in many women's drug use during pregnancy? How can practitioners capitalize on these values to sustain low drug use rates after pregnancy? Does a woman's sexual partner(s) exert a disproportionally large influence on her use of drugs before and after pregnancy? If so, what is the basis for this influence? How can this influence be manipulated? What protective factors reduce the influence of drug-using sexual partners and peers? How can these factors be strengthened?

The goal of tailoring preventive interventions to fit women's lives and needs will require some creative attention to asking researchable questions that will illuminate important aspects of women's lives. The task also will require better assessment tools than are now available. Using theory to construct and then to test assessment procedures for practitioners to use in identifying important foci for intervention is a viable and useful goal for future prevention research. The goal also suggests that researchers expend more energy not only in tailoring qualitative methods to women's unique needs but also in more fruitfully combining them with traditional quantitative methods (Glanz et al. 1990).

Documenting Environmental Contexts

Prevention research to date has been so focused on treatment techniques for individuals that the field hardly has the terminology available to discuss environmental contexts that include service system characteristics. There is some evidence that the way whole service systems are constructed greatly affects and can limit the possible effects of an intervention. Mental health researchers have gone farther than drug researchers in defining and studying organizational environments and how such environments affect program delivery and patient outcome (Morrissey et al. 1982). Currently, there Is great need for drug prevention practitioners and researchers to develop common and explicit definitions of such terms as "case management" and "outreach" so that these intervention processes can be studied in valid and reliable ways. Here again, mental health/mental illness research may be of assistance (Harris and Bachrach 1988).

Research Methodology Issues

Design Issues. Methodological challenges in the more conventional sense for future prevention research involve finding feasible designs for documenting the

impact of prevention programs. The most convincing evidence of any intervention's effectiveness comes from a true experimental design where subjects are randomly assigned to conditions. However, true experimental designs often are not practical and sometimes are ethically questionable. The wait-list control group strategy can be problematic because treatment must be offered to wait-listed individuals within a reasonable period following their recruitment into a study. This "reasonable period" often does not allow for a long enough followup period for drawing valid conclusions about the preventive effects of an intervention, A more viable design strategy is to compare the relative efficacy of two or more prevention strategies, randomly assigning study participants to different (carefully defined) intervention conditions. In this way, all patients/clients/study participants receive treatment, yet random assignment allows more confidence in drawing conclusions about the relative effectiveness of different treatment approaches.

Where random assignment to conditions is clearly not possible, researchers might be more creative in combining features of more than one type of quasi-experimental design to offset some of the threats to internal validity that occur with a single design. Finding a comparable "nonequivalent" control group is the most challenging aspect of quasi-experimental designs. Researchers often match experimental and control groups on the basis of demographic characteristics without any thought as to why those particular characteristics, as opposed to some others, should be the basis for matching. If differences in these demographic characteristics cannot plausibly account for any differences observed between groups on the key dependent variables, then it makes no sense to match on them. Good matching and good choice of a control group requires considerable knowledge about the phenomenon of interest. Recently, some investigators have embedded evaluation experiments on specific interventions within longitudinal survey designs (e.g., Hawkins et al. 1991). This strategy has strong appeal in that the longitudinal data can be used to test hypotheses about factors that predict drug use before, during, and after pregnancy, while at the same time, the evaluation experiment, if carefully conducted, can provide information about intervention effectiveness. The longitudinal data then can be used to assess the long-term effects and the conditions related to success of the intervention.

Data Analysis Issues. If more complex prevention theories and research designs are developed, more complex analysis strategies will be needed to evaluate them. Clearly, multivariate analyses are warranted in which the effects of several variables are taken into account simultaneously. Structural equation modeling appears particularly promising, although it is not a panacea and should be judiciously employed with careful attention to sample size and underlying assumptions. There are three areas in which structural equation

modeling appears particularly useful. First, structural equation modeling is a useful alternative to the traditional analysis of covariance for evaluating the effectiveness of an intervention in a quasi-experimental design. Threats to internal validity can be incorporated explicitly in the model, and the unreliability of measures-which can result in bias when applying the analysis of covariance-is taken into account. With longitudinal data, or designs with pretest and posttest measures, the possibility of correlated error can be examined and, if found, can be explicitly incorporated into the model, thus eliminating a potential source of bias.

Second, structural equation modeling is useful for evaluating "causal" models in which the indirect and direct effects of variables specified by theory are taken into account. It is superior to path analysis in that the unreliability of measures recognized in estimating the model and correlated error that normally represents a threat to validity can be explicitly incorporated in the model. And third, structural equation modeling provides a statistical means to test whether the same model explains drug use equally well for subpopulations such as persons from different ethnic and racial backgrounds. Although infrequently done, structural equation modeling is also useful in evaluating the outcomes of true experiments, especially with regard to detecting flaws in the experiment (Costner 1985; Hawkins et al. 1991).

Finally, even in the best designed studies, some subjects will be lost to attrition. Recent methodological advances have yielded analysis strategies in addition to structural equation modeling to deal with sample selection bias that can be applied to correct for biases due to attrition. Since attrition poses a serious threat to internal validity, such procedures should be considered when analyzing data from studies of intervention effectiveness. The key ideas can be found in the econometrics literature (Heckman 1976; Goldberger 1981); for a less technical explanation and example of an application, Berk's (1983) article is useful. In sum, directions for sophisticated and complex analyses to improve evaluations of prevention programs currently exist. The challenge is to equip individuals who are committed to drug prevention with these skills. This speaks to the need for research training programs and to fostering what the National Institute of Mental Health calls "public-academic liaisons," where community systems experts and community-based practitioners closely collaborate with university-based statisticians and research specialists.

CONCLUSION

The most expeditious direction for growth in research on prevention of drug-related harm to infants might be accomplished by research in which community-based practitioners conduct clinical-developmental assessments-incorporating

attention to gender, culture, ethnicity, and developmental maturity-of carefully defined target communities or social networks of related individuals within carefully defined communities and organizations. This empirical assessment of salient beliefs and values would be incorporated into carefully planned, individually tailored, multifaceted, multisystem, "locally owned," public health-style community or network development campaigns. The goal would be for interventive efforts at the individual and at the community or network level to trigger, support, and reinforce each other to reduce drug-related damage at least to children, if not to all network members. The responsibility for initiating this assessment, planning, and intervention process need not fall solely on health care workers. The following are critical questions to be addressed with this effort: Can valid and workable assessment protocols be developed so that professionals in any community system can use them to begin local, antidrug community development efforts? Can community development strategies that have proven successful in heart and cancer prevention research be used to mobilize and shape values and behavior change in apparently diffuse and disorganized high-risk communities and social networks? What modifications will need to be made in existing community development strategies to maximize the participation of high-risk communities and networks?

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Measurement Issues in the Evaluation of Experimental Treatment Interventions

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INTRODUCTION

Drug abuse among expectant mothers is perhaps the most expensive, complex, and pernicious health care problem of this era. The multiple questions associated with prevention and treatment of drug abuse by the mother, as well as the even more complex questions of drug effects on the development of the child, require years of methodologically sound research. The purpose of this chapter is to outline some of the methodological questions and possible solutions in performing this type of research. The author discusses methodological issues developed through work in the field of treatment evaluation that may be useful to those performing similar types of studies within the perinatal addiction field.

This chapter focuses on issues of patient and treatment measurement that would be encountered in an evaluation of an experimental treatment or a novel therapeutic program. The first part of the chapter deals with the rationale and methods associated with collecting patient information at the start of a treatment intervention; the middle part deals with the measurement of the intervention; and the last part deals with the rationale for and the methodological issues in measuring patient outcome following an intervention.

MEASUREMENT AT BASELINE

Purposes of Patient Evaluation at Baseline

There are clinical and research reasons for measuring patients at the start of a treatment intervention. First, it is important to be able to describe the current and past status of the patient along a variety of dimensions that will be relevant for clinical and research decisions. For example, it will be necessary to get some sense of chronicity of the presenting problems, indications of the severity

of comorbid problems, and characteristics associated with suitability for the research studies for which the patient may be qualified. Second, it is important to collect information that will be useful in the establishment of a treatment plan and the setting of reasonable treatment goals, Finally, these initial measures that are taken at the start of an intervention also will serve as the baseline against which future comparisons can be made. This will be the basis for evaluations of improvement and outcome in the patients and, thereby, the evaluation of the efficacy of the intervention.

An important conceptual point that should be considered at this time (and will be reemphasized in all parts of the chapter) is that it is essential to form a reasonable expectation of what the proposed treatment intervention should be able to achieve in the target patient population in realistic, measurable terms. Perhaps the most common problem in the design and conduct of treatment evaluations occurs at the start of the process where an investigator fails to develop realistic, measurable objectives for the treatment. This, in turn, produces a failure to select patients who have appropriate constellations of problems that realistically can be affected by the intervention, a failure to measure the selected patients on those aspects of the target problem that are expected to change, and a failure to allocate adequate time and resources to fully implement the treatment in sufficient quantity and intensity to produce the desired changes.

Methods of Patient Measurement at Baseline

With regard to the methods that can be used for measuring patients at the time of treatment admission, there are three types and all should be considered in a thorough evaluation. Each type of measure has its strengths and limitations.

Interview. This is a time-consuming and relatively expensive method of collecting information from a patient. Also, there is a possibility of interviewer bias and interviewer error in the collection of information. At the same time, the interview is a personal and clinically engaging method of beginning an interaction with a patient and can be an important consideration in treatment studies where patient retention and patient compliance issues will be significant determinants of the overall efficacy of the intervention. Furthermore, given adequate training and practice, an interview can be an excellent method for ensuring that a patient understands the intent of the questions that are asked, thus maximizing the validity of the reported data.

Questionnaire. This is a rapid, easily administered, inexpensive method for collecting information, However, it is impersonal and can produce questionable results in situations where the specific questions are not easily understood by

the patients or where the reading level of the patients is in question. At the same time, computerized questionnaires can offer a rapid, engaging, and private environment for patients to answer questions that can be understood easily and that lead to clear, unambiguous answers.

Objective Measures. Laboratory-based objective measures include breath and urine samples for drug and alcohol use as well as physical examinations and laboratory test data for other health care problems. These measures have the obvious advantage that they cannot usually be distorted by the patient, but it is important to point out that even these measures are sensitive to methods of collection and methods of analysis. Supervised observation of urine and breath samples is really the only way to ensure that these measures will be valid. In addition, there are many methods of analysis for these tests, and they may vary substantially in sensitivity and cost,

TIme Intervals to Measure

In the collection of the initial baseline data, it is important to remember the subsequent purposes of the information. As indicated, the first purpose of the data often will be to develop an overall assessment of the nature and severity of the patient's condition for treatment purposes. This, in turn, means that problematic behaviors or conditions should be assessed over the entire life of the patient, since the onset and chronicity of problems likely will be an important factor in treatment decisions and possibly in predicting outcome. At the same time, the investigator will want to be able to assess progress and outcome at the subsequent followup points, and this will not be possible if only lifetime measures are taken at baseline. For this reason, the investigator should select a "time window" that will serve as a measure of the recent status of the patient and will serve as a comparison point for future followup measures.

Again, there is no single time interval that is ideal. The factors that go into the selection include the memory limits of the patient (Can she remember the past year, 6 months, or 30 days accurately?) and the needs of the evaluation study. For example, if the time window of measurement is the past 6 months and the investigator wishes to measure improvement, then it will not be possible to do a 1- or a 3-month followup since the intervals will not be comparable. The first followup point will have to be at the 6-month point. Again, while there is no single preferred interval, many investigators have chosen to measure the patient's behaviors during the previous 30 days since it represents a period that is usually (but not always) representative of their lives during the time before treatment admission. Most patients can remember the past 30 days with acceptable accuracy, and this interval enables multiple followup measures (e.g., 1-, 3-, 6-, 12-month followup).

Validity of Measurement

Regardless of the method(s) used, two important issues are reliability and validity of the information that is collected. It is important to note in this regard that absolute validity does not exist. Rather, there are conditions under which validity is going to be maximized, and conversely, conditions that will minimize accuracy of reporting and the ability of the patient to understand or to give accurate information. For example, timing is an extremely important issue with regard to validity. Often, the initial contact with a patient, usually at the time of admission, is not a good time to collect information. First, the patient may be reluctant to provide information without having some assurance that her needs will be met. Second, there may be issues of instability, perhaps due to drug detoxification, withdrawal, or even intoxication effects,

A second important issue with regard to validity is the confidentiality of information. This is of particular concern and, often, especially difficult with regard to the pregnant drug abuser. It is important to be able to know the limits under which the confidentiality of the information collected can be maintained. These limitations are often subject to State and local agreements with prosecutors and human services personnel, and these agreements are important to negotiate before the initiation of the research. For example, it is often (but not always) the case that mothers with drug problems may enter treatment programs and provide complete, candid information that will not be subpoenaed. Furthermore, it is sometimes (but not always) the case that potential charges (e.g., child neglect and abuse) are suspended or not carried forward pending satisfactory participation in treatment. These issues of confidentiality will be important to discuss candidly with the prospective subject at the same time she consents to participate in the study.

It is also possible to maximize the validity of information collected if the subject can clearly understand the purpose of the information. When the information collected can serve the mutual purposes of the patient and the research and clinical staff, the patient can see it is in her interest to provide accurate, valid information. Another major factor in the collection of valid information concerns the interpersonal conditions under which the information is collected. An interviewer should convey a legitimate interest and concern for the patient and her child. It is critical to develop an interpersonal rapport during the course of patient interviews, The interview and all other data collection should be done in a quiet, private setting that will promote concentration and reflection. To the maximal extent possible, it should be stressed to the woman that complete and candid answers will not negatively affect the services or treatments she could receive from the program. This is best done under conditions where a prospective client has voluntarily come to a treatment organization seeking

services. Less than optimal are criminal or judicial situations where judgments are likely to be rendered based on the data collected in the interview. Under these conditions, collecting information as part of intake into a criminal justice intervention is particularly difficult. It is often difficult to have faith in information given by individuals who know their answers will determine their sentence and/or fine. There is no satisfactory method of ensuring validity under these conditions. It is much more likely that valid information can be obtained in a treatment situation where the interests of the patients in obtaining services are consistent with the interests of the researchers and clinicians in getting accurate data.

Continuous vs. Categorical Data

Regardless of the methods used for collecting data, it is important to utilize measures of patient status and behavior that can indicate change from baseline, through treatment, to the posttreatment followup period. For example, rather than ask "if' a patient has used alcohol in the week before admission (i.e., a yes-no categorical measure), it is much better to ask how many days the patient has used alcohol in that week and/or how many absolute ounces of alcohol have been drunk on a typical drinking occasion (i.e., measures that vary on a continuum from 0 upwards). These measures can always be reduced later into discrete categories, but the availability of continuous measures provides the investigator much greater sensitivity of measurement and the opportunity to use more powerful statistical techniques in the analysis of the data. For example, in the question of drinking during the prior week, it is possible that a subject would report, "Yes, I drank every day," at the start of treatment, but, "Yes, I drank only 1 day," by the end of treatment. The categorical measure of this variable (i.e., Did you drink during the past week-yes/no?) would fail to capture the change that occurred following treatment.

Summary

At the time of admission, several factors are important in the collection of information from patients. First, it is important to use multiple types of measures, including interview, questionnaire, and objective laboratory test information. Each of these types of measures not only has clear strengths but also has some limitations. Second, it is important to maximize the likelihood of obtaining valid information by making sure that the patient is able to understand the nature of the questions asked and by developing conditions under which the patient can feel safe and assured that the information provided can be handled in a professional way with the greatest protection of confidentiality. Third, it is equally important to measure the behaviors and qualities of the patient that will be the focus of the interventions to be provided. In this regard, it is crucial to be

clear from the very beginning exactly what aspects of the patient you feel the intervention can realistically change (e.g., attitudes about drug use, alcohol use, substance abuse-related behaviors, health service utilization, etc.).

MEASUREMENT OF TREATMENT INTERVENTION

Purpose of Treatment Measurement

It is no longer adequate in a research design to state only that a particular type of intervention will be provided and that this intervention will be compared against "standard treatment" or "a placebo condition." It is essential to use the same care and effort in measuring the treatment provided as that used in measuring the patient. This is particularly important in the case where the intervention is found to be successful. Accurate measures of the nature and extent to which the treatment is provided will enable subsequent workers in the field to accurately reproduce the intervention and, with it, the positive results.

Treatment measurement is also important for determining whether the results that are seen at followup are due to the effects of the intervention or to some external factor. It often has been the case in treatment evaluation studies that a certain type of treatment has been delivered to patients followed by assessments of drug use or other outcomes 6 months after the end of the intervention. When favorable outcomes have been seen, these good results have been attributed to the behavioral intervention. Without knowing whether the patients have achieved (or even made progress on) the goals of the treatment during the treatment process or whether those who received the "full amount" of treatment did better than those who received little care, it is not possible to conclude that the results are due to that treatment.

Methods of Treatment Measurement

There are quantitative and qualitative measures of treatment. Quantitative *measures* of treatment provide **a** record of how much of each type of service or intervention has been received by the patient. This is important in ensuring that an "intensive, experimental treatment" provides more treatment services and/or sessions than the "control condition" or "treatment as usual."

Qualitative measures of treatment provide indications of whether the treatment was implemented in the intended manner and whether it achieved its intended goals. Given two-stage treatments such as detoxification followed by rehabilitation, or education followed by skill training, it is essential to be sure that the objectives of the first stage (e.g., complete detoxification, full understanding of educational material) have been achieved before initiation of the second stage.

It is often necessary to combine these types of measures, as in the case of multicomponent treatment interventions such as those involving social services, medical care, pharmacological therapies, and, perhaps, with behavioral or skill training techniques. Quantitative evaluation of the components through measurement of the number and types of sessions on a weekly basis can be combined with equally important qualitative measures of the patient's opinions regarding the treatments and staff ratings of the patient's progress through treatment. Combined quantitative and qualitative measures, such as whether the patient has received the amount and duration of the intended treatment and whether that was what she expected, can be important for addressing issues of dropout and treatment retention.

It is important to evaluate the patient with interim measures throughout the course of the treatment intervention, again taking care to target those aspects of the patient that can reasonably be expected to change. For example, regular urinalysis and breathalyzer results can be recorded on a weekly or even daily basis. This is an objective record of patient change and an important dimension throughout the course of treatment. This can be combined with regular assessments of patient knowledge in interventions where the effort is designed to teach the patient about drug use or some other aspect of health care.

These quantitative and qualitative measures applied throughout the course of treatment also can help in the assessment of whether patients have achieved the target goals of treatment. If a treatment is a pharmacologic intervention designed to achieve a target blood level of a medication, it is important to determine exactly how many patients achieved that blood level. If the treatment under study is a behavioral intervention and it is expected that the intervention will be able to teach a patient a new strategy dealing with the problem, it will be critical to determine how many patients learned how to perform the skill by the end of the intervention, prior to assessing outcome. Finally, even in standard drug abuse treatment programs where one of the critical goals is the confrontation of denial, it is important to determine how many patients reduced or eliminated their denial by the end of the treatment.

Techniques of Intervention Measurement

As in the measurement of the patient, it is important to measure multiple dimensions of the treatment intervention using multiple methods of assessment. For example, a simple chart review should provide a quantitative measure of the number of sessions attended. It is possible to ask the patient and/or the treatment provider directly, on a regular basis, how many sessions or services have been received. It is also possible to get qualitative judgments by

independent raters regarding the progress of patients along critical dimensions (e.g., understanding what drugs can do to health, acceptance of addiction, participation in group therapy) during the course of treatment. In addition, it is essential to get measures of alcohol and drug use through objective laboratory tests throughout the course of treatment.

Summary

It is as important to measure the nature and quantity of treatments provided as it is to measure the patients. As in the case of patient measurement, multiple methods are available and suggested: quantitative assessment of the number, intensity, and duration of treatment services provided to patients; and qualitative measures of the extent to which the goals of treatment have been met, the patient's satisfaction with the intervention, and the extent to which the intervention was delivered as intended. These measures will ensure that the interventions studied are delivered in the manner, amount, and intensity necessary to effect the desired changes, Again, it is essential to develop a clear idea of what the treatment realistically ought to be able to accomplish by the end of the intervention. This will be helpful in constructing treatments of appropriate duration, intensity, and focus, It is often the case that interventions are designed to achieve detoxification, patient education, reduction of denial, and the learning of relapse prevention skills. However, the patient population often has multiple problems (drug use, health care issues, psychiatric problems, pregnancy), and the treatment is designed for delivery within a 28-day period. Complicating this immediate problem of overexpectation on the part of the investigator can be the additional problems that the intervention is improperly applied for only a fraction of the time intended and without measures of the progress of the patient during the course of the treatment. This inadequately applied and evaluated intervention often is followed by a 12-month followup with the expectation on the part of the investigator that there will be significant and broad behavioral changes among participating patients. This is truly unrealistic and unfair to a treatment intervention. It is far better to determine realistically what an intervention can do, develop a realistic expectation of the duration and intensity of treatment required to produce the desired change, and then construct measures of the specific behavioral attitudinal factors that are expected to be changed.

POSTTREATMENT FOLLOWUP

Purpose of Followup

The ultimate measure of the efficacy of a treatment intervention is the outcome of the patients receiving the intervention, following its completion. Two types of

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measures are possible at followup. First, improvement from the baseline can be measured through a simple comparison of the experimental group from the baseline to the followup point. Obviously, to achieve this, it will be important to ask the same questions at followup as were asked at the time of treatment admission. This is why so much preparation and thought should go into the initial assessment.

A second measure available at followup is an assessment of the overall status of the patient following treatment (i.e., her outcome) relative to either an absolute goal set before treatment (e.g., abstinence, employment, not being in jail) or against the outcome of a matched control group (i.e., a group of similar patients who have not had the same intervention).

It is important to note that these two kinds of measures are different. Improvement is not the same as outcome. A patient may show a 50-percent "improvement" in drug use from admission to followup but still not have achieved the desired "outcome" of total abstinence. Therefore, it is important to be able to assess both measures for a comprehensive evaluation. Again, in this regard, the use of continuous variables as measures will be extremely helpful for both purposes.

Measurement Issues In Followup

The first issue is that the evaluator at the followup point must be independent of the *treatment process.* A followup evaluation where the person collecting the information was part of the treatment process will not be taken seriously. It is not possible for that person to be completely objective, nor is it possible in most cases for the patients to provide truly accurate answers to a person they have been in treatment with for many months. Thus, it will be important to have independent staff to track and interview these patients.

Another important issue is the length of followup. *There is no standard followup assessment point.* The point following the completion of treatment at which a patient should be assessed is almost entirely a function of the expectations about the effects of the intervention under study. It is pointless to do a 1 P-month followup on a brief, limited intervention such as a detoxification procedure when it is expected that the detoxification will not by itself have long-term consequences and likely will be followed by other interventions. Here, the "real" expectations of the detoxification are that:

- The procedure will safely reduce the drug levels in the patient. (Thus, drug levels and detoxification side effects should be measured daily.)

- The patient will be engaged in treatment. (Thus, dropout levels will be important.)

  The patient will accept referral to ongoing rehabilitation. (Thus, the proportion of patients who accept and remain in rehabilitation for 2 weeks or more would be an example of one appropriate followup measure.) Obviously, longer and more involved treatments will require longer term followup contacts. However, even here, a majority of relapses to drug and alcohol dependence occur within the first 3 months following completion of care. Therefore, even in long-term followup studies, it is wise to include intermediate followup measurement points at 3 and/or 6 months following treatment.

Locating and Contacting Patients at Followup

Perhaps the most important aspect of followup is the tracking and locating of patients. The success of a *posttreatment* followup is almost entirely a function of the preparation and effort employed *during treatment.* It is critical to state that followup efforts cannot be initiated after the patient has left treatment; they must be started at the time of admission and must involve the patient throughout the treatment.

Steps In Preparing the Patient for Followup. There are several systematic steps that must be undertaken to prepare for a followup evaluation. First, the patient should be told at admission and throughout treatment that a followup assessment will be performed. The patient should sign a consent to permit followup at that time. At the time of admission, the patient should be asked to provide the names and addresses of at least three separate persons who will know her location at the time of the followup. It should be stressed to the patient that these sources will be used only to help locate the patient and that no information will be provided to the three contact persons or to any other individual or agency without her consent. In the author's experience, female sources are more reliable and stable sources of patient contact than male sources. Thus, at least one of these names and addresses should be a mother, sister, aunt, or close woman friend. Once these names and numbers are provided, it is important for followup technicians to verify the telephone numbers and addresses while the patient is in treatment. Often, false information is provided at that time, and this can be brought back to the patient and corrected with a reaffirmation of the confidentiality.

It also will be important at the same time to collect any information about sources of money or other benefits or services that the patient may be expecting to receive following treatment. For example, addresses where

welfare, Social Security, veterans' benefits, payroll, and/or unemployment checks will be mailed will be important to record. Similarly, it is important to record the full name and address of the patient's social worker or caseworker at the welfare office, as well as names and addresses of people in the Social Security or the parole or probation office with whom the patient has had contact. These are the kinds of contacts that are likely to know the whereabouts of the patient at followup. The patient should be asked to sign a "release of information" form to those people and those agencies early in the course of the treatment, and again, these sources should be called and verified and the followup worker should inform (where possible) the individuals at these agencies that they will be recontacted at followup for help in locating the patient. This followup information should be checked again at the time of treatment discharge to detect any changes and as a reminder of the followup contact that will occur subsequently.

A final issue regarding the preparation of the patient is the use of financial incentives. Please remember that followup can be a lengthy and intrusive process and unless there is something "in it" for the patient, the investigator cannot always be assured of cooperation. Therefore, the author and colleagues always have found it is essential to provide a minimum of $20 and sometimes as much as $50 to patients to defray their transportation costs and to compensate them for their time associated with coming in and providing with information. This is an excellent investment in that, without the followup information, virtually all the baseline and during-treatment measures will be of little value. The patient should be reminded of the followup financial incentive at the time of treatment discharge and at the beginning of each followup contact effort.

Staff Preparatlon. A second area of preparation involves the institution of standard procedures among research or project staff members. For example, the staff must prepare a log sheet on which the date, day, time of day, and a space for comments are listed for each patient to be contacted. Each contact attempt (telephone call, visit, letter) to anyone associated with the patient must be recorded with ample notation documenting exactly who was contacted, the result of the contact, and the plan for the next contact. This will prevent calls to only one number or repeated contacts at times when it is clear that no one is at home.

It will be important for the research project to have a separate telephone that can accept collect telephone calls from patients. In addition, it will be important to hire staff people who can work flexible hours. It is not possible to do patient followup from "nine to five." It is necessary to have staff members who can work evening and/or late night hours and on weekends. In addition, it will be

important to develop a telephone manner that will ensure confidentiality. That is, the followup telephone must be answered by all personnel in a manner that will convey professionalism and at the same time will not convey any association with alcohol or drug abuse (e.g., "Hello, may I help you?" rather than "Perinatal Drug Research, can I help you?"). Furthermore, the staff must be trained to request information from agencies and relatives of the patient but *nor to provide information* about the patient.

Agency Preparation. It is important to have the backing of the funding agency or agencies, local government agencies, and the sponsoring institution (e.g., a university or hospital). It also will be important to have letters from each of these organizations officially underwriting the followup effort (without identifying it as a drug or alcohol abuse effort), thereby legitimizing the activity. Remember that many people are trying to contact these patients. For this reason, concerned relatives and the other social service agencies will not provide information unless they know that it is a legitimate inquiry (as indicated by these letters) and that it is permitted by the patient (the release of information signed by the patient will help in this regard).

Collateral Informatlon. There have been suggestions regarding the use of collateral information, which is information about the patient provided by an employer, spouse, or some other member of the family or social network. Some investigators in the field do not accept patient reports and seek to confirm the reported data with the reports from "more trusted" collateral sources such as a spouse. This can produce many problems. First, it is rare that a spouse knows detailed information about the patient. Patients often report (under conditions of confidentiality) more alcohol, drug use, and crime than the spouse knows about. Second, the use of collateral information risks the confidentiality of the patient, and this is important in securing the patient's cooperation. It is most important to assure patients that no agency or individual will learn any information about them from the followup effort. Finally, even though consistently reliable information has been provided at followup by using technicians who are not part of the treatment process and by ensuring patient confidentiality, it is wise to obtain breath and urine samples on subjects to confirm these reports.

Summary

The final discussion of followup measurement highlights earlier discussions of patient and treatment measurement. Followup is the best assessment of the efficacy of a treatment intervention. Therefore, it is critical to have a clear set of baseline measures on the patient in those areas that are expected to be able to improve with the intervention and to repeat these measures at followup to assess improvement and outcome.

The measures that are collected at followup are essentially identical to the measures that were collected at the time of treatment admission but in abbreviated form. However, the same methodological issues, techniques, and considerations apply. As at the time of the initial assessment, the patient should be measured in all those areas that are expected to be changed, the patient should be assessed with multiple methods (interview questionnaire and objective laboratory data), and all care should be taken to assure the patient that the information will be treated in a professional manner and that her privacy and confidentiality will be protected.

An effective posttreatment evaluation requires effective tracking, locating, and reinterviewing each patient following treatment. The ability to recontact these patients after treatment is almost entirely dependent on the level of information, patient preparation, and interagency cooperation established during the time the patient was in treatment. Followup is an important but difficult job that must be coordinated from the very start of treatment and must involve the patient, followup staff, clinical program, and sponsoring agency or agencies.

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Discussion: Statistical Analysis in Treatment and Prevention Program Evaluation

Joel W. Ager

INTRODUCTION

This chapter focuses on problems of statistical analysis in the context of evaluations of substance abuse treatment and prevention programs. In another chapter (this volume), Sokol and colleagues address additional statistical issues in the context of research that studies the antecedents and/or consequences of substance abuse (particularly of alcohol) during pregnancy. Of course, appropriate statistical analysis depends heavily on other aspects of the research, including the specific questions asked; the theories, if any, generating these questions; the sampling schemes for inclusion of subjects, situations, and variables: the psychometric properties of the variables: and the designs used. This chapter also comments on implications for analyses of issues discussed in the chapters by Gilchrist and Gillmore and by McLellan.

The statistical and design issues to be discussed fall under four major headings:

1. Types of designs and their associated statistical analyses
2. Covariance and other adjustment techniques in analyses of quasi-experimental design data
3. Modeling change
4. Meta-analysis

STATISTICAL AND DESIGN ISSUES

Types of Designs and Associated Statistical Analyses

Completely Randomized and Randomized Blocks Designs Usually WIth Repeated Measures. In most treatment and prevention program evaluations,

pretest, posttest, and followup data will be obtained. The major differences among designs will be in how subjects are selected and then assigned to treatment and control conditions. The ideal, of course, would be to assign subjects to conditions randomly. The great advantages of completely randomized or randomized blocks designs are well known and need not be elaborated here. For ethical, logistic, or other reasons such random assignment often is not deemed possible. However, the investigator should not overlook the possibilities of random assignment of intact groups (e.g., clinic sites or civic subgroups) to treatments when such subgroups are sufficiently numerous. Most problems in the statistical analysis and interpretation of results occur because randomization was not possible.

When randomization of subjects to treatments is possible, it is almost always desirable also to stratify on factors (e.g., age, gender, race) that might be expected to be related to the outcome(s). There are two major reasons for stratifying. One is the increase in statistical power as a result of smaller within-cell variances. The other, perhaps more important, reason is the ability to assess block by treatment interaction effects. Significant interactions, particularly those of a higher order, may be inconvenient to interpret, but at least they provide a warning about the generalizability of the main and lower order interaction effects. Grant reviewers and others often object that such stratification makes the design too complex or that the resulting cell sizes become too small. On the contrary, power for main effects tends to be higher-not lower-with more refined stratification because the smaller mean square error more than offsets loss of degrees of freedom (df) for error. As noted above, stratification also makes possible better assessment of the degree of generality of the treatment effects.

Corresponding to stratification of subjects is the breakdown of treatments into components. If facets of the treatments are identified, they usually can be arranged in a factorial or in fractional replications layout so that the effects of these facets and their combinations can be assessed. In this context, theories of treatments can make specific contributions (Lipsey 1990). Analyses of data from such designs can be extremely useful in answering questions concerning why and how treatments work or fail to work. When costs can be attached to facet levels, a good basis for cost-benefit analysis should be available from data generated by such designs.

The Regression-Discontinuity Design. When randomization of subjects or units to treatments is not possible, what are the alternatives? A little-used treatment that seems to hold much promise is the regression-discontinuity design (Cook and Campbell 1979; Trochim 1984, 1990). In this design, selection of the subjects for the treatments is made on the basis of a pretest;

only subjects scoring above (or below) the cutoff are selected into the treatment. The pretest need not be the same variable as the outcome but presumably is related to it. The treatment effect then is represented as the difference between groups on the regression surface evaluated at the cutting point on the pretest. Variations of the design are possible; for example, the pretest could be a composite of several selection variables (Trochim 1990). Also, in theory at least, it should be possible to assign the selected subjects randomly to several treatments or treatment combinations.

Analysis of this design can be quite complex. The most difficult task is determining the appropriate regression surface. One suggestion is to use polynomial fitting (including polynomial term by group interactions) using a backward elimination procedure. Visual inspection of scatter-plots of the pretest/posttest relationship also is advocated. Problems can occur when the cutting point on the pretest is not reliably or consistently used in the selection procedure. Also, compared with the sample-randomized design, the statistical power of this design is considerably less; at least 2.75 times as many subjects are needed to give comparable power.

Despite its complexity of analysis and relative lack of power, the regression-discontinuity design has inherent advantages over the nonequivalent groups design even when the latter is analyzed with covariate adjustments. The main advantage is that the internal validity of this design approaches that of the randomized design because the subject selection process is fully known. This design probably should be used more often than it is in situations in which treatment is assigned on the basis of pretest scores.

Adjusting for Selectlon Bias in Nonequivalent Group Designs

Methods of Adjustment. Of all the variations in quasi-experimental designs discussed by Cook and Campbell (1979), the one that probably is used most frequently in evaluations of treatment programs is that involving pretest/posttest measures on nonequivalent treatment and control groups. There is an extensive literature (e.g., Cook and Campbell 1979) on selection and other biases inherent with this design and the consequent problems of interpretation. In practice, these biases may lead to either overestimates or underestimates of treatment effects. Several statistical and/or design methods can be used to minimize such biases: analysis of covariance (ANCOVA), block and matching design, and gain-score analysis. However, none of these is completely satisfactory in eliminating bias.

A major problem with the use of ANCOVA to adjust for initial group differences is that of unreliability of the covariate, even when pretest scores are available to

serve as the covariate. Such unreliability will result in underadjustment of the posttest scores, which in turn leads to bias in estimating the treatment effects. Depending on initial group differences, the bias may be in either direction (i.e., overstating or understating of treatment effects).

As Gilchrist and Gillmore (this volume) point out, use of structural models (e.g., LISREL) (Jöreskog and Sörborn 1979, 1984) has been suggested as a way of eliminating effects of covariate unreliability on estimation of treatment effects. In these nodels, pretest and posttest variables are represented by latent constructs. Each construct is measured by several manifest (observed) variables. Because the measurement model part of the LISREL analysis accounts for unreliability, the constructs can be assumed to be perfectly reliable. LISREL and other structural models (e.g., Bentler 1985) have had fairly extensive use in recent years, particularly in the social sciences. Few studies, however, have applied these models to the problem of evaluating treatment effects in quasi-experimental designs. As Gilchrist and Gillmore point out, this approach appears promising and may be more widely used as investigators become more acquainted with these structural models and trained in their use.

Sensitivity Analysis. Model specificaiton is another problem with the use of covariance adjustments in dealing with selection or attrition biases. If all relevant covariates are not included in the model, then underadjustment will result. Moreover, inconsistencies across studies or even within analyses of the same study may occur if different covariate sets are used. Wainer (1989) gives several examples of such inconsistent analyses in his recent paper, “Eelworms, Bullet Holes and Geraldine Ferraro: Some Problems With Statistical Adjustment and Some Solutions.”

As Gilchrist and Gillmore suggest in their chapter, several sophisticated model-based procedures-some of which are discussed by Wainer (1989)—have been proposed recently that are designed to address the problems of nonresponse and self-selection. Among these are Rubin’s Mixture Model (Rubin 1987) and Heckman’s Selection Model (Heckman and Robb 1986). The purpose of these techniques is to evaluate the robustness of the findings (e.g., treatment effects) over a set of plausible assumptions about distributions of the relevant variables in the nonobserved sample. These “sensitivity” analysis procedures do not guarantee definitive answers to the adjustment problem but allow uncertainties to be more accurately characterized. A good introduction to these methods is found in a set of discussion papers based on the Wainer article that constitute the summer 1989 issue of the *Journal of Educational Statistics.* (These methods are difficult to use, particularly for those unfamiliar with Baysian statistics.)

The Two Groups Pre-Post Score Design. As with covariance adjustment, use of gain scores to adjust for selection factors on the evaluation of treatment effects in quasi-experimental design has been strongly criticized, beginning with the work of Lord (1958) in the late 1950s. In their widely cited paper on this issue, Cronbach and Furby (1970) conclude that use of difference scores is rarely if ever justified with correlational data.

The main criticisms of use of gain scores have focused on two main points. The first problem is similar to one associated with the use of pretest scores as covariates; namely, to the extent that the pretest scores contain measurement error they necessarily will be correlated negatively with the pre-post difference scores. According to the critics, this correlation, in turn, will lead to biased estimates of change. A second criticism of difference scores is that they are alleged to be inherently unreliable. Using the traditional formula for difference score reliability, which assumes equal prescore and postscore population variances, it has been noted that, as the pre-post correlation approached the equivalence reliabilities of the pre and post measures, the reliability of the difference scores tended to zero. Some authors (e.g., Overall and Woodward 1975) even claimed to find a paradox in the mixed design analysis of variance (ANOVA) in that higher pre-post correlations produce greater statistical power for the tests of within-subject effects yet result in a lowered reliability of the difference scores. It should be noted that the mixed design evaluation of the group by pre-post interaction is statistically equivalent to comparing the two groups on their difference scores via an independent groups t-test. Despite these criticisms by Cronbach and others of the use of difference scores in the evaluation of treatments and the seeming paradox involving reliability and power, the mixed design analysis continued to be used widely, although perhaps with some guilt. After all, what were the alternatives? At least **in** describing the mixed design analysis, one did not have to use the term "difference scores" explicitly.

More recently, several methodologists, among them Rogosa and colleagues (1982), have mounted a defense of the use of difference scores. Rogosa showed that imposition of the equal pretest, posttest population variance assumption forces the negative pretest-difference score correlation. In situations in which there are reliable individual (or group) differences in true gain, the posttest population variance could be expected to be larger. As one example, suppose those with higher initial scores tended to show the greatest gains. Under these circumstances the plot of pretest and posttest scores would tend to show a fan-shape pattern and the postscore variance would be larger. In this case, as Rogosa points out, the reliability of the difference scores could

be quite respectable even when the pre-post correlation was high. When the treatment and experimental groups have different mean gains, a similar fan-shape plot results, and again, the reliability of the difference scores calculated on the combined groups (and not within groups) would not be as low as suggested by the paradox discussed above. Rogosa does point out that although difference scores are unbiased and perfectly appropriate estimates of true change, they contain little information about the nature of change. To model change more adequately, one would need to measure the dependent variable at several time points.

Evaluation of Treatment Effects Over Time. When one or more followup scores are obtained on the dependent variable(s), the effects of most interest are the group x time interactions. Because there is usually interest in the nature of change over time, trend components or other planned contrasts can be used for this purpose. Again, evaluating the group by contrast interactions is advisable. Tests of contrast have considerably more power to detect specific patterns of change than the omnibus tests usually performed. Note also that df=1 tests do not assume compound symmetry (or sphericity) as do the df>l omnibus tests. Even when several outcome measures are considered in a multivariate analysis of variance (MANOVA) or multivariate analysis of covariance (MANCOVA) design, such trend contrasts should be considered.

Using TIme Series Analysis To Evaluate Effects of "Natural" InterventIons. Another type of statistical analysis may be appropriate when assessing changes in outcome or other behavior as a function of what might be termed "natural" interventions is of interest. Such interventions might be changes in law, societal attitudes, or more specific institutional changes (e.g., in policies, treatment procedures, or eligibility requirements). For this analysis, observations on the dependent variable(s) of interest, either longitudinal or cross-sectional, for many time points (at least 50) are required. Also needed is specification of the time source of the intervention. The main purpose of the time series analysis (TSA) in this situation is to model and evaluate treatment effects that are presumed to result from the intervention.

An example of this use of TSA is the ongoing evaluation by the author and colleagues of the effects (if any) of the recent liquor-labeling law on maternal drinking. For the baseline data, drinking histories and the MAST questionnaire collected over the past 3 years from all maternity clinic patients at Hutzel Hospital in Detroit are being used. The postintervention series will continue for another 3 years. Other medical background and substance use data are also available on these patients. For the patients seen in any given week, several drinking indices are calculated (e.g., average amount of alcohol per day, the proportion of drinking days). To assess the trend in use among the at-risk

maternal drinkers, the 90th percentile of these measures for the weekly samples also is determined.

The modeling of the time series consists of two stages (Cook and Campbell 1979). In the first, the structure of the correlated error is determined and included in the model. Overall linear trends and possible seasonality effects also are evaluated and included if necessary. The second and most difficult part of the analysis is the modeling of the intervention. Should the effect be represented as gradual or abrupt? If there is a decrease in drinking, will it increase over time to baseline? Because a number of possible patterns of intervention effects will need to be modeled, a cross-validation design will be employed.

Although TSA has not been used much in the health sciences to evaluate natural interventions, it is routinely used in economics. With the wider availability of computerized health records, more use of this approach in the health sciences seems likely.

Meta-Analysis: Aggregatlng Information About Intervention Effects Over Studles

No single study will provide complete information on the effectiveness of a given treatment or prevention approach. It is not surprising that for investigators and policymakers questions about the generality and robustness of results on treatment effects have become more urgent, One method for aggregating results over studies that has found increasing favor is meta-analysis (Glass et al. 1981; Hunter et al. 1982; Hedges and Olkin 1985). One reason for the increasing popularity of this approach has been the development of sophisticated statistical methods for not only aggregating effect sizes but also for evaluating sampling error in the primary studies, determining the homogeneity of results among studies, and developing models of the differences in results among studies.

The results of a meta-analysis, however, are limited by the quality of the primary studies forming the databases. A second and equally serious problem is that reports of the primary study often lack the detailed information needed by the "meta-analyst" to assess the quality of the various facets of the study or even to compute the needed effect sizes.

Another difficulty encountered in aggregating results of treatment and prevention studies is that the studies may use quite different outcome measures. If investigators within a certain research area could agree on a set of core outcomes to be obtained by all studies, this problem could be alleviated.

Looking ahead to the future prospects for this approach, it is ironic to note that as analyses of the primary studies become more sophisticated, the meta-analysis of them will tend to become more difficult. For example, combining results from studies using structural equation modeling as the main statistical analytic method becomes a difficult challenge.

Despite the difficulties, I believe that meta-analysis will become increasingly important as an approach in the health and social sciences. Not only does it contribute to what is known, but it is also a useful basis for assessing what is not. Perhaps its greatest contribution is to the efficient planning of future primary studies.

DISCUSSION

I endorse McLellan's plea for investigators to measure as many different outcome variables as possible and to do so with continuous measures if possible (McLellan, this volume). As he points out, abstinence may not be the only worthwhile goal for a treatment or prevention program. For example, if heavy maternal drinkers can be persuaded to cut down, the effects on improved infant outcomes may be greater than inducing light or even moderate maternal drinkers to abstain. Of course, more detailed dose-response information concerning the relation between maternal substance abuse and infant and child outcomes would be useful in refining goals for programs and outcomes to be assessed.

Gilchrist and Gillmore (this volume) suggest greater emphasis should be placed on evaluating program effect on improving infant outcomes. Although the well-being of the offspring is an ultimate criterion, I suspect that direct program effects on the infant and child variables will be relatively small and probably mediated by maternal substance abuse behavior as well as other maternal variables. Perhaps the best way to evaluate ultimate program effects is through analysis of structural models within which possible mediating variables can be accommodated, as they suggest. Poland and colleagues (1990) have used this general approach in looking at the effects of quality of prenatal care on birth weight.

SOME CONCLUSIONS

No statistical techniques, however sophisticated, can compensate completely for a poorly selected sample, lack of randomization, unreliably measured variables, and lack of theoretical base (or at least specific questions to be addressed). Many of the statistical models and methods designed to overcome the above problems are mathematically complex, difficult to implement, and

difficult to interpret. Despite these factors, such methods are potentially useful, particularly to the extent that they help evaluate the degree of uncertainty inherent in results and conclusions.

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Role of Biologic Markers in Epidemiologic Studies of Prenatal Drug Exposure: Issues in Study Design

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INTRODUCTION

Exposure assessment plays a central role in epidemiologic studies. It is crucial for minimizing the effects of misclassification and the influence of confounding variables and for improving the probability of revealing the true associations between exposure and health effects.

Exposures to risk factors can be assessed by direct or indirect methods. Indirect techniques are used extensively in epidemiologic studies. They focus on using questionnaires and statistical modeling to estimate exposures. In contrast, direct-method techniques employ personal monitoring and biologic markers (biomarkers) to provide an integrated measure of exposure. Personal monitoring refers to objective measurement of an individual exposure to a risk factor of interest (urinalysis of consumed drugs; use of personal monitoring to assess human contact with air, water, or food contaminants; etc.). Theoretically, biomarkers are indicators of dose and can serve as correlates or surrogates of exposure. However, in practice it is difficult to relate biomarkers to specific levels of exposure or to a specific source of exposure because of limitations in the understanding of such factors as drug uptake, distribution, metabolism, and site and mode of action of the agents of interest. Biomarkers by themselves may not identify the mode or magnitude of the exposure and, thus, need to be supplemented by other direct or indirect assessment measures.

Biomarkers are increasingly being used in a variety of epidemiologic studies (Perera 1987; Harris et al. 1987). This chapter argues that the utility of biomarkers will not be fully realized unless they are used within the context of well-designed and properly conducted epidemiologic studies. Indeed, in the

absence of a rigorous methodologic framework, biomarkers could be misleading. The chapter presents an example of a study design, which the authors call a nested prospective study, as an example of how biologic monitoring can be incorporated into epidemiologic studies of prenatal drug exposure.

DEFINITIONS OF BIOMARKERS

In this chapter, biomarkers are considered to measure both exposure and disease outcomes. Our definitions are the same as those of the Committee on Biologic Markers of the National Research Council.

- A biologic marker of exposure is an exogenous substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism.

- A biologic marker of effect is a measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (Committee on Biologic Markers, Subcommittee on Reproductive and Neurodevelopmental Toxicology 1989, p. 2).

A biomarker of exposure is an indicator that an exposure (concentration of the agent multiplied by the time in contact with it) has taken place. It is quantitatively related to exposure through pharmacokinetics, which describe rate of uptake, distribution, metabolism, and elimination of the agent in the body. Biomarkers of exposure are measures of internal dose (amount of the agent or its metabolites retained in the body over a given period) or of biologically effective or administered dose (amount of the agent or its metabolites at the cell or target site where the health or comfort effect occurs). Biomarkers of health or comfort effects can be indicators of early biological effects, altered function or structure, and clinical disease.

Biomarkers can be unchanged exogenous agents (e.g., nicotine or heavy metals), metabolized exogenous agents (e.g., cotinine), endogenously produced molecules (e.g., alpha-1-antitrypsin), molecular changes (e.g., DNA adducts), and cellular or tissue changes (e.g., cell histology).

Within an epidemiologic context, the use of biomarkers has the potential to further specify relationships that may exist between an exposure and a disease outcome. Biomarkers may permit exposure to be modeled more precisely; they may indicate biologic mechanisms by which an exposure may cause disease;

and they may be used to identify the precursors of disease. All the above may bring increased specificity, statistical power, and validity to epidemiologic studies.

Factors Influencing the Choice of Biomarkers

The factors that influence the effectiveness of or determine the suitability for the use of a particular biomarker in an epidemiologic study include the following:

1. Potential for Use—Is there a sensible biologic interpretation of the marker compound? Is there potential for obtaining samples? What is the extent of variability of the marker from individual to individual?

2. State of Development-Has the marker been evaluated in animal, human clinical, or large population studies?

3. Properties of the Marker—Is it specific to the exposure of interest (e.g., cotinine is specific to tobacco smoke exposure, whereas DNA adducts can result from a range of sources)? Is there sufficient sensitivity? (Can it be measured at levels relevant to the exposures of interest or is the lower detectible limit well above levels consistent with normal exposure ranges?) What is the level of understanding of the metabolic characteristics of the compound? What is the invasiveness of sample collection? For example, does blood need to be drawn or can a urine or breath sample be used?

4. Laboratory Issues

   - Sample collection and handling: Do samples have to be frozen? What is the stability of the marker in time? Are there losses to surfaces of storage containers? Is there cross-reactivity?

   - Analytical methods available: What is the accuracy and sensitivity of the analytical method?

   - Cost: Are the samples easily handled and stored? Can inexpensive calorimetric analysis be done, or is gas chromatography (GC)/mass spectrometry analysis required? Is extensive extraction of sample required?

5. Methodological Issues-What is the sample size (e.g., is the collection analysis such that it can be done on a large population, or is the cost and complexity such that only a few samples can be collected and analyzed?), and what is the potential for confounders?

6. Overall Relevance of the Biomarker-What is its relevance to the exposure and etiology of the health effect of concern?

ADVANTAGES OF MONITORING PRENATAL DRUG EXPOSURE WITH BIOMARKERS

First, it is evident that some mothers may not remember, may not wish to remember, or may not wish to report the use of drugs during pregnancy. Although this comment is particularly pertinent to the use of illicit drugs, even the use of pharmacologic agents or social drugs (cigarettes and alcohol) may not be recalled accurately, if at all. Recall of episodic drug use is also often a problem. Respondents may report that they used an over-the-counter or prescription drug for a few days for relief of, for example, a headache, hay fever, asthma, or insomnia. However, they are often uncertain about which specific weeks during pregnancy they used the drug or how many times they used it. Several studies have reported inaccurate recall of drugs in pregnancy (MacKenzie and Lippman 1989; Harlow and Linet 1989).

Of even greater concern than poor recall of drug use is the reporting of exposures that may be biased with respect to the disease of interest. Although this is more of a problem in case-control studies (Werler et al. 1989), even prospective studies may be affected. For example, a woman who is experiencing vaginal bleeding during pregnancy may alter her reports of cocaine use, both of which may increase her risk of precipitous preterm labor.

Second, some exposure may be difficult to measure (e.g., environmental tobacco smoke) or impossible to measure (e.g., radon, electromagnetic fields) in any way other than by monitoring. An investigator might construct an interview to ask about the respondents' perception of how smoky the air is or how many cigarettes their spouse smokes, but even by developing sophisticated questions, this clearly falls short of measuring contaminants in the subjects' breathing zone. Similarly, questions about electric blanket and other electric appliance use, or even the development of complicated house wiring codes (Barnes et al. 1989), are of uncertain validity with respect to a respondent's exposure to electromagnetic fields.

Third, individuals show considerable variation in how well they metabolize drugs. This is due to inherent interindividual differences in the genotype and also to the concurrent use of other drugs. For example, genetic variability in the ability to induce placental enzymes necessary for metabolizing xenobiotic substances has been reported (Nebert and Jensen 1979; Gottlieb and Manchester 1986). Increased induction may prevent teratogens from crossing the placenta and reaching the fetus.

Individuals who smoke show dramatic differences in their ability to metabolize other drugs because cigarette smoke induces enzyme activity for other drugs (Okey et al. 1986), including caffeine. Figure 1 shows lower caffeine levels in urine among active smokers compared to nonsmokers, with daily caffeine intake held constant. To fully understand the role of either maternal smoking (Martin and Bracken 1986) or caffeine (Martin and Bracken 1987) on fetal growth retardation, for example, the interactive effects of the two exposures must be evaluated, preferably through the use of biomarkers of exposure. In many circumstances, exposure to the fetus of a particular drug may be estimated more precisely from a biomarker in the mother's urine than from reports of her own consumption of or exposure to a particular product.

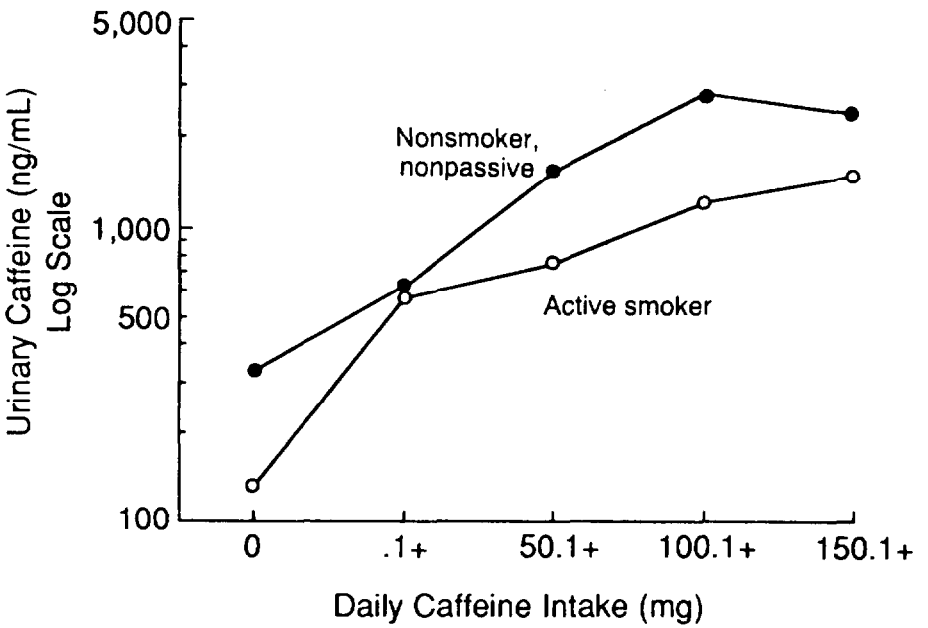


FIGURE 1. *Relationship of urinary caffeine to daily caffeine intake by smoking status*

SOURCE: Yale Perinatal Epidemiology Unit, unpublished data 1990

Fourth, women metabolize drugs differently during pregnancy. Thus, exposure to the same amount of a drug leads to different levels in the circulating system in early pregnancy than exposure to the same amount of drug later in pregnancy. Figure 2 shows the rate of urinary caffeine at four points in pregnancy for three daily levels of caffeine based on coffee, tea, and soda use only. The interactive effects of smoking are avoided by using nonsmokers only. Women who reported not using coffee, tea, or soda still consumed caffeine from other sources. Among women using 50 mg or less caffeine daily, there is a marked increase in urinary caffeine levels as pregnancy progresses, reflecting a decreased ability to metabolize caffeine. This effect appears to be less marked in the highest consumption group in these data. This finding supports theoretical models developed earlier by Mattison (1966). The effects of caffeine

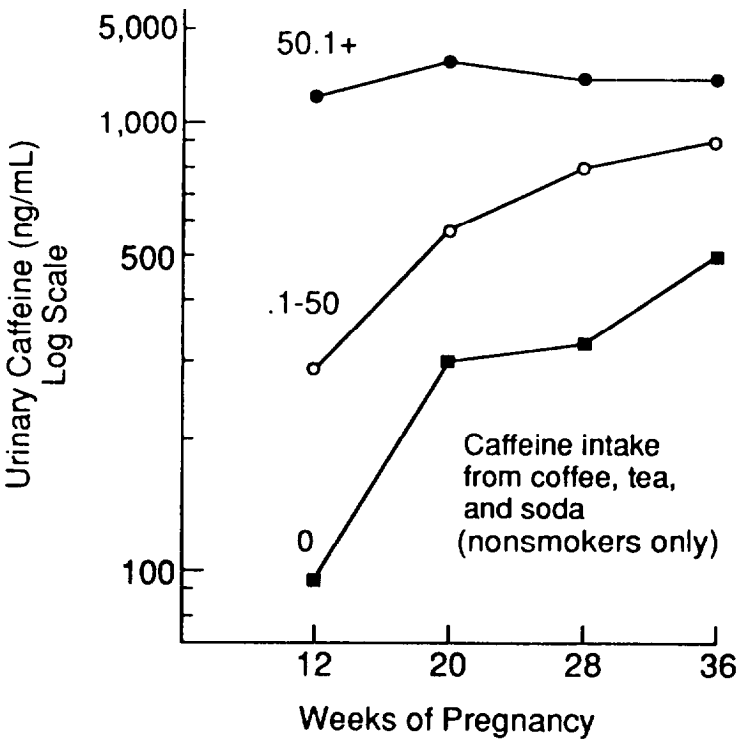


FIGURE 2 *Relationship of urinary caffeine to stage of pregnancy by daily caffeine intake*

SOURCE: Yale Perinatal Epidemiology Unit, unpublished data 1990

on the fetus are further enhanced by the inability of the fetus or newborn to metabolize caffeine (Lambert et al. 1986). Thus, fetal exposure to a drug differs at various stages of pregnancy. This can be modeled with precision only by using biomarkers.

Fifth, for many drugs of interest, the metabolic product may be of greater teratogenic potential than the drug. For example, ethanol metabolizes to the more toxic acetaldehyde, although lower levels are found in maternal blood (Adickes 1989). For reasons cited above, the metabolic products circulating in the individual cannot be predicted with any accuracy, and their direct measurement is preferred.

Finally, hypotheses concerning the relationship of an exposure to a health outcome may require that a distinction be made between total exposure and peak exposure or between frequency and recency of exposure-all of which may be more accurately characterized with biomarkers. Recency of exposure will relate to the half-life of a drug's metabolism, and this is most accurately assessed by actual measurement since it may be confounded by other exposures. Similarly, while peak intake exposures may be assessed by a questionnaire, peak blood levels of a drug may more accurately predict a health outcome.

THE NECESSITY FOR REQUIRING QUESTIONNAIRE DATA TO COMPLEMENT BIOMARKERS

The advantages offered by biomarkers should not be viewed as precluding the use of more traditional questionnaire data. These two types of data collection complement each other rather than one being a substitute for the other. Some reasons for this follow.

1. Many drugs (e.g., cocaine and marijuana) have short half-lives, and use will be missed unless extremely frequent urine analyses are taken (Little et al. 1986).

2. Sporadic and infrequent exposures that may have great etiologic relevance (e.g., drinking and drug binges) are likely to be missed in a large proportion of the exposed population. Some of these exposures may be measured more accurately by well-constructed questionnaires.

3. For case-control studies, monitoring does not necessarily reflect exposure at the time of the etiologic event. For example, a study that measures electromagnetic fields in the homes of mothers who delivered a child with a birth defect may be inaccurate because of seasonal changes in electric

use, remodeling of the house that changes the wiring configuration, or changes in the inhabitants' patterns of electric use.

4. Monitors placed in the home will measure only part of the individual's total exposure. For example, a woman's exposure to environmental tobacco smoke may occur primarily at her workplace or while commuting, situations in which monitoring may not be feasible.

5. Some exposures may be expected to change during pregnancy-for example, occupational exposures, since a woman may change jobs, change job responsibilities, or stop working at some time during her pregnancy. Although a biomarker might be the best measure of a specific occupational exposure, a brief telephone interview is probably the most cost-efficient way to determine whether the woman still is working at the same job.

6. Questionnaires provide the data from which exposures for large populations can be estimated or modeled. Validating questionnaire measurement with a biomarker helps develop questionnaires that can be used in large population studies to estimate exposure or dose.

INTERRELATIONSHIP OF BIOMARKERS WITH MORE TRADITIONAL METHODS OF DATA COLLECTION

Based on the above arguments, we see no circumstances where biomarkers would be collected in the absence of questionnaire data to evaluate exposure to the same substances. Moreover, biomarkers must be related to time "windows," which are related to the questionnaire data whenever possible. For example, an investigator may measure dietary nutrients from a blood sample at the end of a period for which the respondent is asked to provide a 24-hour or 7-day food frequency questionnaire.

The rationale for the foregoing recommendation is twofold. First, respondents may not accurately recall data being obtained by interview. In this case, the biomarker can be considered a measure of "compliance," not unlike the use of markers in a randomized trial, to check that a drug regimen is being followed.

Second, the validity and reproducibility of many of the biomarkers being proposed for epidemiologic research need to be established. Collection of concurrent interview data may facilitate this work. Conversely, the validity of questionnaire data also needs to be studied, and the biomarkers may assist with this. Important methodological contributions may arise from research that has used both types of data collection.

THE NESTED PROSPECTIVE STUDY

In a large prospective study, it is generally not feasible to monitor the entire cohort for biomarkers. Not only would this entail great expense, from laboratory costs and from the cost of collecting the data, but also it is likely to be inefficient. If subgroups of the population under study can be monitored in more detail, then conclusions drawn from them may be generalizable to the entire population. For this process to be reliable, however, it is necessary that the monitored subgroups be representative of the population from which they are drawn, and the only guaranteed method of ensuring this is by picking them at *random.*

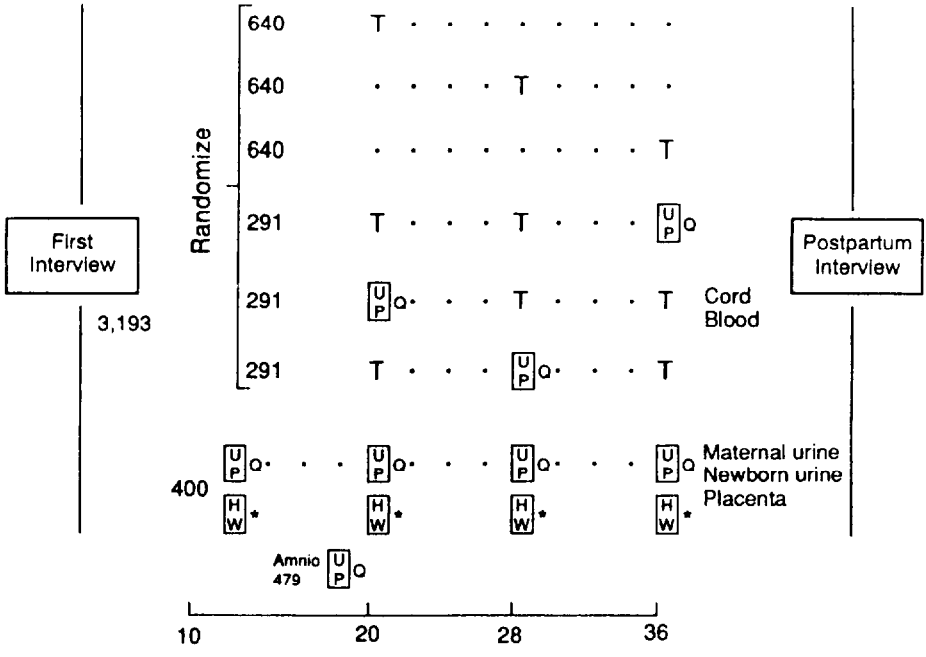
A second feature of the nested prospective study is the need to calculate a more complex set of power calculations. In most prospective studies, an estimate of exposure in the population is made together with a statement of what difference in clinical outcome the study wants to be able to detect. In the nested study, additional calculations must be made to estimate the exposure levels anticipated by the biomarkers and to take into account the randomization in the study design. The number of subjects randomly chosen for the monitored group may be determined by the ability of the marker to identify an exposed group and by the degree to which significant clinical outcomes in the exposed subgroup can be observed. Moreover, although appropriate randomization should allow a reconstruction of the entire cohort, the process incurs some loss of statistical power that should be adjusted for in the overall analyses.

AN EXAMPLE: THE YALE STUDY OF ENVIRONMENTAL TOBACCO SMOKE AND INTRAUTERINE GROWTH RETARDATION

Overall Design of the Yale Study

Figure 3 displays the principal elements in the Yale nested prospective study. Overall, it is anticipated that 3,193 respondents will enter the study. From a previous study, we estimate that 400 women will have their first antenatal visit before 12 weeks of pregnancy and, therefore, will be eligible to enter an intensively monitored group who will be monitored four times in their pregnancy: The first time will be soon after their first interview, at approximately 12 weeks gestation, and then at 20, 28, and 36 weeks. The intensive group is studied for interindividual changes in exposure and in response to exposure as pregnancy progresses. Their monitoring protocol is described in more detail later.

Some of the analyses of differential exposure across pregnancy require a larger sample size than will be derived from the intensively monitored group. Thus, a further 873 women are randomly selected from all women admitted to the study



*Randomly pick one
T=telephone interview: Q=questionnave; U=urine sample; PHW=personal. home, work nicotine monitor

FIGURE 3. *Nested prospective study of effects of environmental tobacco smoke on fetal growth retardation; randomization and data collection in monitoring window*

SOURCE: Yale Perinatal Epidemiology Unit, unpublished data 1990

after 12 weeks gestation, and they form a biochemically monitored group. It is not necessary that every woman in this group be monitored at each period; consequently, they are randomly selected for monitoring at 20, 28, or 36 weeks gestational age. At times, when a subject is not being biochemically monitored, exposure is assessed by a telephone interview.

To obtain sufficient statistical power to address the study's main etiologic hypotheses, a further 1,920 women have their exposure during pregnancy monitored by telephone interview alone. Again, a third of this group is randomized for telephone interviews at 20, 28, or 36 weeks.

Because each subject was randomized to her particular monitoring group, each of the entire cohort of 2,793 subjects can have her overall exposure assessed by generalizing from other groups in the randomized cohort. The intensively monitored group cannot be compared directly with the rest of the cohort because they are selected on the basis of very early first antenatal care visits. However, they can be contrasted statistically with the rest of the cohort to see how they compare on exposure. Moreover, change in biologic exposure during pregnancy, as assessed by biomarkers, is unlikely to be differentially biased in the intensively monitored group.

Every woman in the entire cohort of 3,193 subjects is given a standardized interview before monitoring starts and a postpartum interview within 2 days of delivery, and her child is examined by a trained perinatal nurse. These sessions provide data that describe the characteristics of the entire study cohort, elicit data about potential confounders, and form the basis for the variables describing study outcomes.

Monitoring Protocols

Intensively Monitored Subjects. In each of the four 1 -week monitoring periods, the subject wears a passive smoke monitor and, on the morning of the last monitoring day, provides a urine specimen for cotinine analysis. Therefore, the cotinine measure overlaps with some of the monitoring period evaluated by the passive smoke monitor. At the end of each monitoring period, the respondent is given a brief interview that elicits her responses to questions about exposure during that period. The same questions are used in the telephone interview for the rest of the cohort.

One of the four monitoring periods is picked at random for home and work monitoring. During the same 7-day period that the respondent wears a passive nicotine monitor, she places one in her home for 7 days and, if she works, one in her workplace for the days she works. Standard protocols are used.

After delivery, a maternal urine is collected so that nicotine exposure can be assessed for the latter part of pregnancy. The neonate's urine also is collected so that a more direct measure of fetal exposure to nicotine can be obtained by assessing cotinine. Placentas of the women in the intensively monitored group also are collected and examined according to protocols described in a following section.

Biochemically Monitored Subjects. During 1 week picked at random from weeks 20, 28, or 36, the subjects in the biochemically monitored group follow the same protocol as that of intensively monitored subjects for using the personal nicotine monitor and for providing a urine sample.

Importance of Monitoring Windows

The Yale study uses 7-day exposure windows during which time biomarkers are obtained. The use of precise monitoring windows also serves to focus the period over which questionnaire data can be collected and permits a direct comparison of data collected by both methods, Since the 7-day monitoring windows are based on specific weeks of gestation (using each subject's first day of last menstrual period), data from one subject also can be compared with other subjects in the study cohort. In addition, using gestational age-based monitoring windows permits precise replication of the study by other investigators.

The use of monitoring windows during pregnancy also permits more precise analysis of the effect of time of exposure on a reproductive outcome. It is well known that exposures to some teratogens late in pregnancy have no effect on embryologic development, whereas earlier exposure during a "critical" period can have devastating effects (Bracken 1984). For intrauterine growth retardation (IUGR), differential exposure at various points in pregnancy may have a variety of effects on the developing fetus, leading to IUGR, no IUGR, or particular patterns of growth retardation (Keirse 1984).

Three primary measures of exposure are used in this study. First, we ask very detailed questions about exposure to environmental tobacco smoke (ETS); second, we use a passive smoke monitor that measures the air in the subjects' breathing zone for nicotine; third, we collect maternal urines to measure cotinine. The three exposure measures, the passive smoke monitor, and the urinary and placenta analyses are described more fully below.

ENVIRONMENTAL MONITORING

Passive Smoke Monitor

ETS is a complex mixture of more than 4,000 chemicals found in the vapor and particle phases. Given this complex mix, it is necessary to identify any air contaminants or class of air contaminants for monitoring that would be indicative of the presence and amount of ETS in an indoor environment. Some of the ETS contaminants are associated solely with the combustion of tobacco (e.g., nicotine or tobacco-specific nitrosamines), whereas others are emitted by several other sources in the indoor and outdoor air (e.g., carbon monoxide or nitrogen dioxide). In addition, individual or classes of ETS air contaminants have not been singled out as being principally associated with the health and comfort effects of concern. Therefore, it is neither practical nor feasible to measure all contaminants associated with ETS. Assessing exposure to ETS is

best accomplished by monitoring concentrations of a proxy or marker compound. A proxy or marker compound for a complex source, such as ETS, is one that is easy and inexpensive to monitor and whose concentration is directly related to the source and concentrations of important contaminants emitted from the source. A proxy compound need not be directly related to the effects under study.

Over the past few years, several compounds have been proposed as possible markers for ETS (National Research Council on Environmental Tobacco Smoke 1988; Surgeon General 1987). Although no single compound has been identified as an "ideal" marker, vapor phase nicotine in ETS has been shown to be a suitable marker (Leaderer and Hammond 1991). Nicotine is unique to tobacco, is emitted in similar quantities from different brands of cigarettes, exists indoors at concentrations that are easily measured, and is related to other ETS contaminants. In addition, nicotine and cotinine—a metabolic byproduct of nicotine measured in blood, urine, and saliva-have been used extensively for many years as biomarkers of exposure to ETS and active smoking. Hammond and Leaderer (1987) described an inexpensive and accurate passive monitor for vapor phase nicotine that makes it possible to measure personal nicotine exposures and concentrations in indoor environments over periods from 1 day to several weeks. This passive monitor allows for the measurement of personal exposures to ETS in many individuals and in a variety of indoor spaces.

The passive monitor, shown in figure 4, is small, lightweight, and unobtrusive (Hammond and Leaderer 1987). Its principle of operation is based on passive diffusion of nicotine to a chemically treated filter. The monitor consists of a modified 37mm diameter and 16mm high polystyrene air sampling cassette containing a support pad and a filter treated with an aqueous solution of 4-percent sodium bisulfate and 5-percent ethanol. The monitor samples at a rate of 24 mL/min. After exposure, the collected nicotine and bisulfate are desorbed in water, the pH is adjusted with 10 N sodium hydroxide, and the neutral nicotine molecule is concentrated into 250 mL of heptane by liquid/liquid extraction. An aliquot of the heptane solution is injected into a gas chromatograph with nitrogen-selective detection for quantitation of the nicotine.

The passive nicotine monitor is used to assess the personal exposures to ETS and the levels in various indoor environments in which the respondents spend their time. As a personal monitor, it is worn by respondents on the outermost garment, as near as possible to their breathing zone, during the waking hours for a 1-week period. During sleep hours, the monitor is placed on the respondent's nightstand. To monitor indoor spaces, respondents place a monitor for a 1-week period in the main living space of their home and near their

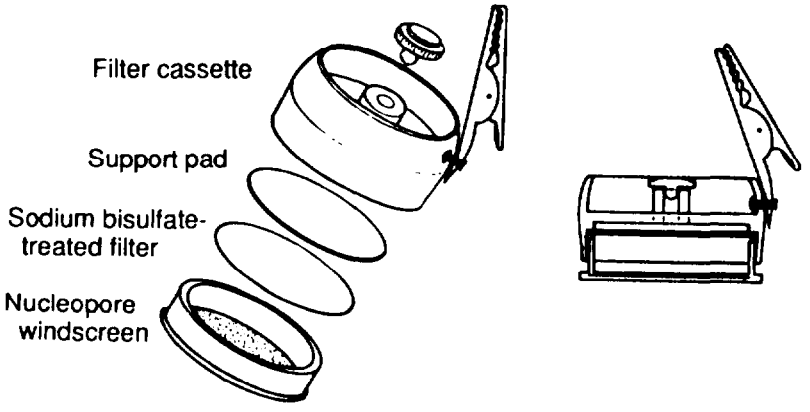


FIGURE 4. *Passive monitor for nicotine in the air*

SOURCE: Hammond and Leaderer 1987, copyright 1987, American Chemical Society

work station. Personal and indoor space monitoring is conducted over a 1-week period corresponding to the respondents' reported exposure via a short questionnaire and the collection of the respondents' urine samples on the last day of the monitoring period. For quality control, a 5-percent duplicate sample and field blanks are collected. Laboratory technicians are blind to the exposure status of the respondents' home and workplace samples.

BIOMARKERS

Urinary Cotinine Analysis

The principal biochemical markers that have been used as a measure of ETS exposure include carboxyhemoglobin, nicotine, cotinine, and thiocyanate (National Research Council on Environmental Tobacco Smoke 1986; Surgeon General 1987). Carboxyhemoglobin is not considered a reliable measure since it is affected by sources of carbon monoxide other than tobacco smoke (Jarvis and Russell 1984). Thiocyanate may be a good indication of chronic exposure since it has a relatively long half-life (14 days) (Lynch 1984); however, assays are not sensitive at low levels and, therefore, are inappropriate to measure ETS. Nicotine and cotinine, a metabolite of nicotine, are the most specific indicators of tobacco smoke (Lynch 1984); and of these, cotinine has a longer half-life (2 days vs. 30 minutes for nicotine) and can be measured at low levels in serum, saliva, and urine. Cotinine urine levels are highly correlated with cotinine blood levels (Jarvis 1984). For these reasons, we have chosen to use cotinine as a

measure of ETS in our study, and we obtain urine for the analysis since this is less invasive and more acceptable to study respondents than using blood.

Urine specimens are collected by the respondents in **a** sterile plastic container during the first morning void. The samples are kept under constant refrigeration until they are transported to the laboratory, usually within 48 to 72 hours of collection. Each sample is measured and aliquoted into three 5 mL containers, which are frozen at -80°C . One aliquot is used for GC analysis.

There are two methods of cotinine analysis in use, radioimmunoassay and GC. A correlation of 0.93 (Peyton et al. 1981) has been reported for measuring cotinine in urine by these two methods. We have chosen to use GC because this method allows us to measure cotinine, nicotine, and caffeine In the same analysis. Since a 24-hour urine sample is not collected, creatinine also is measured, and the cotinine/creatinine ratio is used to eliminate differences due to variability in urine volume. Maternal and infant urine samples are analyzed in exactly the same way.

Amniocentesis

During the initial interview, respondents are asked if they anticipate having an amniocentesis during their pregnancy. Approximately 15 percent of women in this study have indicated they plan to have an amniocentesis and have agreed to have a portion of the amniotic fluid reserved for cotinine analysis. When the amniocentesis is performed, no additional fluid is removed since, after the amniotic fluid is centrifuged to obtain fetal cells for genetic analysis, the supernatant is reserved. This fluid, essentially fetal urine, is analyzed using the same procedures as described for the maternal and infant urine.

Newborn Urine

The first urine from each newborn in the study is collected by taping a small plastic bag over the infants' genitals and waiting for them to void within the next 2 hours. Approximately 5 mL can be obtained by this method, which is sufficient for analysis. The newborn urines are analyzed by GC using the same procedures as those for maternal urines.

Placenta Analysis

We are investigating the use of biomarkers in the placenta to study the mechanisms whereby exposure to environmental tobacco smoke during pregnancy may result in IUGR. Two specific types of marker are being used: (1) placental enzymes, which are usually considered to modify exposure; and

(2) DNA chemical addition products (adducts), which are considered to represent measures of effect.

Placental Enzymes. Since enzymes may be induced in response to the presence of specific substrates in human tissue, enzymes may be induced in the placenta to metabolize chemical exposures of the mother. A substrate of particular interest is benzo[a]pyrene, a toxic component of cigarette smoke. Using the aryl hydrocarbon hydroxylase (AHH) enzyme assay (as modified by DePierre et al. 1975), we can measure the overall ability of the placenta to metabolize benzo[a]pyrene. Preliminary data (M. Sanyai, personal communication) indicate that women who report smoking during their pregnancy have higher levels of the enzyme than do women who do not smoke during pregnancy. However, higher levels of enzyme activity alone may not be indicative of a negative effect since the same enzyme system has the potential to metabolize benzo[a]pyrene to more toxic or less toxic intermediates. A more specific indication of toxicity is the potential of metabolites to bind covalently with DNA. The covalent binding of some metaboiites (e.g., anti-BD-diol epoxide [BPDE]) is sufficiently strong to alter the fidelity of DNA replication or transcription processes in cells. It is likely that similar metabolites also may be produced in the placenta from benzo[a]pyrene substrates. To estimate the DNA binding potential of these metabolites in the placenta, human placenta homogenate is incubated with radiolabeled benzo[a]pyrene and salmon sperm DNA. After DNA extraction, a liquid scintillation counter is used to measure the radioactivity. In the preliminary data, the ratio of total benzo[a]pyrene metabolites produced (measured by AHH activity) to reactive DNA binding molecules has shown a dose-response relationship to the number of cigarettes smoked during pregnancy.

DNA Adducts. Although DNA damage may play an important role in the etiology of many important diseases, direct investigation has been limited by a lack of well-established methods that are sensitive enough to provide direct measurements of chemical damage occurring in human DNA. Preliminary studies (M. Sanyal, personal communication) indicate that the recently developed 32P-postlabeling assay (Randerath et al. 1981, 1985) is capable of measuring chemical alterations in DNA at levels of sensitivity low enough to detect DNA damage resulting from environmental exposures. ^{32}P-postlabeling is performed by isolating DNA, digesting it to mononucleotides, and postlabeling the mononucleotides with radioactive phospate using an enzymatic process that is highly specific for DNA nucleotides, including adducts. Nucleotides containing aromatic adducts then are separated from normal nucleotides by thin-layer chromatography, and autoradiograms are made showing maps of DNA adducts. Levels of the adducts then can be estimated by the density of the autoradiograms or, more accurately, by scraping the thin-layer

chromatograms and quantifying the radioactivity present. The procedure can detect many different chemical addition products of either known or unknown structure, although present methods typically are most sensitive at detecting relatively large aromatic adducts.

The measurement of DNA adducts may provide an important means to quantify the biologically effective dose of environmental exposures because the quantity of adducts present in the placenta may integrate exposure over time and take into account individual differences in the pharmacokinetics and metabolic activation of agents capable of interacting with DNA. These refined estimates of dose have great potential for improving our ability to demonstrate dose-response associations in epidemiologic studies. In addition, the assay to be used in these studies is not specific for a single adduct, but detects adducts from many aromatic hydrocarbons. Thus, human DNA can be treated to detect a range of alterations, and the sources of exposure causing those changes can be identified.

CONCLUSION

The use of biomarkers in epidemiologic studies of prenatal drug exposure is becoming increasingly more common. A range of markers is already available and, if carefully chosen, they may offer some advantage over more traditional methods of assessing exposure to teratogens and provide new measures of disease outcome. However, there are also significant disadvantages to using many biomarkers, and the precise role of biomarkers in epidemiologic studies remains unclear. To elucidate the problems and benefits of specific biomarkers, epidemiologic studies that use them should be carefully constructed so that methodological studies of the validity and reproducibility of the biomarkers can be carried out alongside the primary etiologic question that is being addressed.

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Detection of Prenatal Drug Exposure in the Pregnant Woman and Her Newborn Infant

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INTRODUCTION

In 1985 a survey by the National Institute on Drug Abuse showed that about 23 million people in the United States used illicit drugs (Abelson and Miller 1985). A sizeable portion of these drug users are women of childbearing age or are pregnant. In a recent survey of 36 major hospitals, the prevalence of drug abuse among pregnant women ranged between 0.4 and 27 percent (Chasnoff 1989), and these figures probably are underestimated (Ostrea et al. 1990a).

Drug abuse during pregnancy is a major health problem since the associated perinatal complications are high. These include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage *(abruptio placentae* or *placenta praevia),* and fetal distress (Ostrea and Chavez 1979; Chasnoff et al. 1985; Oro and Dixon 1987; MacGregor et al. 1987). For the newborn infant, the mortality as well as the morbidity rates are high (Zuckerman et al. 1989; Zelson et al. 1971; Ryan et al. 1987; Fulroth et al. 1989; Chasnoff et al. 1986, 1989; Ostrea et al. 1976, 1987; Oleske et al. 1983). For instance, there is a high incidence of asphyxia, prematurity, low birth weight, infections, pneumonia, congenital malformations, cerebral infarction, and drug withdrawal and an increased risk of acquired immunodeficiency syndrome. Long-term sequelae in the infants are also not uncommon and include delays in physical growth and mental development, sudden infant death syndrome, and learning disabilities (Wilson et al. 1979; Chavez et al. 1979a, 1979b; Chasnoff et al. 1982; Wilson 1989). Because of these immediate and long-term problems, infants born to women who have abused drugs during pregnancy should be identified soon after birth so that appropriate intervention and followup can be done. For other reasons, an accurate identification of the neonates who are exposed to drugs *in utero* is important. The data are vital for epidemiologic surveys for identification of women who will need postnatal support or for assessment of the effectiveness of programs designed to reduce the incidence of drug abuse among pregnant women.

Unfortunately, the identification of the drug-exposed mother or her neonate is not easy. Maternal admission to the use of drugs is not frequent and is often inaccurate because of fear of the consequences stemming from such admission. Even with maternal cooperation, such information regarding the type and extent of drug usage is often inaccurate (Ostrea and Chavez 1979). Similarly, many of the drugs to which the fetus is exposed *in utero* do not produce immediate or recognizable effects in the neonates (Kandall and Gartner 1974). Currently, there are several methods used to detect prenatal drug exposure in the pregnant woman or her infant. Each method has its advantages and shortcomings. An update and critical assessment of these various methods is the subject of this chapter.

Methods to detect substance abuse in a pregnant woman or intrauterine drug exposure in a neonate ideally should address not only the type(s) of drug abused but also the amount, frequency, and duration of drug exposure. Although the acquisition of all this information is not usually possible, two general methods are employed to achieve this: maternal interview (maternal self-report), laboratory tests, or both.

MATERNAL INTERVIEW

Maternal interview, if accurately used, has the greatest potential for obtaining comprehensive information on the type, amount, frequency, and duration of drug use in the mother. The two systems of maternal interview generally used-routine and structured-are described below.

Routine Interview

Routine interview forms an integral part of the obstetric history, which is obtained either prenatally or when a woman in labor is admitted to a medical facility. The accuracy of the data obtained by this method depends on the attention devoted to the interview (Chasnoff 1989). Cursory interviews often result in underreporting of drug use, whereas the incidence increases by threefold to fivefold if a more organized protocol to monitor drug use is employed. Still, there are many elements inherent in the routine history-taking that affect its accuracy: maternal fear of the consequences of admittal; underestimation of drug use, even by those who admit to the use of drugs; and physical discomfort experienced by the woman, particularly if she is in labor (Ostrea et al. 1990b; Ostrea and Chavez 1979). Under these circumstances, the reporting of drug abuse by the mother can be as low as one-fourth of the true incidence (Ostrea et al. 1990a).

Structured Interview

Structured interview follows a more organized approach to the maternal interview, frequently employing a standard questionnaire. Examples of this are the Khavari Alcohol Test (Khavari and Farber 1978) or its modification (Khavari and Douglass 1981) and the Cahalan Volume Variability Scale (Cahalan et al. 1969). The structured interview is more accurate since more time is spent in the interview, which is frequently conducted in a more favorable environment. Commonly, the interview is obtained on several occasions over the pregnancy. As such, structured interviews frequently are used as research tools. On the other hand, structured interviews are expensive to conduct and time-consuming and, therefore, may not be practical for routine clinical use.

There are some methodological problems inherent in structured interviews as a measure of substance use during pregnancies (Day et al. 1985). First, in the assessment of frequency and quantity of drug use, the recall phenomenon by the patient may not be accurate, particularly if interviews are spaced far apart. For instance, an interview obtained at the end of each trimester frequently will reflect only recent drug use. Second, the frequency of drug use often is reported as a constant and seldom reflects variability in use. Therefore, the major effects of episodic excesses that may be relevant to a teratogenic problem may be masked. Similarly, quantity of drug use may reflect only the "usual" amount used and miss episodes that are greater or less than usual. Potency of drugs abused also varies and may not be assessed by the usual counts employed. Third, there is also the problem of patients deliberately misrepresenting their drug use. To some extent, this problem is addressed by the use of a bogus pipeline technique (Jones and Sigall 1971).

LABORATORY TESTS

The following questions should be addressed in any laboratory test that is used to detect prenatal drug exposure in the pregnant woman or neonate: (1) How broad should the screen be? (2) What is the sensitivity of the test? (3) What is its specificity? The broadness of the screen determines how many drugs can be identified in a single test panel. The spectrum can be limited or broad. A limited or narrow spectrum is usually less expensive; however, its use is limited to situations where only specific drugs are of interest. The sensitivity of a test determines the ability of the test to detect a drug when present at concentrations greater than or equal to its predetermined analytical cutoff point. Tests that are used for screening purposes usually have high sensitivity (99 percent) even at the expense of a low specificity (high false-positive rate), since once a test result is negative, further testing usually stops. The specificity of a test expresses the measure of certainty in the identity of a substance that is

detected by the test. Tests with high specificity are used to confirm the results of initial screening tests. Cross-reactivity is low in tests that have high specificity; consequently, false-positive results are few.

Most of the laboratory tests for drug detection are used for screening. Confirmation with the use of another, nonrelated procedure usually is needed if results are to withstand further scrutiny. As mentioned, the confirmatory test should be highly specific. For medicolegal purposes, further forensic confirmation may be needed to establish the unequivocal identity of the drugs initially identified. It is apparent that, as more confirmatory tests are done, the testing process becomes more expensive. Thus, the extent to which tests beyond the initial screen are carried out is determined by the reasons that initiated the test.

Analytical Procedures

The various analytical procedures that currently are used for drug detection are shown in table 1 (Schonberg 1988). These are color or spot tests, thin-layer chromatography (TLC), immunoassays, high-performance liquid chromatography (HPLC), gas chromatography (GC), and gas chromatography/mass spectrometry (GC/MS).

Color or Spot Test. The color or spot test is the simplest and the earliest of the drug tests. The test is based on a color reaction that develops when a small amount of urine is added to a reagent that reacts with the drug present in the urine. The procedure is easy to perform, quick, and inexpensive. Neither special equipment nor experienced technical skill are required to perform the test. However, the color or spot test has a high rate of false-positive and false-negative results. Furthermore, high concentrations of the drug must be present in the biologic fluid to form the color reaction. Examples of color or spot test are the tests for salicylate (Trinder 1954), ethchlorvynol (Frings and Cohen 1970), and ethyl alcohol (Kozelka and Hine 1941).

Thin-Layer Chromatography. TLC is the ideal analytical method for the broad spectrum screening of a drug. Development of the technique over the years has increased its sensitivity and ease of operation. However, there are several drawbacks to the use of TLC. The procedure requires extraction and concentration of the drug metabolites, which have to be separated from other endogenous compounds so that interference with the drug's migration and identification are minimized. The color development of the migration spots may differ, depending on the freshness of the reagents. Further staining also is needed to develop reactions by other types of drugs. A permanent copy of the results is also difficult because the color reproduction of the spots may not be

TABLE 1. *Comparison of commonly used analytical techniques*

Technique	Preanalysis Treatment of Sample	Major Instrumentation	Drug Identification	Can Specimen Be Adulterated	Limits of Sensitivity	Instrumentation Costs ($)	Confirmation Required	Multiple Drug Analysis at Once	Level of Personal Experience
TLC	Yes	No	Position on plate	No	1g/mL	. . .	Yes	Yes	High
Modified Toxi-Lab	Yes	No	Response to color reagents fluorescent pattern	No	0.2-5 mg/mL	500	Yes	Yes	Moderate
HPLC with scanning ultraviolet detector	Yes	Yes	Relative retention times; comparison of ultraviolet spectra with standards	No	0.02-10 mg/mL	20,000-50,000	No*	Yes	High
Dual-column capillary GC with nitrogen detectors	Yes	Yes	Relative retention times matched in both columns; comparison of peaks with standards	No	0.01-10 mg/mL	20,000-50,000	No*	Yes	High
Capillary GC/MS	Yes	Yes	Relative retention times; comparison of mass spectra with standards	No	0.001-5 mg/mL	20,000-200,000	No	Yes	High

TABLE 1. *Comparison of commonly used analytical techniques (continued)*

EMIT	No	Yes	Variation in enzyme activity	Yes	0.025-5 mg/mL	7,000-100,000	Yes	No	Moderate
RIA	No	Yes	Variation of bound radiolabeled tracer	Yes	0.001-10 mg/mL	5,000-100,000	Yes	No	Moderate
Color or spot tests	No	No	Response to color reagents	Yes	0.1-10 ng/mL	. . .	Yes	No	Moderate

*Confirmation is necessary only if results must meet a forensic challenge.

KEY: Modified Toxi-Lab=modified thin-layer chromatography; EMIT=enzyme-multiplied immunoassay technique; RIA=radioimmunoassay

SOURCE: Schonberg 1988. copyright 1988. American Academy of Pediatrics

accurate. Last, since TLC has a broad spectrum in the detection of drugs, its specificity is low and usually will need confirmation with other techniques (Sunshine 1963; Sunshine et al. 1966; Davidow et al. 1968; Heaton and Blumburg 1969; Kaistha and Jaffe 1972).

Immunoassay. The advent of immunoassays and the ability to produce antibodies to various drugs (haptens) have added a powerful, sensitive, and rapid analytical method for drug detection. The two most commonly used methods are RIA and enzyme immunoassay (Baselt 1984).

RIA is based on the principle that a radioactive-labeled drug will compete with the unlabeled drug for binding sites in a specific antibody, and the amount of binding of the radiolabeled drug to the antibody is related to the concentration of the unlabeled drug in the sample. Since the level of radioactivity can be measured, RIA is semiquantitative It is a highly sensitive test that can detect drugs and their metabolites at very low concentrations in the sample.

There are some disadvantages to the use of RIA. The procedure requires expensive equipment (gamma scintillation counter) and special training of personnel to conduct the test. The test can detect only one drug at a time, so that testing for a panel of drugs can be time-consuming. Cross-reaction with other compounds also can occur. Compared with TLC, the test is more expensive due to the cost of reagents, equipment, and personnel time.

Enzyme immunoassay is a more commonly used procedure compared with RIA since it is semiquantitative, more rapid, and less expensive. The reagents used in enzyme immunoassay are also stable and have longer shelf life. The principle of the test is similar to that of RIA except that it uses an antigen or hapten labeled to an enzyme instead of to a radioactive element. The test is based on the competition between the enzyme-labeled and unlabeled antigen (hapten) for the antibody. The hapten enzyme compound is enzymatically active unless bound to an antibody. The enzymatic reaction can be quantitated spectrophotometrically or flourimetrically.

In general, there are two types of enzyme immunoassay that are commonly used in drug detection: EMIT and fluorescence immunoassay. EMIT consists first of incubating the serum with a buffered mixture that contains a limited amount of antibody, a small amount of enzyme-labeled drug, substrate, and cofactors for the enzyme. Enzyme activity is measured kinetically (e.g., generation of NADPH) by a spectrophometer. The drug concentration is obtained from a standard curve in which enzyme activity is plotted against drug concentration. Fluorescence immunoassay, on the other hand, utilizes antibodies that react with the antigen (drugs) and produce fluorescence that can

be quantitated. The various types of fluorescence immunoassay differ in the kind of fluorophors they use. One added modification to fluorescence immunoassay has been the use of light in a polarized plane (fluoresence polarization immunoassay) to excite the fluorophore and detect its flourescence in the polarized plane. Other systems of immunoassay, such as the enzyme-linked immunoabsorbent assay (ELISA), recently have been introduced for drug analysis. However, the principal use of ELISA has been in the identification of microbiological agents.

Enzyme immunoassays have their disadvantages. The test is expensive, principally due to the cost of reagents. Cross-reaction with other substances also occurs, so confirmatory tests are required.

High-Performance Liquid Chromatography. HPLC is another highly sensitive and specific method for drug detection. The method consists of the extraction of the drug from the biologic sample, the derivation of the drug, its injection and elution from the column using specific solvents, and the identification of the substance in the eluate from its elution time. Commonly, flame ionization or electron capture detectors are used. Recently, the use of diode array/ultraviolet (UV) visible spectral detectors has further enhanced the specificity of the method. Like the mass spectrometer, the UV spectrum of the specific eluate can be matched by computers against the spectrum of known standards to achieve a high degree of accuracy in specific identification, Again, like the mass spectrometer, HPLC is expensive and requires experience and skill to operate. Likewise, the technique is time-consuming and, therefore, has been used principally for confirmatory purposes (Mule 1971).

Gas Chromatography. GC has been one of the most sensitive and specific techniques in drug detection. However, the analysis is time-consuming since the procedure involves the extraction of the drug into a solvent, its concentration and conversion into a volatile derivative, injection into a gas chromatograph, elution from the column, and detection and quantitation by comparing its retention time with a known standard. Furthermore, the equipment is expensive and requires considerable technical skill to operate. Therefore, GC has not been used for mass screening but as a confirmatory test for other more sensitive and broad screening procedures,

Gas Chromatography/Mass Spectrometry. The most specific tool for the identification of drugs has been a combination of GC with MS. GC separates the biologic extract into its various peaks, and MS is used to establish the identity of each peak. The latter is achieved by the conversion of the compound in each peak into its electrically charged ion fragments. Different compounds break down into different fragment patterns, and like fingerprints, no two

fragment patterns are alike, These fragment patterns then are matched by a computer with the known fragmentation patterns of analytic standards. Because of its high specificity, GC/MS is commonly used for the ultimate identification of drugs and their metabolites in biologic samples. Thus, it is an indispensable tool in forensic work (Costello et al. 1974).

The drawbacks to GC/MS are (1) the enormous expense of the equipment; (2) the time involved with the preparation, separation, and identification of drugs in the samples; and (3) the highly technical skill that is needed to operate the system.

SPECIMENS USED IN DRUG TESTING

Urine

The testing of drugs in biologic fluids is by far the most common method used to detect drug abuse in a pregnant woman or intrauterine drug exposure in a neonate. However, there are several limitations to this method. Identification of drugs in biologic fluids will differentiate only those who have been exposed to drugs vs. those who have not. The test cannot provide information on the amount, frequency, duration, or time of last drug use.

Among the biologic fluids, urine has been most often tested owing to several advantages (Schonberg 1988): (1) Urine collection is easy and noninvasive; (2) drug metabolites in urine usually are found in higher concentrations than in serum due to the concentrating ability of the kidneys; (3) large volumes of urine can be collected; (4) urine is easier to analyze than blood since it is usually devoid of protein and other cellular constituents; (5) the metabolites in urine usually are stable, especially if frozen; and (6) urine is amenable to all the drug testing methods described above.

However, there are several drawbacks to the use of urine for testing. Foremost is the high rate of false-negative results (Ostrea and Chavez 1979; Ostrea et al. 1990b). Urine collection, unless closely watched, easily can be substituted with a clean specimen. Urine samples can be tampered with by dilution or by the addition of ions, such as salt, that may interfere with the testing methods. Drug metabolites in urine also only reflect very recent use of the drug; therefore, negative results may occur if the woman abstains from use of the drug a few days before testing (Schonberg 1988). In the infant, the incidence of false-negative urine tests is also high, ranging from 32 to 63 percent (Halstead et al. 1988; Ostrea et al. 1989; Osterloh and Lee 1989). Urine specimens must be obtained as close to birth as possible to reflect the intrauterine exposure of the infant to drugs. The longer after birth that urine is collected and tested, the

greater the likelihood of a false-negative test. Likewise, as in the mother, drug metabolites in the infant's urine only reflect recent use of drugs by the mother. Recent abstention by the mother from the use of drugs may result in a negative urine test in the infant. The detection rate for drugs in the urine can improve if a battery of tests, rather than a single test, is used (Osterloh and Lee 1989).

Meconium

In the past 2 years, the author and colleagues at Wayne State University have developed a new method for identifying the intrauterine exposure of infants to drugs by testing their meconium for drugs (Ostrea et al. 1988, 1989). The concept behind this method was based on our initial research in pregnant, morphine-addicted monkeys (table 2), which showed that a high concentration of morphine metabolites was present in the gastrointestinal tract of their pups (Ostrea et al. 1980). This was interpreted to be a consequence of morphine being deposited in the gastrointestine through the bile or in swallowed fetal urine through the amniotic fluid. This hypothesis was further tested in rats that were given cocaine, morphine, or cannabinoids during pregnancy (table 3). The presence of corresponding drug metabolites was substantiated in the intestine of their pups (Ostrea et al. 1989).

TABLE 2. *Distribution of morphine in the tissues of addicted newborn monkeys*

	Monkey Number					
	A13	A84	A83	A24	A23	A87
Gestational age, days	118	125	135	147	155	161
Fetal weight, g	240	368	340	365	372	510
Age of addiction, days	71	89	80	104	113	100
Total maternal morphine, g	11.9	14.8	13.6	17.9	19.4	15.7
	Tissue Concentration of Morphine, mg/g Tissue					
Gastrointestines	15.8	128.9	108.4	53.7	66.4	42.1
Liver	0	0	0	47.6	169.5	0
Cerebellum	—	—	—	17.2	46.2	—
Heart	15.7	37.9	—	73.9	9.8	6.8
Spleen	16.2	72.5	—	0	0	53.3
Thymus	0	0	69.7	0	31.9	16.2
Lungs	0	0	35.5	0	13.2	0
Kidneys	0	0	0	0	24.5	3.0
Cerebrum	0	0	15.4	0		0
Brain stem	—	—	—	0	0	—

SOURCE: Ostrea et al. 1980, copyright 1980, S Karger

TABLE 3. *Recovery of drug metabolites in intestines of rat pups whose dams received drugs during pregnancy*

Drug (route)	Dose per Day	Rat Weight (g)	Number of Pups	Drugs In Pups' Intestines* (mg/g)
Pup 1: control animal†	0	212	15	0.00
Pup 2: cocaine HCl (sc)	50 mg/kgx10 days	198	11	0.47
Pup 3: morphlne SO_4 (sc)	50 mg/kgx12 days	216	13	1.38
Pup 4: cannablnold (oral)	25 mg/kgx12 days	223	12	2.50

*Represents drug concentration in pooled intestines
†Dam received no drugs durlng pregnancy.

KEY: HCl-hydrochloric acid; sc=subcutaneous

SOURCE: Ostrea et al. 1999, copyright 1989, Mosby-Year Book, Inc.

In subsequent clinical studies, we tested the urine and meconium of 20 infants of drug-dependent mothers for the metabolites of cocaine, morphine, or cannabinoids (table 4). High concentrations of drug metabolites were found in meconium during the first 2 days, and some stools still tested positively on the third postnatal day. In contrast, only 37 percent of the drug-dependent infants had positive urine screens, and for each positive result only one drug was identified, usually corresponding to the drug that had the highest concentration in the stool samples (Ostrea et al. 1989).

The sensitivity of meconium analysis is high when compared to other methods of drug detection, such as maternal hair analysis (see below) and structured interview (see above) of the mother (Ostrea et al. 1990b). In a study of 26 subjects (table 5), the abuse of at least one drug (besides alcohol) during pregnancy was identified in 73 percent of the subjects by structured interview, using a modified Khavari questionnaire (Khavari and Douglass 1981), in 69.2 percent by meconium analysis, and in 75 percent by maternal hair analysis. Abuse of two or more drugs was identified in 23 percent of the subjects by history and in 35 and 50 percent of the subjects by meconium and hair analyses, respectively. There was a 96-percent concordance in cocaine detection by meconium and hair analysis and a 73-percent concordance for heroin and cannabinoid (table 6). This study showed that meconium analysis has a high sensitivity in detecting maternal drug abuse. Compared with maternal hair analysis, it has the advantage of being noninvasive. The sensitivity and specificity of meconium analysis also have been confirmed recently by other investigators (Maynard et al. 1991). Compared with maternal and neonatal urine testing, meconium analysis was found to be 96 percent sensitive and 77 percent specific.

TABLE 4. *Recovery of drug metabolites in meconium of drug-dependent infants (n=20)*

Cocaine (mg/g stool)			Morphine (mg/g stool)			Cannabinold (mg/g stool)			
Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Urine Screen*
6.35	3 23	(-)	3.26	1.72	0.56	(-)	(-)	(-)	(-)
2.34	2.17	1.17	1.19	1.17	(-)	(-)	(-)	(-)	(-)
1.77	9.68	3.67	(-)	(-)	(-)	(-)	(-)	(-)	(-)
10.86	11.29	(-)	(-)	(-)	(-)	0.13	0.29	(-)	(-)
(-)	(-)	(-)	5 3 6	12.11	(-)	0.05	(-)	(-)	Opiates
4.54	17.78	1 0 3	(-)	(-)	(-)	0 34	0 66	(-)	Cocaine
(-)	(-)	(-)	0 69	0.97	0.54	(-)	(-)	(-)	(-)
2.39	2.16	1 0 7	3.75	2 43	2.31	(-)	(-)	(-)	(-)
5.40	6.41	0. 41	(-)	(-)	(-)	(-)	0.09	(-)	Cocaine
(-)	(-)	NS	11 74	14.97	NS	(-)	(-)	NS	Opiates
(-)	(-)	(-)	(-)	(-)	(-)	0 06	0 09	(-)	(-)
11.48	0 4 1	(-)	(-)	(-)	(-)	0 1 3	(-)	(-)	Cocaine
7 40	6 70	NS	5 36	5 73	NS	0 .48	0 3 7	NS	Cocaine
11.42	0 29	NS	6.95	0 73	NS	0 67	(-)	NS	(-)
3.29	1991	6.10	(-)	(-)	(-)	(-)	(-)	(-)	NS
0.26	(-)	NS	2 2 6	0 7 7	NS	0 14	(-)	NS	(-)
1 76	3.52	2 4 2	1 2 4	1 21	1 2 4	(-)	(-)	0.12	(-)
NS	16.23	13.15	NS	0 4 1	(-)	NS	0.22	0.09	Cocaine
0.95	0 14	(-)	(-)	(-)	(-)	0.07	(-)	(-)	(-)
0.06	0.03	(-)	(-)	(-)	(-)	0.19	0.17	0.05	(-)

*Urine drug screen by the TD_x imnunoassay system (Abbott)

KEY: (-)=negatwe for drug tested. NS=no sample

SOURCE Ostrea et al. 1989, copyrlght 1989, Mosby-Year Book, Inc.

Ostrea and colleagues (1990a) recently have used meconium analysis to determine the prevalence of illicit drug abuse in a large population of women delivering at a tertiary perinatal center. By self-report, the incidence of drug abuse in the mothers was 10.5 percent. In contrast, 42 percent of the infants tested showed cocaine, heroin, or cannabinoid metabolites in meconium; 38.9 percent were positive for cocaine or heroin alone (table 7) (Ostrea et al. 1990a). These results indicate an extent of the drug abuse problem in pregnancy in the population studied and a magnitude that was unrecognized.

TABLE 5. *Antenatal drug exposure in 26 pregnant women as determined by analysis of infant stool and maternal hair and by maternal history*

	Infant Stool	Maternal Hair	Maternal History
Number of subjects with samples	26/26 (100%)	16/26 (61.5%)	26/26 (100%)
Detection of 1 drug	69.2%	75.0%	73.0%
Detection of ≥1 drug	34.6%	50.0%	23.0%
Exposure to:			
Cocaine	61.5%	66.8%	76.9%
Heroin	34.6%	25.0%	7.7%
Marijuana	26.9%	31.3%	19.2%

SOURCE: Ostrea et al. 1990b

TABLE 6. *Concordance of drug detection by meconium and hair analysis*

Drug Detected	Meconium vs. Hair Analysis			
Cocaine		Hair		
	Meconium	-	+	
	-	4	1	Sensitivity=(11/12) 92%
	+	0	11	Specificity=(4/4) 100%
Morphine		Hair		
	Meconium	-	+	
	-	8	1	Sensitivity=(3/4) 75%
	+	4	3	Specificity=(8/12) 67%
Cannabinoid		Hair		
	Meconium	-	+	
	-	8	2	Sensitivity=(3/5) 60%
	+	1	3	Specificity=(8/9) 89%

TABLE 7. *Prevalence of intrauterine exposure to cocaine, opiates, or cannabinoids in 1,000 infants delivered in a tertiary perinatal center*

Means of Detection	Percent Positive
Meconium analysis	
For cocaine, morphine, or THC	42
For cocaine or morphine	38
Maternal self-report	10.5

SOURCE: Ostrea et al. 1990a

Recent developments in meconium testing have included tests for methamphetamine in addition to tests for cocaine, opiates, and cannabinoids (Silvestre and Ostrea 1991). Similarly, meconium testing, formerly analyzed only by RIA, also can be analyzed by enzyme immunoassay (Ostrea et al. 1991a), latex agglutination inhibition test (Gervasio and Ostrea 1991), GC/MS (Ostrea et al. 1991 b), and solid-phase RIA (Lucena and Ostrea 1991).

Meconium analysis is a new, sensitive, and noninvasive method for detecting intrauterine exposure of infants to drugs. The procedure is quantitative, rapid, and easily performed. The test is useful for diagnostic purposes and is also an important, sensitive, and noninvasive research tool for clinical and epidemiologic studies.

Hair

Analysis of hair for drugs has been developed recently (Baumgartner et al. 1989). The test is based on the principle that illicit substances and their metabolic products in the patient's blood become incorporated in the hair follicle and grow into the cuticle and hair shaft. The drug, once deposited in the hair shaft, remains for an indefinite period. As the hair grows, at the rate of one or one-half centimeter a month, the deposited drug follows the growth of the hair shaft. Thus, hair analysis not only will allow the detection of drug use in a person but also (through sectional analysis) will provide information on the duration and time of drug use. The information, particularly on the chronicity of drug use, makes hair analysis advantageous over urine or other body fluid testing. Furthermore, quantitative detection of drugs in hair has been correlated to the amount of drug use in the past.

Hair has been successfully analyzed to detect use of opiates (Baumgartner et al. 1979), cocaine (Baumgartner et al. 1982) phencyclidine (Baumgartner et al.

1981), and methamphetamine, antidepressants, and nicotine (Ishiyama 1983). The analytical procedures that have been employed include RIA (Baumgartner et al. 1989), GC/MS (Balabanova and Homoki 1987), HPLC (Marigo et al. 1986), and collisional spectroscopy (Pelli et al. 1987).

The validity of hair analysis for drug detection also has been demonstrated in the neonate (Graham et al. 1989) and in pregnant women (Welch et al. 1990). In these situations, the technique has been found to be highly sensitive (Welch et al. 1990).

There are some drawbacks to the use of hair for testing (Bailey 1989). The test is expensive and time-consuming since extraction and concentration of minute amounts of drugs in the hair are necessary. The amount of hair available for a sample may be a problem, particularly in the newborn infant or in patients with cropped hair. Patients can refuse to give hair samples if fearful of self-incrimination (Ostrea et al. 1990b). Last, since hair grows slowly, very recent or acute use of drugs may not be detected by hair analysis.

Other Specimens

Other types of specimens have been tested for drugs. These include perspiration, nail clippings, menstrual blood, semen, and saliva (Smith 1981; Smith and Liu 1986). However, the use of these specimens for drug detection has been uncommon.

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Methodological Issues in Obtaining and Managing Substance Abuse Information From Prenatal Patients

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INTRODUCTION

Heavy prenatal alcohol exposure has been increasingly recognized as a major perinatal risk particularly in the last two decades (Jones and Smith 1973). Illicit drug abuse, especially of cocaine, in reproductive-age women and in association with pregnancy also has been associated with worsened perinatal outcomes (Dombrowski and Sokol 1990). Cocaine abuse is now epidemic. Clearly, there is increased need for ongoing clinical studies, both animal and human, on the antecedents and consequences of polysubstance abuse for pregnancy and antenatal outcomes.

This chapter deals with key methodological issues involved in obtaining and managing substance abuse information. There is a vast refereed literature that is, for the most part, readily available to investigators and clinicians dealing with these issues, Since the authors have been involved with prenatal screening of patients for substance abuse for over 18 years and, using various methodologies, have screened more than 40,000 consecutive prenatal clinic patients in two inner-city environments, the experiences of this research group will be shared as “tricks of the trade.”

To present these “tricks” the chapter is presented in two parts: (1) key problems and issues in data collection and (2) key issues in quantification, data management, and statistical analysis of substance abuse variables in relation to outcomes of the offspring.

DATA COLLECTION

How to obtain reliable and valid information reflecting the prenatal exposure of the fetus to alcohol has been described previously (Sokol et al. 1985a). This section presents a potpourri of issues evolving from experiences in this area

because of its particular value to other researchers studying substance abuse in pregnancy.

Avoid Denial

Denial is a recognized component of alcohol dependence. In addition to alcohol, the most widely abused drugs in pregnancy are illicit, including marijuana, cocaine, and opiates (i.e., heroin). Thus, denial also complicates obtaining reliable estimates of prenatal exposure for these substances. Although the phenomenon of denial of heavy alcohol use has been studied in detail (Nadler et al. 1987), how this phenomenon applies to other substances is much more "impressionistic" and has not yet been studied. Biochemical detection of drugs in meconium is substantially more accurate than interview in documenting exposure history (Welch et al. 1990), and this method can be used as a basis for studying denial of drug use. Thus, the issue is overcoming patient denial to obtain data that will reflect perinatal drug exposure with adequate precision, accuracy, and reliability for research use.

Heavy maternal drinking is a major fetal risk that must be detected to be prevented. Currently, obtaining an alcohol history is the only practical way to identify heavy exposure. Anecdotal evidence suggests that acknowledging problem drinking is complicated not only by psychologic denial but also by warnings not to drink. A "natural experiment" in a prenatal clinic permitted testing of this hypothesis. In a pilot for a large prospective study of 314 pregnant women, 269 patients were assessed for alcohol abuse using the Michigan Alcoholism Screening Test (MAST) and the "cut down-annoyed-guilt-eye opener" (CAGE) questionnaires, measures of chronic alcohol problems and dependence, and prenatal and current drinking histories. The rate of problem drinking among these 269 women was markedly lower than that found in more than 8,000 previous histories in this and another large antenatal clinic. These 269 patients had been seen by a nurse who interviewed the patients before any other health care provider warned them of damage to the fetus by drinking and drug use. The interview order was changed so patients were seen by the alcohol/drug screener first. Trimmed t-tests showed no significant demographic differences or differences in rates of abstinence in groups interviewed Nurse First (n=150) and Nurse After (n=164) the change in order. For those who drank, MAST and CAGE scores were significantly higher in the Nurse After group (MAST $p<.006$, CAGE $p<.009$); reported embryonic (periconceptional) absolute alcohol/day increased significantly ($p<.01$); and reported current absolute alcohol/day was statistically unchanged. These results document quantitatively an increase in reported drinking related to nonjudgmental patient/health care provider interactions and are consistent with the interpretation that guilt-inducing warnings increase denial and are counterproductive. Thus, the

first step in minimizing denial is to maintain a nonjudgmental, focused approach in obtaining an alcohol history. Patients should be reassured that if they abstain from or limit drinking in pregnancy they can have a healthier baby (Nadler et al. 1987).

A second step to avoid denial is not to ask quantity and frequency initially but rather to focus initially on the consequences of substance abuse on the patient's life (Sokol et al. 1989a). For example, a four-question battery with high sensitivity and adequate positive predictive value (i.e., the T-ACE questions in table 1) was developed. The T-ACE sidesteps denial and has the advantage of brevity, making it particularly useful in the prenatal clinic. Other short questionnaires have been evaluated (Mar-tier et al. 1990; Bottoms et al. 1989).

TABLE 1. *The T-ACE questions. A score of ≥2 is considered positive, suggesting that the patient may be a risk drinker (i.e., an individual drinking enough potentially to damage her baby).*

T	**Tolerance.** How many drinks does it take to make you feel high? (Score 2 if ≥3 drinks.)
A	**Annoyed.** Have people *annoyed* you by criticizing your drinking? (Score 1 if positive.)
C	**Cut down.** Have you felt you ought to *cut down* on your drinking? (Score 1 if positive.)
E	**Eye opener.** Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (Score 1 if positive.)

SOURCE: Sokol et al. 1989a, copyright 1989, Mosby-Year Book, Inc.

A similar approach is used for other drugs. Questions about illicit substances are avoided until the end of the first interview. As the patient leaves, she is asked, "By the way, do you use cocaine.?" Cocaine is asked about because of current patterns of use. If the patient says, "Yes," she is asked about quantity, frequency of use, and drug use by her significant other.

At the second prenatal visit, a more structured approach to eliciting drug history is taken. In settings where prevalence of illicit drug use is very high, the interview should begin with questions about licit (prescription) drugs and then move to illicit drugs (i.e., the "oblique approach"). This represents a third step to minimize denial.

Although necessary, helping the pregnant woman avoid denial of illicit drug use is not sufficient for a valid history. Manuals are available that list drugs and their street names, but terms vary from community to community. Listening to the patient and keeping abreast of popular drug names is a must. This also applies to quantification of drugs (e.g., knowing what a "dime" is for drugs and a "jumbo" is for beer). Knowing the amount of money spent on drugs might be a useful indicator, but because costs change, further refinement is needed. Routine urine drug screens are well known to most clinic populations, and the steps clients take to avoid detection may account for the low sensitivity of these screens. Nonetheless, a positive initial urinary drug screen should initiate a probe for use of other drugs (Sokol et al. 1985a). The same is true of drug abuse by a patient's partner.

In summary, a nonjudgmental but aggressive approach to eliciting substance use/abuse information is valuable in avoiding denial and, thus, in obtaining a valid history of use.

Assume She Uses a Lot

Over the years many individuals have been involved with screening for prenatal drug use, on both a clinical and a research basis. In our present study, more than 20 people have been trained for screening over the past 3 years. Evaluating the experience of these screenings is enlightening. Even though rates of abstention and drinking levels have remained consistent throughout the study, there has been a wide variation in rates by screeners. Abstention rates by screeners have ranged from 4.9 percent to 26.0 percent, whereas the frequencies of problem drinkers have ranged from 2.2 percent to 7.9 percent. To deal with this variability and the implied underascertainment, it is important to maintain a clinic staff with a fresh outlook-screeners who continue to probe, who do not become bored with following the same script in the same way, and who are persistent. Role playing between screeners, duplicating interviews, should be done weekly to help screeners deal creatively with problems that arise within a structured format.

The most successful screeners assume that any given patient has a reasonable probability of using one or more substances. Therefore, the attitude has to be, "Don't take no for an answer." This is not a particularly risky strategy as there is little if any evidence of "overreporting" (Morrow-Tlucak et al. 1989; Jacobson et al. 1989).

This approach is extended by "overestimating" substance use. For example, if the patient admits to drinking one bottle of beer, the interviewer responds with the supposition that the patient is drinking jumbos (a 40-ounce bottle). The

message to the patient is that it is okay to admit to drinking jumbos. Also, when asking a patient how much wine it takes to make her feel "high," quantity is suggested in bottles rather than glasses. Experience indicates that patients are much less likely to report amounts above that initially suggested by the screener. As applied to other substance use, if the patient admits to smoking, the term "regular cigarettes" is used, implicitly suggesting to the patient no surprise at her smoking marijuana or other substances,

A final component of these tactics involves a "meta-approach" of monitoring the detection rates of screeners. This is a very valuable method from two perspectives. First, many study designs utilize weighted samples, often in a block design, which requires modification of proportions of patients admitted to the study at various use levels. Thus, monitoring the frequency of reported substance use is a natural part of the study design. Second, monitoring the frequency of abstinence/use can document any deterioration in performance, detected by comparing one interviewer with others and/or with previous detection rates.

Where, How, and With Whom?

Patients do not think in ounces of absolute alcohol or in milligrams of tetrahydrocannabinol; thus, one can expect substantially better detection if substance use is placed within social context, For example, it is useful to associate drug use with special events (holidays and birthdays), the site of use (bars or the home of a friend), or sexual behavior. Further, the use of an occasion-by-occasion (day-by-day) approach requires much less "mental agility" than asking an individual to apply the concept of "on the average" to a week or a month-which may be well beyond the patient's capacity, especially if he or she is poorly educated.

QUANTIFICATION, DATA MANAGEMENT, AND STATISTICAL ANALYSIS

Data Input and Preliminary Analysis

Data Preparation. Problems inherent in the preliminary stages of data input, construction of appropriate database systems, data cleaning, and evaluation of data integrity and reliability usually are underestimated. In this section, some techniques and procedures are outlined that we have found helpful in dealing with these data preparation problems.

Computerized data entry screens can be set up, naming each variable and its makeup in character fields, integers, or floating points. Upper and lower limits are stated for each variable so that entry is stopped if a value falls outside the

range. The data entry person reviews the screen for each case entered before signaling the computer to continue. The authors' experience indicates that the efficiency and reliability of direct entry using such screens fully justifies the initial additional effort required to construct them.

Coding and Data Cleaning. An aspect of data preparation that requires careful thought is coding. This is particularly a problem when there are various types of missing data, including "no response" and "not applicable." For example, in screening women for alcohol history, one should differentiate among women abstinent all their lives, those with no problems associated with drinking, and those to whom a screening device was not administered for other reasons. For example, if using the MAST, it is useful to specify a separate code for each of these categories. Generalizing from this, it is best to code as many categories of response as may be determined reliably. These may be collapsed for various statistical analyses. Thus, distinctions that may be useful later are not lost.

One problem in statistical analyses is ensuring that missing data and other special codes are not included in the statistical calculations, These are assigned values very different from actual scores (e.g., -99 or -88) which makes their inadvertent inclusion in analysis easy to spot. Furthermore, the descriptive statistics in most statistical packages include output of the maximum and minimum scores used in the analysis. Again, this makes inadvertent inclusion of codes representing missing data easy to flag.

Problems in Longitudinal Evaluation of Fetal Exposure: Relational Databases

The fact that maternal data are collected throughout pregnancy represents a rich source of longitudinal information and, at the same time, a set of most difficult design and analysis problems. The main difficulties stem from the fact that the women will have varying numbers of visits at different gestational ages. An additional difficulty is that often the gestational age itself cannot be ascertained as accurately as one would wish. Consequently, the record for each patient must be individualized. Because of the problems of differential record size, the use of relational databases is recommended rather than the traditional rectangular type. For example, the use of INGRES (Epstein 1977) running under UNIX (McGilton and Morgan 1983) allows up to 49 variables to be represented in each relation; relations then can be joined as necessary using a maternal identification number for the purpose of conducting a particular set of statistical analyses.

Despite the problems in representing complex longitudinal data sets, there are questions that can be addressed with this type of data that are difficult, if not impossible, to answer with cross-sectional data. For example, the pattern of abuse behavior within individual patients over the course of pregnancy can be tracked and then related to outcome. The timing of the substance abuse or change in abuse over trimesters may be important and may have differential effects on specific outcomes (Ernhart et al. 1987). All such questions essentially require longitudinal data and analyses.

Missing Data Problems and Estimating Missing Values

The problem of missing data is endemic in field research, especially in studies with a longitudinal component. As a first step in preparing the data for multivariate analysis, it is useful to screen the data array for both individuals and variables having excessive amounts of missing data. Typically, dropping relatively few subjects and/or variables will eliminate the bulk of the missing values. For estimating the remaining missing values, several procedures are available, ranging from the simple, but crude, to the more complex, but precise. An example of the former is replacing the missing value by the group mean for that variable. More elaborate methods use multiple regression procedures to estimate the missing values from the data that are available for the given subject. In some cases, iterative procedures are used for this purpose.

List-wise deletion is the most common technique for handling missing data available in the widely used statistical packages (e.g., SPSS, SAS, BMDP) (SPSS 1986; SPSS, Inc. 1988; SAS Institute, Inc. 1985; Dixon 1985). In this method, those subjects missing a score on any variable in the analysis are eliminated. Unfortunately, this procedure often results in a large drop in sample size with the consequences of both lower statistical power and bias in the remaining sample. The most widely used statistical packages, for the most part, have not included as options the more sophisticated multiple regression-type methods for estimating values; an exception is BMDP (Tabachnik and Fidell 1983). There is reason to believe, however, that such routines will become available in future versions.

Skewed Distributions and Outliers. Many of the variables, both independent and dependent, used in substance abuse research tend to have highly skewed distributions. Certainly this is true for the abuse variables themselves (e.g., smoking, alcohol and other drug use), as well as for some extraneous variables (e.g., medical risks). Infant outcome variables (e.g., number of birth anomalies) are also often positively skewed. Even birth weight, which in its continuous form may be only slightly skewed, becomes highly skewed when trichotomized into very low, low, and normal.

There are two major consequences of skewed distributions for statistical. analysis. The first is that most inferential techniques used with the usual multivariate techniques (e.g., multiple regression, linear discriminant function analysis, analysis of variance) assume a multivariate normal distribution of the variables. Although the statistical tests (e.g., F) are relatively robust to moderate violations of normality assumptions, such tests become problematic when skewness is extreme. (It also should be noted that kurtosis [e.g., a relatively heavy frequency of cases in the tails of the distribution] also tends to have a biasing effect on sampling distributions of the usual test statistics.)

There are several techniques that can be used to minimize the degree of skewness and its effects on the analysis, One common method is use of the log or square root transformations. Other nonlinear transformations also can be used, but transformed values often have little psychological “reality” (i.e., they are harder to interpret and understand than the raw values). Another approach is to recategorize the variable, in effect collapsing the extreme categories. Robust and nonparametric analyses that involve less restrictive distributional assumptions also might be used when available for the particular analysis of interest.

Another problem concerns variables with different marginal distributions, In this case, the maximum magnitude of the Pearson correlation coefficient is less than unity (Carroll 1961). This can be a problem with dichotomous or trichotomous variables with a relatively small proportion of cases in the extreme category. For example, the maximum point biserial R between a normally distributed variable and a dichotomous variable with 5 percent of cases in the less frequent category is only .47. As Carroll has shown, it is always possible to calculate R^2 max for any two marginal distributions, The R^2 max then represents the predictable variance in y. The same interpretation can be made for multiple R^2 max.

An example of the effects of extreme splits on R arose in the Cleveland study (Sokol et al. 1985a) on the antecedents of fetal alcohol syndrome (FAS). Of the 8,331 patients in this study, 25 (.3 percent) had a diagnosis of FAS. A multiple regression model, including as predictors MAST, proportion drinking days, parity, and race (all significant), yielded a multiple point biserial R^2 of .061. Although the 6.1 percent of variance accounted for seems almost inconsequential, this interpretation changes radically when one considers that the max R^2 with this split on the outcome is only .118; that is, over one-half of the predictable variance is accounted for by these predictors.

A final problem that can be considered an extreme form of skewness is that of outliers. Such scores are so extreme that they are considered not to be from

the same distribution as the rest of the scores. Outliers are a particularly serious problem because such scores can have a very large, and possibly biasing, effect on the analysis. Recategorizing such scores (e.g., by "Windsorizing") or eliminating them (e.g., "trimming") is usually recommended.

Interrater Reliability

Problems with the various types of biases that may affect measurements of the various independent and dependent variables (e.g., attrition and ascertainment) are well known and will not be discussed here. Issues of reliability and validity are also generally recognized. One type of reliability, however, that is of critical importance but is often overlooked is that of interrater reliability. Raters viewing the same behavior in a number of patients can differ both in ranking individuals on the scale and also in the absolute scale value assigned. A reliability index that takes both types of error into account is the intraclass correlation (ICC). Use of the ICC for different interrater study designs has been discussed by Shrout and Fleiss (1979). For categorical variables, coefficient kappa can be used (Cohen 1960).

Interrater reliability was an issue in the Detroit (Jacobson et al. 1988) study in the assessment of infant dysmorphology. Training was continued until the interrater agreement on the dysmorphology counts was viewed as adequate-in this case, the ICCs improved from .69 to .92.

Statistical Analysis

Drug Research-Inherently Multivariate. Research on the antecedents and consequences of alcohol and other drug abuse in human populations is usually correlational in design and almost always multivariate in analysis. To ensure validity and interpretability of such analyses, it is necessary that the study design include a sampling of the relevant variables that is as complete as possible. In generating such a list of variables, it is useful to organize them into domains. On the predictor (independent variable) side, such domains typically include (1) background/demographic information, (2) medical risks, (3) other substances of abuse, and (4) the target abuse variable set. On the outcome (dependent variable) side, domains might include neonatal outcomes and later cognitive development.

The first three domains represent extraneous variables and are used primarily to make appropriate statistical adjustments of the target variable. They also may be evaluated as possible moderator variables as discussed below. In studies of the effects of maternal drinking on infant outcomes, a relatively small set of background variables has been found to be consistently related to

target variables and to outcomes. This background set usually includes the mother's age, parity, and race.

Under medical/obstetric risks (excluding other substance abuse), such conditions as hypertension, diabetes mellitus, and other major medical complications are usually included. One usually excludes from medical risks those medical conditions or previous pregnancy outcomes that may, in large part, be due to abuse of either the target drugs or other substances. A case in point might be previous spontaneous abortions. Although certainly a risk factor for adverse outcome in the present pregnancy, inclusion of this variable in the predictor set might well inappropriately reduce the outcome variance attributable to abuse of the target drug or other substances.

Designation of certain of the substance abuse variables as target variables and others as "extraneous" variables is to some extent arbitrary. Polydrug use and abuse is the rule, and the challenge is to root out their individual and joint (interactive) effects on the specific outcomes. The way in which the treatment of the target set differs from that of the other abuse variables is that the target set tends to be measured more extensively and in depth. Investigators need to be aware that the effects of target variables may be overstated because they, in aggregate, are likely to be more reliably measured.

In most investigations, several outcome domains are apt to be of interest. Effects of the abuse variables and their combinations may be specific to certain outcomes. In addition, certain immediate outcomes in turn may be mediators or moderators of later adverse effects. For example, using the Cleveland data set, Greene and colleagues (1991) found that occurrence of alcohol-related birth defects (ARBDs) apparently mediated the relationship between maternal drinking and later cognitive development, in that those infants who had a higher anomaly count tended to have the lower IQs.

Adjusting for Extraneous Variables. The term "extraneous" does not mean that the variables so labeled are unimportant; on the contrary, they are absolutely critical in the multivariate analysis. As briefly outlined below, there are several types of extraneous variables, including confounders, covariates, mediators and partial mediators, moderators, and suppressors. Appropriate specification of type of extraneous variable implies a path-type causal model, whether or not the model is made explicit. Agreement between a particular model and data does not prove that the model with its causal pathways is correct, as many models may be in reasonable concordance with the data. Nevertheless, one may be able to conclude that the model is a viable one at least. Furthermore, and perhaps more importantly, construction of such models requires investigators to make their causal assumptions about the variables explicit.

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Confounders, as defined by Schlesselman (1982), meet the following criteria. First, a confounder is related to, but not caused by, the exposure variable. Second, it has a relationship, not necessarily causal, to the outcome. Finally, a confounder is expected to relate to outcome even in the absence of the exposure variable. Thus, in studies of effects of maternal drinking on birth weight, smoking would qualify as a confounder, whereas, as mentioned above, previous spontaneous abortions probably would not because previous abortions might be due in part to the exposure variable of maternal drinking. When variables of this latter type are treated as confounders, they tend to adjust out valid variance in the exposure variable leading to an underestimate of the exposure effect. In multiple regression, linear discriminant function (LDF) and logistic regression analyses confounders are included in the predictor set.

Although analysis of covariance (ANCOVA) has been criticized as a method of adjusting for extraneous variables in correlational designs, the problems of possible overadjustments or underadjustments also arise in the other multivariate procedures, for example, multiple regression (MR) and LDF analyses. In ANCOVA, the dependent variable is residualized for the covariates based on the (pooled) within-group regressions, ANCOVA has been used in the determination of thresholds for ARBDs using race, parity, smoking, and "examiner" (dummy-coded) as the covariates; this last covariate represented an adjustment for an aberrant examiner who consistently underreported the number of ARBDs (Sokol et al. 1989b). A variation of ANCOVA developed for use in the Cleveland studies also should be noted (Sokol et al. 1985b). In this approach, only the control group (e.g., combined light drinkers and abstainers) is used to determine the regression coefficients. Use of this approach avoids possible problems with heterogeneity of regression. Little precision in estimating the regression coefficients is lost since the low abuse groups are typically much larger than the heavy abuse groups.

The concern with mediation and *partial mediation* is the issue of direct vs. indirect effects of the abuse variable on the outcomes. For example, quality of home environment might act as a mediator of the effects of maternal alcohol abuse on cognitive development. In this path model, maternal alcohol abuse would lead to a deficient home environment, which in turn would result in poorer cognitive performance of the offspring. If, in addition, there were direct effects of maternal drinking on cognitive development, this would be an example of partial mediation. Again, we emphasize that such mediators and partial mediators are only identified as such within hypothesized path models.

Suppressor relationships between variables occur when the part correlations are (reliably) larger than the corresponding zero-order correlations (Smith et al., in press). Addition of a suppressor variable to a multiple regression equation

results in improved prediction, primarily because nonvalid variance is partialled out of the target predictor(s). When two variables both have positive correlations with the criterion variable but are *negatively* correlated with each other, suppression is said to occur. A pattern in which two highly correlated variables have greatly different validities also can give rise to the suppression phenomenon. Suppression is probably often overlooked. Unfortunately, no satisfactory significance tests are yet available to establish reliability of the patterns of suppression.

If the relationship between two given variables (e.g., a predictor xand an outcome *y)* changes as a function of third variable *z,* then *z* is termed a *moderator.* Moderators usually are identified in correlational designs by including crossproduct terms in LDF or MR analyses. Thus, moderator effects are closely akin to interaction effects in ANCOVA. The identification and interpretation of moderator effects is based on significance of the regression coefficients for the crossproduct terms. In interpretation, the sign of the regression coefficient needs to be carefully noted. Assuming both predictors are positively related to the criterion, a positive crossproduct term denotes a *synergistic* moderator effect (i.e., the joint effect of the predictor and moderator is greater than would be expected from their individual effects). An antagonistic effect occurs when the regression coefficient is negative, indicating that the joint effect is *less* than predicted from the individual effects. Antagonistic effects can occur, for example, when each of two substances acting alone produces a negative infant outcome but the addition of the second abuse variable produces a relatively small incremental effect.

Interactive effects may be of considerable importance given the typical pattern of polydrug abuse. A study of the impact of substance use on perinatal loss demonstrates this. Although alcohol and cocaine abuse have been reported to be associated with late spontaneous abortion and preterm delivery, critical appraisal of polydrug use and risk for pregnancy loss is lacking. Based on a Detroit sample of 3,943 consecutive black gravidas registered for care in a core city prenatal clinic and screened for substance abuse, 133 (3.4 percent) experienced fully documented pregnancy loss (Sokol et al. 1986). Using discriminate analyses, 77 pregnancies resulting in spontaneous abortion, 40 in stillbirth, and 16 in neonatal death were contrasted for substance abuse and control variables with those resulting in survival. First trimester registration was uncommon. The median gestational age of the mothers' first antenatal clinic visit was 23 weeks, Abortion was related to alcohol abuse and to narcotic use. Stillbirth was related only to alcohol abuse, but neonatal death, at a mean of 26 weeks, was associated with cocaine in conjunction with cannabis or narcotic use (Sokol et al. 1990). Though substance abuse occurred in 14.5 percent of pregnancy losses, the effect sizes were small, ranging up to 2 percent. The

odds of pregnancy loss for substance (alcohol and other drug) abusers was increased 1.8±.5-fold ($p<.002$). These results confirm a relationship of alcohol abuse to late abortion and stillbirth. They also demonstrate the difficulty of differentiating drug effects given underreporting of polydrug use, the infrequency of pregnancy loss, and selection bias against pregnancy losses in perinatal databases, Thus, it is likely that the strength of these associations is considerably underestimated. Further studies of the potential synergistic effects on perinatal outcomes of substances of abuse are needed (Sokol et al. 1990).

Race is another example of a strong moderator effect on the effects of maternal drinking and occurrence of ARBDs as discussed below.

Modeling the Nature of Relationships. There are three major questions for the statistical analysis of relationships between predictors and outcomes. The first is that of the existence of a reliable relationship as determined from tests of the null hypothesis of no relationship. A second question is that of the magnitude of relationships (e.g., as assessed by a multiple correlation). The third and probably most important set of questions concerns the nature of these relationships.

In the initial stages of analysis, emphasis tends to be on the problems of identification of those target independent variables and extraneous variables to be retained in a reduced model. The focus is on identification of reliable linear relationships. Once a reduced set of variables has been identified, attention turns to the determination of the nature of the relationships between target variables and outcomes.

For studies of the effects of substance abuse on infant outcomes, two critical issues are threshold and susceptibility. For the first, one must establish, if possible, a point on the abuse scale below which there are no discernible negative effects on outcome (“no-effect zone”) and above which such negative effects can be reliably detected. The presence of a threshold indicates nonlinearity of the relationship. For this purpose, we have used an ANCOVA approach in our studies of the effects of maternal drinking on ARBDs. Women were categorized into five groups based on an estimate of absolute alcohol per day; the dependent variable was number of ARBDs adjusted for age (or parity), race, smoking, and possibly examiner bias. Pair-wise differences between adjacent group means were evaluated using one-sided t-tests. Although this approach inflates Type I error, the concern in this case was Type II error (not finding a true difference), which is minimized in this analysis (Ernhart et al. 1987).

In the above analysis, there was an interaction with race. That is, for the groups at a lower level of drinking (the first three groups), there was no difference between blacks and whites on ARBDs. For the two heaviest drinking groups (above threshold), there was a significantly greater number of ARBDs for the black infants. Analyses for each group separately revealed a higher threshold for whites (above 4.0 ounces of absolute alcohol per day) than for blacks (3.0 ounces). These results were interpreted to represent a susceptibility effect for blacks with regard to the effect of maternal drinking on ARBDs (Sokol et al. 1989b).

A similar methodology was used to study threshold exposures, by race, for full FAS. Alcohol-attributable adverse perinatal outcomes ranged from subtle neurobehavioral abnormality to anatomic ARBDs, FAS, stillbirth, and abortion, thus suggesting a "continuum of reproductive causality" for this fetotoxic/ teratogenic agent. A no-effect zone below and a dose-response relationship above a threshold of more than four drinks a day during the embryonic period for ARBD in a sample of 1,290 pregnancies is noted above. A threshold for a more severe adverse outcome with greater fetal exposure has not been documented in humans. To test the hypothesis that higher doses lead to worse outcomes, the dose-response relationship for FAS (25 cases) in the same sample was evaluated by logistic regression analysis. The model (shown in table 2) was highly significant (x^2=28.004). There was no significant increment in risk with increased exposure until Group 5, indicating a higher threshold for FAS than for isolated ARBD. These results provided a step in defining an overall dose-response relationship for prenatal alcohol exposure and adverse pregnancy outcomes in the "continuum of reproductive causality." Results are encouraging for prevention since the high-risk population appears well defined and delimited (Sokol et al. 1988).

COMMENTS AND CONCLUSIONS

Research in this area is not easy. Ideally, one should be able to explicitly formulate and test models based on animal work, known biologic mechanisms, previous human studies, and clinical studies. Indeed, measurement and analysis strategies, particularly adjustments for extraneous variables, imply such models whether or not they are stated explicitly. Nevertheless, much of the work with humans must be considered largely exploratory. Consequently, one needs to measure and evaluate large numbers of variables with (if possible) large samples. Because of multiple comparison problems inherent in such exploratory research, cross-validation designs are often useful.

As indicated at the outset, this chapter does not attempt to be comprehensive in the discussion of data collection preparation and analysis problems and

TABLE 2. Logistic regression model relating increasing prenatal alcohol *exposure to risk for FAS*

Exposure Groups	Number Drinks/Day	N	0 bserved % FAS	Expected % FAS
1	0	374	0.3	0.4
2	>0, ≤2	507	1.4	1.0
3	>2, ≤4	265	1.9	2.4
4	>4, ≤6	79	5.1	5.4
5	>6	65	12.3	11.7

SOURCE: Sokol et al. 1988, copyright 1988, Research Society on Alcoholism

solutions but rather to focus on those problems we have found to be most troublesome (and challenging).

In summary, our major points are outlined below:

1. For data collection, one must (1) minimize denial (underreporting) of substance abuse; (2) improve accuracy of reporting history of substance use by placing such use by the patient in her own chronological and geographic setting; and (3) train, retrain, and monitor data collection personnel to maintain reliability and motivation.

2. With regard to data preparation, areas to be considered are (1) the use of coding schemes that distinguish among different types of responses, (2) strategies to eliminate the bulk of the missing data and to estimate the remaining missing values, (3) problems in analysis due to extreme skewness and transformational techniques for these, (4) problem of "outliers" and methods designed to minimize their effects, and (5) assessment interrater agreement whenever observer judgments are required in obtaining the measurements.

3. In comments on data analysis, noted are (1) the inherently multivariate and correlational nature of research in substance abuse and pregnancy; (2) the usefulness of considering domains (or sets) of independent, extraneous, and dependent variables; (3) the problem of attributable risk and the related problems of appropriate adjustments for extraneous variables; (4) the various types of extraneous variables—confounders, covariates, mediators, and suppressors—with some examples; (5) the important problem of the nature of relationships among the independent, extraneous, and dependent

variables; and (6) the specific question of existence of thresholds for effects of the various substances on various outcomes, an increasingly important problem for human studies.

As important as it is to document the existence, nature, and magnitude of relations between substance abuse variables and maternal and infant outcomes, an equally important question is the delineation of reasons for abusive behavior in pregnancy. Once these reasons are better understood, more appropriate interventions can be developed, evaluated, and implemented.

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Discussion: Caveats in Testing for Drugs of Abuse

David A. Kidwell

INTRODUCTION

In an effort to combat drug abuse and provide for a safe workplace, widespread testing of urine for drugs of abuse has become a reality. Drug screening laboratories have emerged in a variety of environments, including government and industrial facilities, emergency rooms, psychiatric centers, and substance abuse centers. To stay within budgetary constraints, the tests must be inexpensive. Yet, through the courts, society has demanded that urine tests meet accepted scientific criteria for validity.

A good testing program must employ two independent assays, and these must be in agreement before a sample is considered positive. The first test is a screening test, which serves to filter out the many negative samples and to identify the drug to be confirmed. To meet cost criteria, the first test inevitably is based on thin-layer chromatography (TLC) or an immunoassay. Since the second test is performed on fewer than 5 percent of the samples, it can be more expensive. Gas chromatography/mass spectrometry (GC/MS) generally is used as the confirmation test.

Drug testing also has played a role in epidemiological studies evaluating the effects of drugs. Since many drugs of abuse do not show obvious permanent effects, a long-term measure of drug exposure is desirable. For most studies, urinalysis is employed partly because of familiarity with the technology, although other matrices could be used. This chapter reviews some of the techniques used in screening and confirmation of drugs of abuse in various matrices and discusses the principles, advantages, and disadvantages of each, with special emphasis on application of these results in a research program.

METABOLISM OF DRUGS

Before discussing the issues involved with testing drugs, a basic understanding of how the body deals with drugs is necessary. Figure 1 depicts the urine levels

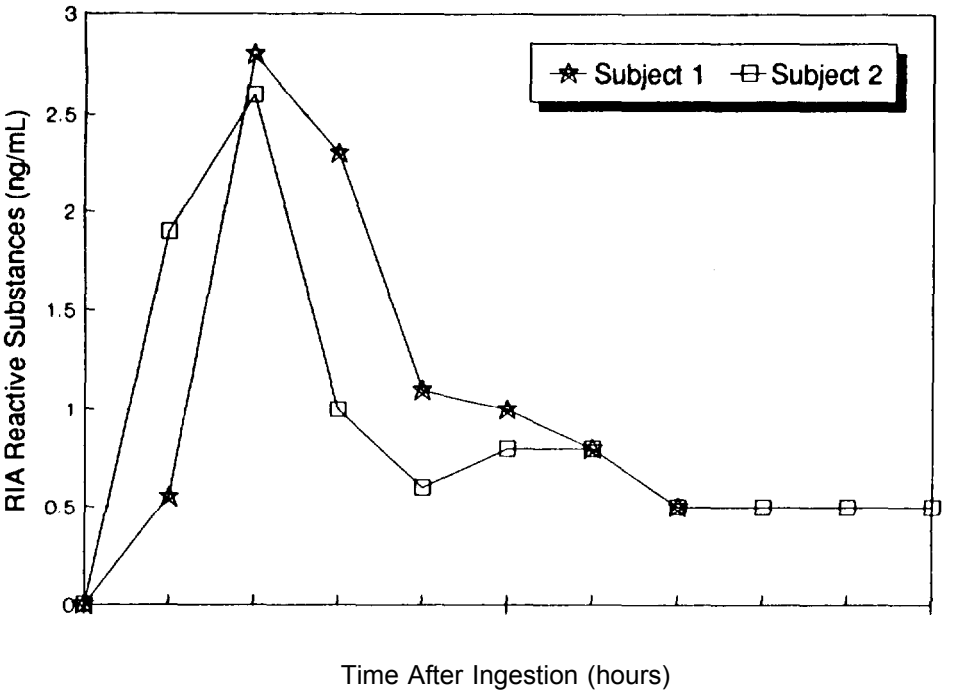

FIGURE 1. *Excretion curve for LSD*

SOURCE: R.L. Folte, personal communication, 1964 (also, see Francom et al. 1986)

of LSD in two individuals who ingested identical doses of LSD (Francom et al. 1986), Figure 1 illustrates two points: (1) The excretion of a drug is time-dependent. Usually after the initial dose, the concentration of a drug increases rapidly in the urine, reaches a maximum, and then declines in an exponential manner (Chiang and Hawks 1986). (2) Individuals show variation in the rate of excretion and total amount excreted in various body fluids for a given dose of a drug. Therefore, amounts found in urine cannot be readily correlated to amount used or degree of intoxication (Chiang and Hawks 1986).

CUTOFF LEVELS

To state that a sample is positive for drugs, at least two criteria must be met: (1) The sample must be positive by the screening test above a set cutoff level; and (2) the sample must be positive by a confirmation test above a set cutoff level.

Cutoff levels are used to ensure that the screening and confirmation tests are sensitive enough to reliably detect the presence of a drug. A low cutoff level may give so many positives in the screening test as to overwhelm the slower and more costly confirmation test. However, cutoff levels often are set with consideration of the workload of the laboratory and the possibility of passive ingestion of drugs rather than the sensitivities and specificities obtained by a given test. For these reasons, comparison of two matrices, such as blood/urine, saliva/urine, or meconium/urine, is difficult since the cutoff levels may not be comparable. Thus, if a single cutoff level were employed, one matrix may be favored over another. Cutoff levels employed in most testing laboratories for urine can be found in the *Federal Register* (DoD Civilian Drug Testing Program 1987). Any research employing an independent laboratory for testing of a sample is likely to have that sample tested at these cutoff levels unless prior agreement is reached.

SCREENING TECHNOLOGY

The screening test does not need to be infallible (Warner 1987). It may call some samples positive for a drug when none was present (i.e., a false-positive), but it should detect all those samples that have drugs present (i.e., no false-negatives). Therefore, only two requirements must be met by the screening test: (1) It must be specific enough to avoid an excessive number of false-positives; and (2) it must have a sensitivity equal to or less than the cutoff levels determined by the researcher to avoid false-negatives.

The following sections discuss the two types of screening tests that are commonly employed: (1) TLC and (2) immunoassays-radioimmunoassay (RIA), enzyme-multiplied immunoassay technique (EMIT) (Syva Corporation, Palo Alto, CA), and fluorescent polarization immunoassay (FPI). The principles, advantages, and disadvantages of each test are examined.

Thin-Layer Chromatography

TLC requires extraction of the urine sample before the analysis. This is more labor-intensive than an immunoassay, which can be run on the sample directly. Nevertheless, TLC can be as cost-effective as immunoassay since it can detect many drugs simultaneously, whereas immunoassay can detect only one drug or drug class per test (Kaistha and Tadrus 1975).

The detection levels for TLC are in the 0.5-1.0 µg/mL range for most substances (Kaistha et al. 1975; Kaistha and Tadrus 1976). These sensitivities are much higher than the cutoff most frequently used and, therefore, are not adequate for most testing. Nevertheless, TLC often is

employed for testing drugs where immunoassays are unavailable or a broad screen is desirable, such as in a hospital emergency room to identify a substance causing an overdose.

One of the most widely used commercial systems is Toxi-Lab. This system is supplied with an extensive compendium of drugs and their TLC characteristics, Cullen and Kidwell (1987) evaluated Toxi-Lab for the analysis of more than 400 randomly selected, drug-free urine samples. These samples were being tested to determine if other drugs may be present that were not detected by immunoassay. Since samples are mailed by surface mail from distant places, they may be weeks old before testing. The age of the sample has not been shown to be a problem for immunoassay. However, Cullen and Kidwell (1987) have observed that with TLC urine degradation can lead to more than a 30-percent false-positive rate for the barbiturates. Often, a spot would appear that was identical in all respects to phenobarbital, but no phenobarbital could be detected by GC/MS. Also, due to the simple extractions employed in Toxi-Lab, many neutral compounds are coextracted. These have led to large brown streaks that obscured any compound present and reduced the sensitivity tenfold from that achievable with fresh samples. For these reasons, TLC is not recommended for older samples that have not been refrigerated.

Immunoassays

The alternative method for drug screening Is an immunoassay. All immunoassays employ antibodies, Antibodies are proteins made in mammals that recognize, bind to, and elicit defenses against foreign substances. The compound that an antibody binds is termed the antigen. Two general types of antibodies are employed in immunoassays: polyclonal and monoclonal. Poiyclonai antibodies are isolated from animal serum and are often mixtures of antibodies with different specificities. In contrast, monocionai antibodies are frequently single protein molecules grown in cell culture and have a single specificity. In a mixture of polyclonal antibodies, there are generally antibodies that will recognize and bind different parts of an antigen. In contrast, monoclonal antibodies, being a single compound, will recognize and bind only one type or part of an antigen. Therefore, monoclonal antibodies may not recognize related compounds such as metabolites.

As employed in immunoassays, antibodies may be considered to function as a lock and key. The antibodies are the lock and the drug is the key. The specificity of the lock will determine the number of keys that will fit. The more specific the antibody, the less interference from other materials of similar structure will occur. However, with a specific assay, there is little chance of observing related compounds such as metabolites or designer drugs. Therefore, researchers should select the immunoassay depending on their

goals. If detection of only a single compound, such as cocaine, is desired, a monoclonal-based immunoassay should be used. If detection of cocaine and its metabolites—such as ecgonine, benzoylecgonine, methylecgonine, and norcocaine—is desired, then a polyclonal immunoassay should be used.

If a new matrix is being explored where concentrations of the potential metabolites are unknown, then the choice of immunoassay is critical. For example, meconium testing has been proposed to measure long-term drug exposure by the newborn in the mother's womb (Ostrea et al. 1988). Since a fetus does not have the mature enzyme system of an adult, the application of an assay that detects only benzoylecgonine as the principal metabolite of cocaine (out of five) may miss many positives if benzoylecgonine is not produced by the fetus and secreted into meconium. Also, cutoff levels for meconium may be entirely different than those for urine. Thus, several specimens of a new matrix should be analyzed either by a nonspecific method, such as GC/MS, or by several immunoassays to determine the most prevalent metabolite profile and appropriate cutoff levels.

The binding of an antibody, be it monoclonal or polyclonal, is the fundamental part of any immunoassay. The distinction between all immunoassays is the manner in which this binding is measured. Described in the following sections are three different immunoassays that employ different techniques to measure binding of the antibody to its antigen.

RadioImmunoassay. RIA was first described in 1959 by Rosalyn Yalow as a method to detect insulin (Yalow and Berson 1960). For her work in this area, she received the 1977 Nobel prize in Medicine or Physiology. To perform the test (figure 2), a known amount of radioactively labeled drug (antigen) is mixed with a small quantity of urine (a few hundred microliters). Then, an antibody to the drug is added. The antibody is not able to distinguish between the radioactively labeled drug and the drug that may be present in the urine. The antibody and drug-antibody complex are separated from the urine, and the radioactivity is measured. The more radioactivity bound to the antibody, the less drug present in the test sample.

The separation of bound drug from unbound drug is the labor-intensive part of RIA and may be performed in many ways (Skelley et al. 1973). Two methods are most popular. One method relies on the addition of a second antibody that is directed against the first antibody. Because the second antibody crosslinks the first antibodies, a large insoluble molecule is formed. This precipitate is pelleted by centrifugation, and the supernatant containing the unbound antigen is discarded. Then the radioactivity in the pellet is counted directly in the tube.

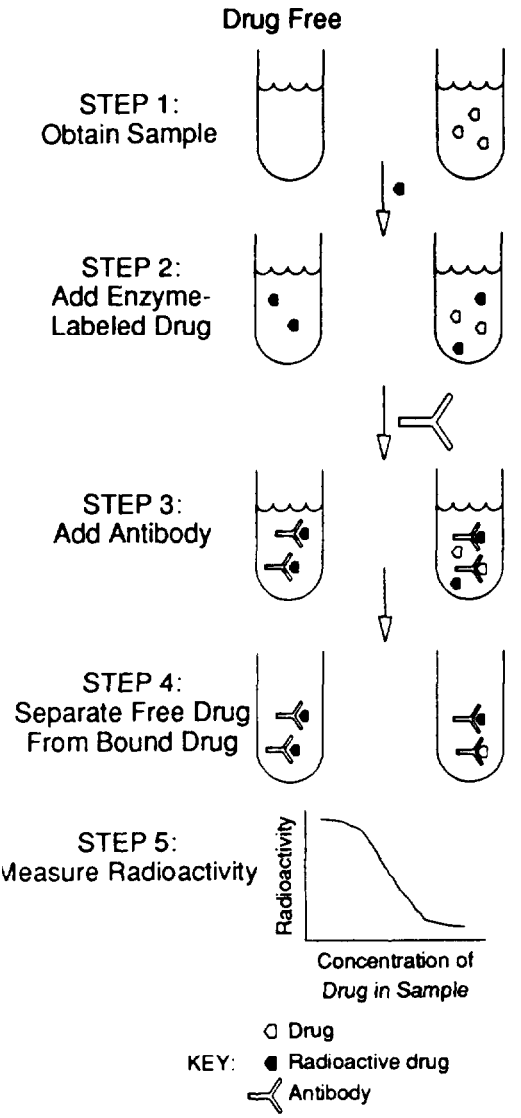

FIGURE 2. *Steps used in RIA*

The other popular method relies on binding the antibody to the walls of the reaction vessel. After the initial drug-antibody reaction, the unbound materials are poured out. The radioactivity bound to the antibodies, which are coated on the walls of the tube, then is determined.

A typical plot of radioactivity observed vs. concentration of antigen is shown in figure 3a. This curve is similar in shape and principle to an acid-base titration curve. This curve also may be made linear, as shown in figure 3b (Henson et al. 1985). One should note that the linear curve generated mathematically in figure 3b from the normal binding curve is somewhat misleading. The precision near either end of this curve can be poor. Therefore, in measuring either small drug concentrations or high ones, severe errors may occur. High concentrations must be measured by diluting them into the working range of the RIA. In contrast, low concentrations are problematical since the binding of the antibody may be affected depending on the matrix being analyzed. Often, an extraction and concentration step is used to reduce the matrix effect and increase the concentration of the analyte to a more precise part of the working curve.

The advantage of RIA lies in its sensitivity; 10^{-12} to 10^{-15} moles of antigen can be determined routinely. This sensitivity is the result of the low radioactive background of most materials and the high sensitivity of radioactive measurements. Also, RIA is rugged; as long as the antibody-antigen reaction is specific, few false-negatives will occur. The major disadvantages of RIA are the risk of exposure to radiation and the restrictive laws regulating the distribution, use, and disposal of the low-level radioactive waste generated.

Enzyme-Multiplied Immunoassay Technique. In 1972 Rubenstein and colleagues (1972) developed the homogeneous assay on which EMIT is based. EMIT employs enzymes rather than radioactivity as the determinant of antibody binding. A common enzyme system used for EMIT is glucose-6-phosphate dehydrogenase, which uses nicotine adenine dinucleotide phosphate (NADP) as a cofactor to oxidize glucose and reduce the NADP. The reduced NADP absorbs ultraviolet light at a longer wavelength than does the oxidized form. The activity of the enzyme can be measured as a rate of increase in absorbance due to the production of reduced NADP. The binding of the antibody to an enzyme-labeled drug decreases the activity of that enzyme. Only a few enzymes with the active site close to the surface show this effect (Rubenstein 1978).

The principle behind EMIT can be seen in figure 4. To perform the assay, the rate of turnover of the enzyme must be measured. The decrease in activity is measured as a decrease in absorbance after a set period compared with a

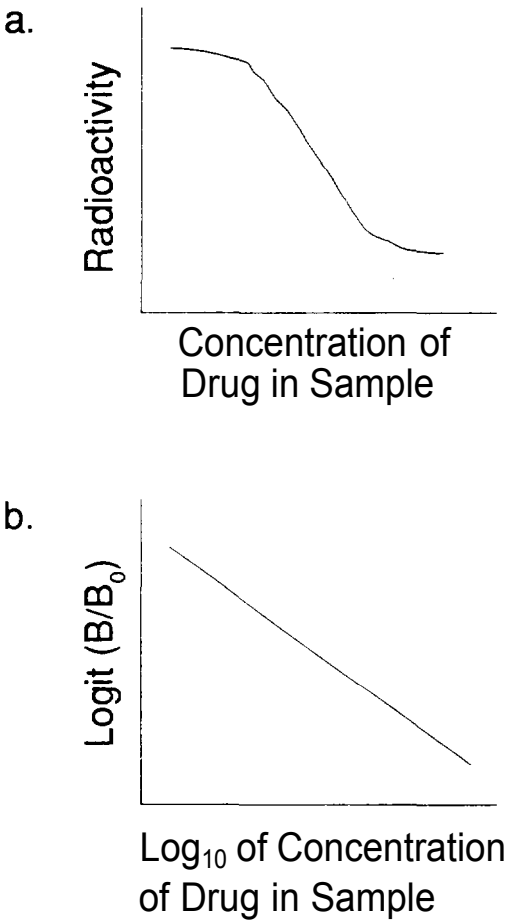

FIGURE 3. *Typical data generated by RIA. Figure 3a shows a* raw *calibration curve, and 3b shows a calibration curve after mathematical processing.*

standard. If no drugs are present in the test sample, then all the enzyme-labeled drug is bound and the activity of the enzyme is reduced. The bound enzyme-labeled drug produces little reduced NADP, and the absorbance at 340 nm is correspondingly low. If a detectable quantity of drug is present in the test sample, then the drug competes with the drug-enzyme conjugate for the antibody binding sites (recall the discussion of RIA above). This releases some

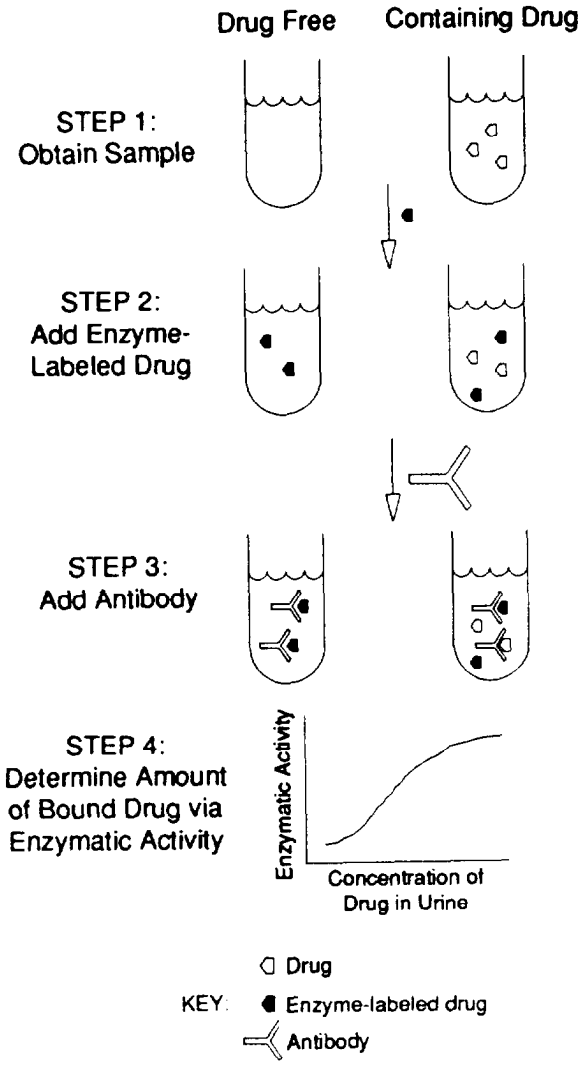

FIGURE 4. *Steps used in an EMIT immunoassay*

of the enzyme-labeled drug, restores its activity, and produces more reduced NADP. Therefore, the absorbance at 340 nm increases.

The advantage of EMIT over RIA is that no radioactivity is involved, which makes disposal of waste products relatively easy. Also, the shelf life of the

reagents is increased since no radioactive decay is present, and therefore, the signal can be started and stopped and labor can be saved since the assay is performed without a separation step. A disadvantage of EMIT is that it cannot be used if the test sample is cloudy or has interfering substances that absorb at 340 nm. Since binding of antibodies is necessary, all the discussion about the cautions in measuring of very high or low concentrations of analyte that apply to RIA also apply to EMIT.

Possible Problems With EMIT. EMIT is the test that has had the most publicity about its susceptibility to adulteration. Like RIA, an adulterant that prevents binding of the antibody to the drug-labeled enzyme would generate a false-positive. Unlike RIA, EMIT is vulnerable to generating a false-negative by reducing the activity of the enzyme or changing the NADP cofactor.

One system that could be used to test for adulteration in urine tests that employ EMIT technology is to monitor the initial rate of the enzyme reaction before the antibody is added. If this rate was too low, then that sample would be flagged as not testable. Few laboratories use this method as it increases the complexity of the analysis slightly and, more importantly, *few customers ask* for these data.

Fluorescent Polarizatlon Immunoassay. The principles of FPI were first developed by Perrin in the 1920s (Perrin 1926), and its application to the detection of antigens bound to antibodies was first described by Dandliker and Feigen (1961). The principles and practice of FPI and its application to biological systems have been the subject of several review articles (Soini and Hemmila 1979; Dandliker and de Saussure 1970; O'Donnell and Suffin 1979).

FPI is related to light scattering, and its basis can be seen in figure 5. If a polarized light beam excites a stationary, fluorescent molecule, the molecule will emit light that is polarized. If the molecule rotates before the light is emitted, then the polarization of the emitted light is lost. Small molecules, such as drugs, rotate faster than larger molecules, such as antibodies. An antibody binding to the smaller, fluorescent molecule would make a large complex with a slower rotational period. This large complex would not rotate significantly before fluorescence of the molecule had occurred; therefore, the polarization of the initial exciting light would be retained. If the antibody is prevented from binding the fluorescently labeled drug (because other molecules fill the site), then the polarization is lost. The steps used in FPI are similar to those used in EMIT, with the only difference being how the signal is interpreted.

The shelf life of the reagents in FPI is increased over both EMIT and RIA since no radioactivity or enzymes are involved with this analysis. Like EMIT, labor can be saved since the assay is performed without a separation step. The

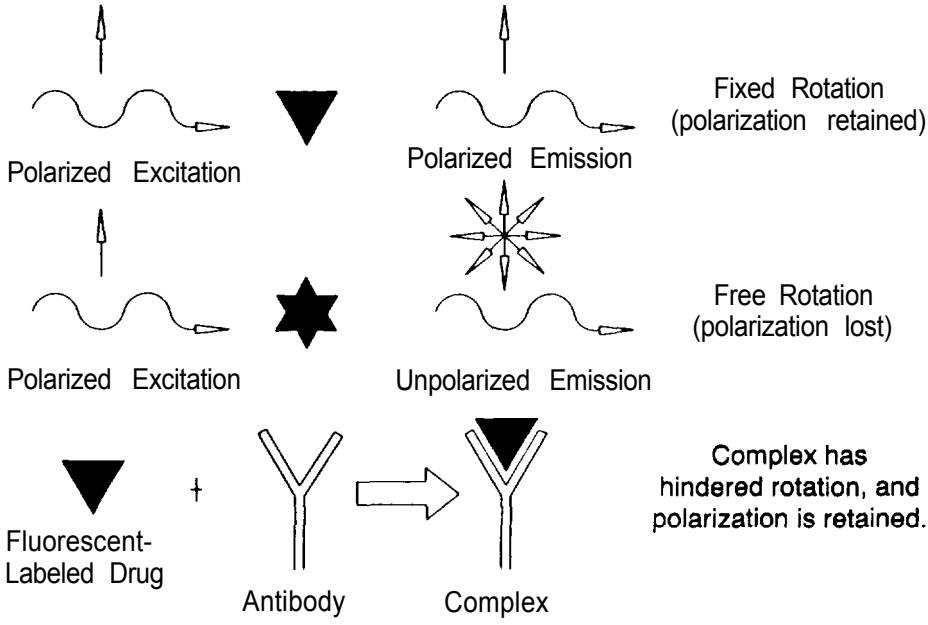

FIGURE 5. *Principle of FPI*

sensitivity of FPI is somewhat less than can be achieved by RIA and EMIT, but it is sufficient for most drug assays (Caplan and Levine 1989). The sensitivity is limited by the theoretical maximum of polarization being 0.4 (due to the random distribution of molecules) and by the inherent fluorescence of the sample. Interference by fluorescence is especially severe if proteins, as in blood plasma, or certain vitamins are present.

Like EMIT, FPI also is sensitive to several adulterants (Dandliker and de Saussure 1970). The TD_x system (Abbot Laboratories, Irvine, TX) reduces or eliminates all known interferences by a 250-fold dilution of the urine in buffer before an assay is performed and a careful background subtraction routine. However, such fluorescent materials as endogenous riboflavin metabolites or surreptitiously added fluorescence dyes still pose a problem. Abnormally high levels of such species are indicated to the operator as an untestable sample by the TD_x instrument (Wilkerson et al. 1989). In these cases, a policy decision must be made as to whether such a sample should be tested by alternative technology to avoid discarding a potential positive.

CONFIRMATION TESTS

Some people in the forensic and parole community rely exclusively on immunoassays or TLC to detect drug abuse and forgo the confirmation test. This is a mistake. Hoyt and colleagues (1986) surveyed legal professionals, forensic experts, and arbitrators about the legal defensibility of various test methods and found that, without a confirmation test, little confidence was placed in the result. For research purposes, where no punitive action possibly could be taken against the individual, a confirmation test may be unnecessary as long as the 5- to 10-percent potential false-positive rate is considered in the analysis. However, for new matrices with little history of usage, such as meconium, or for drugs where false-positive rates are unknown, the false-positive or false-negative rates may be quite high and severely bias the data. In these cases, GC/MS confirmation would be desirable. Where the results may be used in a punitive action, the National Institute on Drug Abuse guidelines require confirmation by GC/MS. Since this chapter deals mainly with research studies, no further discussion of confirmation by GC/MS will be done.

ALTERNATIVES TO URINALYSIS FOR DRUG TESTING

Saliva Analysis

Saliva analysis would be an ideal alternative to urinalysis since saliva can be obtained under direct observation without the privacy issues involved in urinalysis. Previous research has indicated that many drugs are present in saliva in concentrations that parallel those found in blood (Thompson et al. 1987; Cone et al. 1988; Danhof and Breimer 1978; Sharp et al. 1883). Thus, there may be a better relationship to the concentrations of drugs in saliva and the degree of intoxication of an individual. However, drugs do not remain in saliva or the blood for as long as in urine. Also, since the kidneys concentrate many species approximately 100 times, the concentrations of drugs in saliva are lower than in urine.

Few studies of cocaine in saliva have been completed, with most relying on detection by immunoassays (Thompson et al. 1987; Cone et al. 1988). The first report of the detection of cocaine in saliva came from a study of the metabolism of radiolabeled cocaine (Inaba et al. 1878). Later, cocaine was found in the saliva of impaired drivers (Peel et al. 1984). Most studies show similar pharmacokinetics of plasma and saliva levels for cocaine. However, in a recent controlled study, cocaine was found in saliva of chronic addicts 5 to 10 days after abstinence (Cone and Weddington 1989). This long detection window was attributed to accumulation of cocaine in deep body compartments.

Only two studies on the saliva levels of morphine have been reported (Leute et al. 1882; Gorodetzky and Kullberg 1874). The latter was a controlled study examining the metabolism of heroin in plasma and saliva. This study followed the metabolism of heroin by several immunoassays. Heroin was detected for only 2 to 4 hours in each medium, but this short detection window may have been due to the insensitivity of the immunoassays employed.

A study on saliva (Kidwell 1990) was initiated that had four objectives: (1) develop sensitive mass spectrometric-based techniques to analyze drugs in saliva, which would allow for a confirmation test; (2) determine what metabolites may be present in saliva and their approximate concentrations, which would assist with development of screening tests; (3) evaluate the SalivaSac (BioQuant, Ann Arbor, MI) as a collection device for saliva; and (4) compare saliva to urine for ease of detection and generation of false-negatives. This initial study concentrated on the drugs cocaine and heroin.

An analytical technique for cocaine and heroin and their metabolites based on liquid chromatography (LC)/MS was developed for saliva analysis. LC/MS has an advantage over GC/MS in allowing the analysis of larger volumes of samples (50 to 500 µL) and the direct analysis of aqueous solutions, LC analysis has been employed before for the analysis of cocaine and its metabolites in urine (Jatlow et al. 1978).

Selected ion traces for an individual with a high level of drugs in the saliva is shown in figure 6. The chromatography for cocaine and methylecgonine is poor because the conditions available for analysis in LC/MS are limited since the buffers used must be volatile and in high concentration and only acetonitrile/water or methanol/water eluents are practical. Still, with deuterated internal standards, the analysis is acceptable.

In contrast to GC/MS spectra, LC/MS spectra typically only show protonated molecular ions with little or no fragmentation. Thus, only the relative retention time and the intensity of a single ion are available for determination of the presence of a substance. If more information is necessary, such as a fragmentation pattern, tandem mass spectrometric techniques must be used.

Saliva Collectlon—The SalivaSac. The SalivaSac is a “pill” consisting of a bag made of dialysis material and containing an osmotically active material. The dialysis membrane serves two purposes: (1) It filters the aqueous portion of the saliva from the mucopolysaccharides, which gives saliva its slimy feel. The SalivaSac produces a solution much like water. (2) It controls the rate of absorption of water to prevent a dry-mouth feel. The osmotically active material (sucrose in the devices employed in this study) facilitates the flow of water. The

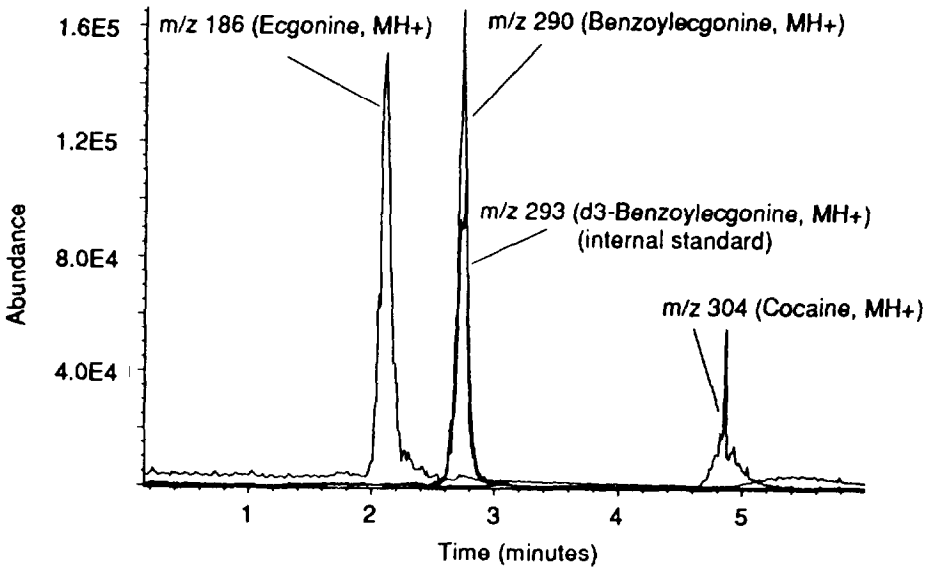

FIGURE 6. *LC/MS ion trace of saliva from a cocaine user*

NOTE: The retention time and peak shape of the benzoylecgonine and the d3-benzoylecgonine internal standard are identical.

SalivaSacs used in this study were of the stimulatory type containing citric acid, which increases the production of saliva (Kidwell 1990).

One problem occurs with the SalivaSac: The large amount of sucrose used as the osmatic material produces a saturated solution when dissolved by the saliva. This changes the concentration of the saliva and any materials contained inside by diluting it with sugar. This dilution effect was found to be about a factor of two in this study (Kidwell 1990). The manufacturer recommends measuring the density of the saliva solution and adjusting the concentrations of drugs accordingly. No adjustment was made to the data in this study because this factor should be constant and inconsequential if the saliva is always obtained in the same manner. An adjustment to the drug concentrations should be made if they are compared with other collection devices or for correlation to blood plasma levels.

Concentration of Drugs In Saliva and Urine of Drug Users. Table 1 lists the total amount of drug or its metabolites in urine of the individuals tested compared with saliva. The concentrations of the drugs in table 1 for urine

TABLE 1. *Total concentration of cocaine species and opiates in urine and saliva (ng/mL)*

Sample	Cocaine (urine)	Cocaine (saliva)	Opiates (urine)	Opiates
1	(627)	14	—	—
28	—	—	—	—
45	4,470	—	—	—
52	1,970	315	—	—
91	—	183	—	—
115	1,400	42	—	—
130	—	—	—	—
138	—	—	—	—
140	—	—	—	—
149	150	17	3,000	3
151	3,700	78	1,288	?
159	9,200	34	—	—
171	—	—	—	—
175	14,600	478	1,600	25
184	—	—	—	—
185	5,900	58	—	—
194	4,100	81	639	—
195	(571)	17	—	—
212	7,900	6	325	?
218	2,381	22	—	—
222	—	—	—	—
223	(600)	17	—	194
233	181	857	1,627	69
272	11,000	87	—	—
"DF"	238	84	—	—

NOTE: ?=possible low level by LC/MS; values in parentheses derived from LC/MS data after negative results by immunoassay

were measured mostly by immunoassay. In a few cases (not shown), the concentrations of drugs were confirmed by LC/MS. The concentrations in saliva were the total of all the various metabolites as measured by LC/MS. In only a few cases were immunoassays run since the sensitivity would have been inadequate. Because of the cross-reactivities, EMIT is most sensitive to benzoylecgonine and morphine, with the other metabolites being only sightly cross-reactive.

Comparison of Saliva and Urine Results-The Pitfalls. The cocaine results in table 1 illustrate the problem in comparing different matrices by a specific test such as an immunoassay. If EMIT was the only method used to test the urine and saliva, then 14 to 25 urine-positives and only 2 to 25 saliva-positives would have been found. Therefore, saliva would have appeared to be a much poorer matrix than urine, partially due to the high cutoff level of the EMIT tests. If EMIT was used to test the urine and LC/MS to test the saliva, then 14 of 25 positives for urine would have been found and 17 of 25 positives for saliva. In this case, saliva would have appeared a better matrix since LC/MS is more sensitive than EMIT and has a broader screen. When the saliva/urine samples that showed a discrepancy were tested by LC/MS, the missed urine positives were due primarily to the incorrect metabolite present. This is indicated by parentheses in table 1.

Further research may show that saliva is likely to be a poorer matrix than is urine due to the lower concentrations of drugs present. However, saliva's ease of collection and less opportunity for dilution, substitution, or adulteration still may make it a worthy test medium.

Hair Analysis

The short half-life of many drugs of abuse in urine makes detection of infrequent drug use difficult. On the other hand, hair sequesters many drugs of abuse and retains them for long periods (Baumgartner et al. 1981, 1982; Marigo et al. 1986). Since hair grows at a rate of approximately 1 cm per month (Meyers and Hamilton 1951), a time line of drug use could be established. However, before hair analysis could be employed in any research program, several important questions need to be answered. For example, what is the sensitivity of hair analysis? Could a single use be detected? What if the results of urinalysis and hair analysis disagree? What confirmation technology is appropriate? What are the mechanisms of incorporation, retention, and loss of drugs of abuse in hair? Only the last question will be addressed in this chapter (for a more complete description, see Kidwell and Blank 1990).

Mechanisms for the Incorporation of Drugs. One hypothesis for the incorporation and retention of drugs in hair may be that of a dynamic equilibrium. Two opposing forces are interacting between incorporation and retention of the drug in the hair and loss of the drug to the environment. Drugs may be incorporated into the hair shaft as one of three possibilities. They may be incorporated from the blood as the hair grows, from sweat, or from another external source. Sweat could be a potential rich source of drugs of abuse since drugs are known to be excreted in sweat (Smith and Liu 1986; Ishiyama et al. 1983; Smith and Pomposini 1981), and the concentrations of materials in it

would increase as water evaporates. The retention in the hair may be by ionic forces; in this case, differences in the charge on the drug would affect profoundly the amount retained. For example, negatively charged species such as aspirin are not well retained in hair (Harrison et al. 1974), whereas cationic species such as hair dyes are well retained. The loss from the hair could result from such things as normal washing, dyeing, perming, and bleaching or by degradation of the drug in the hair shaft.

One model of a dynamic equilibrium is the dying of hair. If you apply red hair dye to blond hair, the hair will turn red. The incorporation of the dye into the hair is rapid and the binding of the dye quite tenacious. Yet, exposure to the sun for several weeks or repeated washing will decrease the red color intensity. The color would fade either through leaching of the dye from the hair or through gradual degradation of the dye into colorless compounds. If the hair was redyed several weeks later, the original red color would be restored. In this example, a rapid uptake of dye is followed by a slow decrease in dye concentration. Interestingly, most hair dyes are cationic compounds and so are most drugs of abuse that are found in halr in high concentrations.

If this dynamic equilibrium mechanism is reasonable for drugs of abuse, several concerns arise. Dynamic equilibrium implies that drugs endogenously deposited into hair can be removed and also that drugs exogenously present could be incorporated into hair. Therefore, the amount of drug ingested may not be correlated with the amount found in the hair. For example, as hair ages, drugs endogenously deposited would have had time to leach out and their concentrations fall below the detection limit of the assay. On the other hand, drugs deposited in recently grown hair would not have had time to leach out and may be detected in hair at high concentrations even though usage was constant.

Passive Exposure. To determine if external contamination and passive exposure can mimic drug use, hair from a cocaine user was soaked in an aqueous solution of p-bromococaine, a derivative of cocaine, at 1 µg/mL for 1 hour. It then was rinsed and air-dried and extracted according to literature procedures for cocaine (Baumgartner et al. 1982). The hair was washed once with ethanol, three times with phosphate buffer (pH 7), rinsed three times with water, and then the cocaine remaining in the hair was extracted two times with 0.6N HCI. Cocaine and p-bromococaine were quantitated in all solutions by GC/MS; the results are shown in figure 7.

The washout kinetics for the cocaine and the externally introduced p-bromococaine are similar, again implying that external contamination can mimic drug use even at as low a concentration as 1 µg/mL. Significant amounts

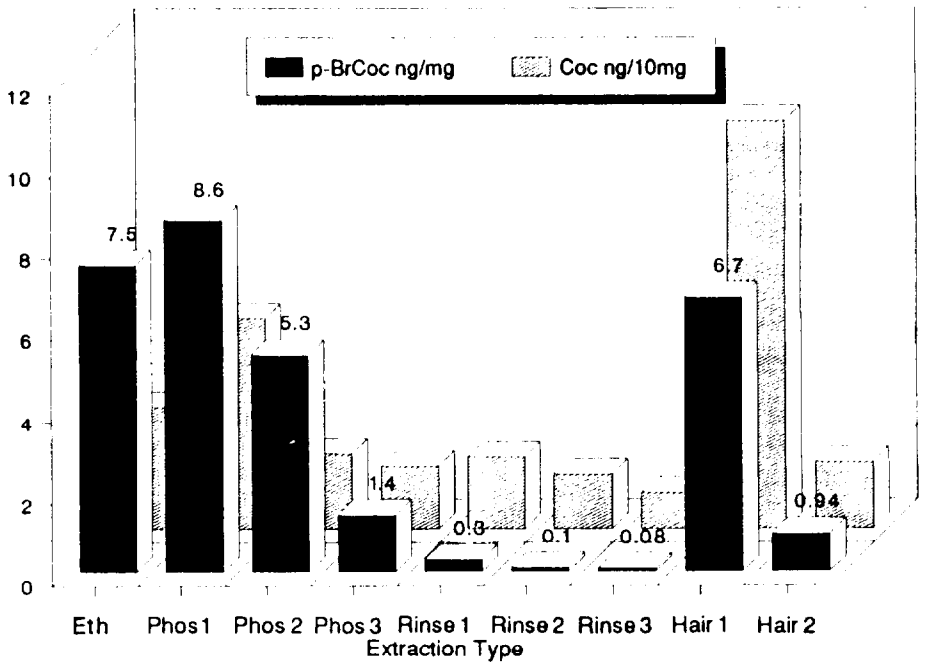

FIGURE 7. *Extraction profile of a cocaine user's hair*

NOTE: The p-bromococaine axis is 10 times the cocaine axis. Hair 1 and hair 2 are final extraction steps with acid.

of cocaine and p-bromococaine were found in the final hair extracts. Note that even though the hair in both cases was not dissolved in the drug extraction step the quantity of p-bromococaine was 67 times greater in the extract than in the last wash. This ratio between the quantity extracted from hair and that in the last wash has been suggested by some to distinguish between active and passive exposure (Baumgartner et al. 1989). Although the criteria are arbitrary, those researchers used a factor of 10 between the extract and the wash. In this case, the cocaine user would have been considered a user of p-bromococaine. Little added discrimination would be gained by increasing this ratio since, at that point, most users of drugs would be considered negative.

Metabolite Screening as a Possible Solutlon to Passive Exposure. One method to distinguish between active ingestion of a drug and passive exposure is to measure the metabolites of the drug rather than the parent compound. Cocaine is one of the few drugs that is excreted primarily as its metabolites.

Many of the other drugs of abuse are excreted as the parent drug; in this case, passive exposure could be of concern. Presumably, if the metabolites of cocaine were found in the hair, then it would be assumed that the individual ingested the drug. This is only partially true. Cocaine is metabolized via the esterases present in the human body to three primary metabolites: benzoylecgonine, methyl ecgonine, and ecgonine. However, these "metabolites" also may be formed *in vitro* by hydrolysis with base. For example, if negative urine is spiked with cocaine and then made basic with sodium carbonate to pH 10, the cocaine will completely degrade to ecgonine within 12 hours at room temperature. *In vitro* basic conditions will produce exactly the same metabolites from the parent drug as will human metabolic processes, depending on time, pH, and temperature.

As is well known, hair typically is washed with detergents in normal personal hygiene. These detergents are basic, typically a pH of 10. In fact, even tap water is pH 8 and buffered at this pH to prevent lead from leaching from the water pipes. With normal hygiene, hair is constantly being exposed to basic conditions under which cocaine, if present, may degrade into "metabolites." Whether this occurs is unknown.

Differences Between Hair Types. Hair is an extremely heterogeneous media, which is treated differently among probably every individual on earth. Are there differences between hair types on the uptake and retention of drugs? One answer to this question is to compare the self-reported drug use history between users with two types of hair: black and brown, The use histories were matched as closely as possible. As shown in table 2, the results indicate a dramatic difference between hair types. For example, one individual with black hair indicated use of 250 mg of cocaine on only one occasion, and 6.4 ng/l 0 mg of cocaine was found. Compare that to an individual with brown hair who also indicated use of 250 mg of cocaine on five separate occasions. In this case, the cocaine level in the hair was below the detection limit of about 1 ng/10 mg (Kidwell and Blank, unpublished data).

Similarly, data for a heavier user—100 mg/week—with black hair showed a small amount of cocaine in the hair. Compare this to an individual with brown hair who uses 2 1/2 times as much cocaine per week. In this individual, the amount was below the detection limit. Incidentally, differences in uptake and retention of drugs with hair coloration also were shown in some controlled animal studies (Harrison et al. 1974; Forrest et al. 1972).

TABLE 2. *Comparison of cocaine present in different hair types*

Black		Brown	
Use	Amount Detected ng/10 mg	Use	Amount Detected ng/10 mg
250 mg once	6.4	250 mg once	0
4-5 g total	3.5	250 mg 5 times	0
100 mg/wk	2.2	2-4 g total	2.2
500 mg/wk	18	5 g total	0
		250 mg/wk	0
		250-500 mg/day	20

SOURCE: Kidwell and Blank, unpublished data

SUMMARY

Four mass screening techniques for drugs of abuse (TLC, RIA, EMIT, and FPI) have been described. For small-scale screening, TLC is the most cost-effective. Although it cannot achieve the sensitivity of the other three immunologically based techniques, TLC is sufficient for many purposes. All screening techniques are subject to interferences that can generate false-negatives or false-positives. These results must be taken into account in analysis of the research data.

In applying technology in new areas of research, one has to be aware of the basis and limits of that technology. Testing of drugs of abuse in urine is a well-known technology in which most of the problems have been discovered. This technology is less proven for other media, such as hair, saliva, or meconium, leaving potential pitfalls for the unwary researcher.

NOTE

1. The detection limits listed in the *Toxi-Lab Drug Compendium* are all within this range. Other TLC procedures are sensitive down to 0.1 µg/mL for certain drugs (see Kaistha and Tadrus 1976).

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Who Is It Going To Be? Subject Selection Issues in Prenatal Drug Exposure Research

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INTRODUCTION

In the area of research on the effects of prenatal drug exposure on infants and children, the most powerful tool available is the longitudinal design. This approach can come closest to answering the two fundamental questions that underlie the at-risk research discussed in this monograph. The raison d'être of prenatal developmental drug research is to discover whether the maternal drug use affects the development of the exposed offspring and, if so, to identify at an early age those children who will develop behavioral problems.

However, although the longitudinal approach may be the design of choice, it is encumbered with a host of problems (not necessarily unique to the longitudinal design), many of which focus around aspects of subject selection. To explicate some of these issues, this chapter refers to several longitudinal studies reported in the literature (and, in many cases, currently under way). However, the primary focus is on the prospective study with which the author has been involved since 1978, with emphasis on the relevant methodological procedures rather than on the data collected.

This work-the Ottawa Prenatal Prospective Study (OPPS)—has focused on the consequences of prenatal exposure to marijuana and cigarettes. During the development and course of this research, a host of subject selection issues have arisen. The resolution of the issues and the logic behind the resolution serve as the focus for this chapter. The general testing procedures that have been followed, are being followed, and are projected have been outlined elsewhere (Fried 1989) and are not described or discussed here in detail.

Information describing the potential role that marijuana might play in the course of human pregnancy and developmental outcome was, prior to the late 1970s limited to two polydrug case reports. This virtual absence of objective

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information, the findings reported from animal studies (for a review, see Fried 1984), the relatively widespread use of marijuana by women of reproductive age, and the cooperation of the major teaching hospitals in Ottawa were the impetus for OPPS. These factors also contributed to the approach to subject selection and subject maintenance.

RAMIFICATIONS OF RECRUITMENT STRATEGY

Between 1979 and 1985, approximately 700 women residing in the Ottawa area were recruited into OPPS. The study was brought to the attention of the mothers-to-be by their obstetricians and/or notices in waiting rooms of prenatal clinics. Any information that was disseminated at this juncture in the work did not mention marijuana but, rather, discussed in general terms how certain lifestyle habits during pregnancy may affect the unborn child in infancy and in the future. The pregnant woman could contact the research staff either by mailing a prepaid postcard available at all locations where the study was publicized or by telephoning the research facility. Upon contact, the prospective subject was given further details about the lifestyle habits that were of particular interest to the researchers, namely, the use of marijuana, cigarettes, and alcohol. The initial conversation emphasized that, for purposes of comparison, it was of considerable importance that the staff members recruit women who did not use any drugs during the course of their pregnancy. If, at this point, the woman was interested in participating in the study, a time was arranged for a one-on-one meeting (almost always at the home of the mother-to-be) where an informed consent form was signed and an interview took place. During this visit, which lasted about 2 hours, the female interviewer attempted to establish rapport with the subject while gathering information on parental health and medical history, demographics, and maternal drug use (Fried et al. 1980).

At numerous points in this research, decisions must be made about subject selection-as a result of problems common to most if not all longitudinal, prospective (cohort) prenatal drug studies. Furthermore, as in OPPS, the decision options often are restricted. All too frequently the option chosen, while not optimal from a research point of view, is the only possible pragmatic choice. If this is the case, it is essential for the researcher to be explicit about the decision(s) and, as much as possible, to ensure that the consequence(s) is borne in mind in the interpretation of the results.

An illustration of this dilemma revolves around the volunteer nature of the subjects entering OPPS. Like all longitudinal prospective studies of maternal drug use, random selection and random assignment to groups are not feasible, and the researcher is left with, at best, a quasi-experimental design and all the drawbacks that such a research approach entails, Dictated by ethical, financial,

and other pragmatic limitations, participation in OPPS was of a more voluntary nature (i.e., less implicit psychological coercion) than is usually the case in similar, parallel types of work. With the procedures employed in OPPS, it became readily apparent that the women who entered the research were, in general, self-selected on the basis of being highly motivated. Although not investigated systematically, it was noted that there was a variety of reasons for volunteering, including the desire to know the consequences of their own particular drug habit, the feeling that they were doing everything right and wished to be reinforced (both drug users and non-drug users), and the wish to prove that their particular habit was not harmful to their offspring. Furthermore, the high degree of initiative required to participate, the inclination to read notices or pay attention to statements made by obstetricians, and the attendance in prenatal care situations all are factors that potentially can contribute to bias. The potential bias of a sample recruited in this fashion must be considered. The term “bias” is used in the sense of a difference between the target population to which one plans to generalize the findings and the population from which the sample is drawn,

The self-motivation of the women who initially volunteered to participate in OPPS clearly restricts the degree of generalizability of much of the epidemiological and maternal characteristic data collected. It should be emphasized that this type of voluntary approach also has advantages, among which are the reliability of self-report and the enhancement of a long-term commitment of the women to the study. These aspects have been elaborated on elsewhere (Fried 1989).

Recognizing the limitation of subject entry procedures and the role they play in the interpretation of the findings is only the first step. The researcher must, to the extent possible, attempt to document qualitatively and quantitatively the extent of bias within the sample used in the research. In OPPS, this was undertaken using two sources of information. The most recent Canadian government census with respect to such demographic variables as family income, level of education, parity, and drug use prevalence was utilized. In addition, by using obstetrical records of the hospitals involved with OPPS, information was gathered on nonparticipating women who gave birth during the same period as the study group sample.

As alluded to above, entry into OPPS was of a more voluntary (i.e., subject-initiated) nature than is typically the case in prospective, longitudinal studies. For example, in a study examining prenatal marijuana and alcohol exposure (Scher et al. 1988; N. Day, personal communication, November 1989), women were approached by researchers when the mothers-to-be came to the university-affiliated hospital during their fourth prenatal month. The refusal

rate was approximately 15 percent. A similar initial recruiting procedure and refusal rate was noted in Streissguth and colleagues' longitudinal, prospective study of social levels of drinking (Streissguth et al. 1981). A somewhat more "aggressive" recruiting procedure is described by Chasnoff and colleagues (1985) in their pioneering work examining cocaine use in pregnancy. In this project, all cocaine-using women referred to a perinatal chemical dependence program in a university-affiliated hospital were enrolled in a longitudinal study. Eighteen percent of the women referred to the program refused to cooperate with the project.

With recruitment procedures in which researchers actively contact all or most subjects in a given center over a specific period, the risk for bias along certain dimensions may be reduced, but it still exists. There is the limitation that the subjects may not represent those eligible but not appearing at the particular recruiting site. One way of at least partially overcoming such a shortcoming is by using a multicenter research design. However, logistical and financial burdens often prevent this approach from being undertaken. Therefore, once again, it is essential that the representativeness of the study population be detailed so that those who read the reports emanating from the work can determine whether the findings are applicable to their subject pool.

Once the initial recruiting has taken place, it is often necessary to screen subjects for relevancy to a study's objectives. In other words, in a longitudinal, prospective study, cases frequently have to be selected on a "risk" variable(s), with not all subjects being "of interest." Pragmatism dictates that only those mothers-to-be for whom the variable(s) is relevant (and relevant comparison subjects, as discussed below) will be chosen for followup. The choice typically involves consideration of the following criteria.

What is the risk variable in question? Within OPPS the primary drug of interest is marijuana. When the study was initiated in 1978, very little information was published with respect to lifestyle habits of marijuana users, and no information was available pertaining to such habits in a predominantly middle-class sample such as the population from which the expected participant in the OPPS would be drawn. Obviously, the ideal situation would be to recruit and follow up women who used only marijuana and no other potential neurobehavioral teratogens during pregnancy. However, it was felt that it would be unlikely to find sufficient numbers of such "pure" use. Subsequent investigation substantiated this concern, For example, at least 85 percent of middle-class women consume caffeine-containing beverages during pregnancy (Jacobson et al. 1984; Watkinson and Fried 1985; Streissguth et al. 1989). The pilot work that preceded OPPS also suggested that there would be a significant correlation between marijuana use and cigarette smoking. A similar expectancy

was that a correlation (not as strong as cigarettes) would exist between alcohol and marijuana use. Thus, the decision was made to include women who used these substances either together with the risk factor of primary interest or on their own without marijuana. On the other hand, the use of hard drugs was known to be relatively low among the population from which the OPPS sample was to be drawn. Given the reports in the literature of the time of neurobehavioral teratogenic effects of such substances, subjects were excluded from the study if they reported use of such substances as amphetamines, LSD, or opiates more than twice either during the year before pregnancy or during pregnancy.

Inclusion and exclusion criteria for sample selection are dependent on the risk variable under investigation. For example, in the area of cocaine and pregnancy, the high rate of marijuana use among crack users would result in severe limitations to sample size and generalizability if cannabis users were excluded.

Other, not so clear-cut factors also influence the decision to retain exposed subjects for followup. An illustrative problem is in the domain of personality traits and drug use. Depression is frequently reported among drug-using women (Burns 1986). It is difficult to determine whether the depression contributed to drug use or whether the depression is a consequence of the drug habit. Should depression be considered as a criterion of exclusion? Most researchers with this or analogous problems include all subjects and rely on statistical procedures to disassociate such variables. Although not a subject selection issue, it bears mentioning at this point that the statistical approach appropriate for evaluation of these variables is not “cut and dried.” Entering into the decision is the issue of whether the potentially confounding variables are possible outcomes of drug use, are independent of drug use, or are mediating variables.

The extent of usage of the risk variable being investigated is a factor in subject selection. For example, does one include those who used the drug in question on a very infrequent basis? The approach that many researchers have taken is to stratify subjects for the drug(s) in question (e.g., heavy users, light users, and nonusers), with the heavier category being oversampled (Streissguth et al. 1989; Fried and Makin 1987). A slightly different procedure has been described by Day and colleagues (1989) in which the study cohort was selected from the women who received an initial interview. Each woman who reported, in that first screening, an average of at least three drinks a week during her first trimester was included in the followup sample. In addition, the next woman who reported drinking a lesser amount also was retained in the followup cohort. This sampling approach permitted the recruitment of all of the heavier drinkers and a proportional sample of other drinking patterns.

SELECTION OF COMPARISON SUBJECTS

The selection of subjects for comparison is a vital component of longitudinal work. Control subjects, whether nonusers of the drug in question or drug users with differential (lesser) patterns of use than the principal group under investigation, are required for all studies that go beyond pure description. Although many studies match along particular dimensions, this procedure is not essential and, in fact, can lead to practical and interpretative problems. Matching cannot be assumed to solve the problem of the impact of the confounding variable for which the procedure was implemented. Having similar values on a particular measure between matched groups does not guarantee that the matched variable has a similar effect, for there may well be an interactive component coming into play. From a design point of view, there are such issues as the following: (1) On how many variables should matching be attempted (a conflict between the ideal design vs. the practicality of finding sufficient subjects)? (2) How exact should the matching be (e.g., with age within 8 months, 2 years, etc.)? (3) If one loses a subject, what does one do with the match? (4) Matched variables cannot be analyzed as potentially confounding (potential risk) factors because their distribution across risk and control groups has been equalized artificially. Further pros and cons of matching are discussed elsewhere (Anderson et al. 1980; Martin 1986; Strauss and Allred 1988).

For control subjects to serve their assumed purpose, they must be derived from a population similar to that of the cases of primary interest. They must be followed to the same extent and be exposed to the same manipulations (e.g., testing, care, observation). Relying on established, historical norms as a basis of comparison may be inappropriate because of such factors as the length of time that has elapsed since the norms were established and the makeup of the standardization sample. A preferable approach is to select controls randomly or, in some otherwise nonbiased fashion, from a population similar to that of the experimental subjects to reduce preexisting group differences on nuisance variables. Two examples drawn from OPPS emphasize the importance of this,

Means of vocabulary scores obtained from the 4-year-old children of very light, moderate, and regular users of marijuana are seen in figure 1. Pertinent to the present discussion are the scores of the regular users, which are nine points above the standard age score equivalents. Only by comparing those scores to the other two user categories can one observe a drug effect. The overall high scores in all three groups on this test of verbal comprehension are presumed to reflect the effect of environmental factors common to all the subjects.

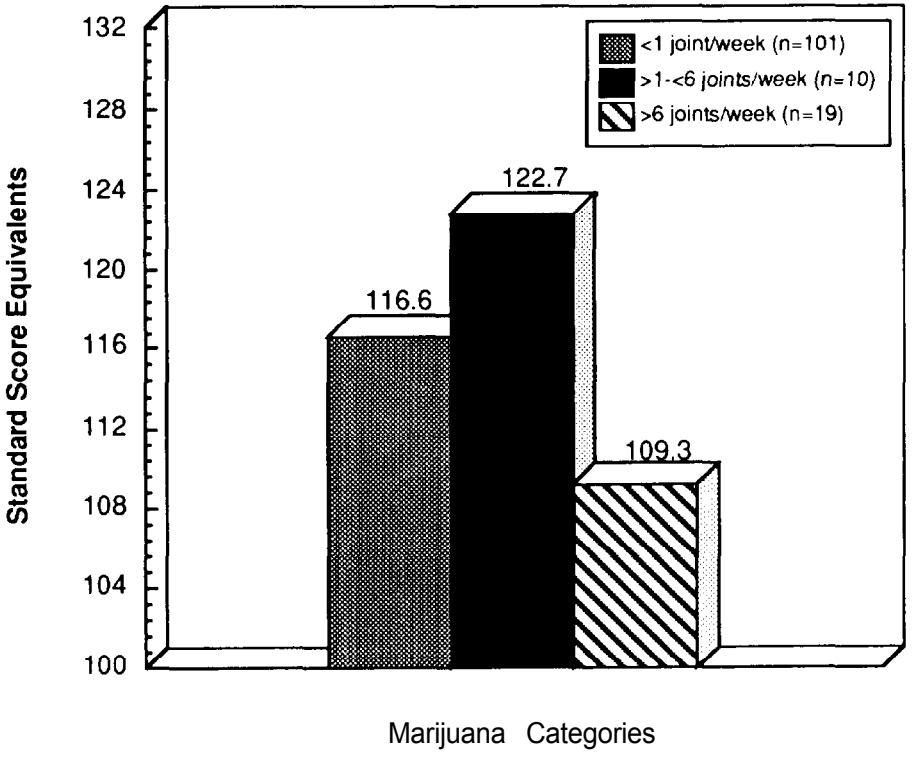

FIGURE 1. *Peabody vocabulary scores of 4-year-old children of marijuana users*

In figure 2, a reverse situation is demonstrated in tests of academic achievement for children born to active and passive smokers. Although the children in the experimental groups performed below age-corrected standard scores (norm=100), the impact is lessened by the fact that the control children also scored lower than the norm on two of the three tests. In this case, performance in all three drug conditions was affected by the fact that most of the children were in a French immersion program in which virtually all instruction was in French, while the tests administered were normed on children attending English schools.

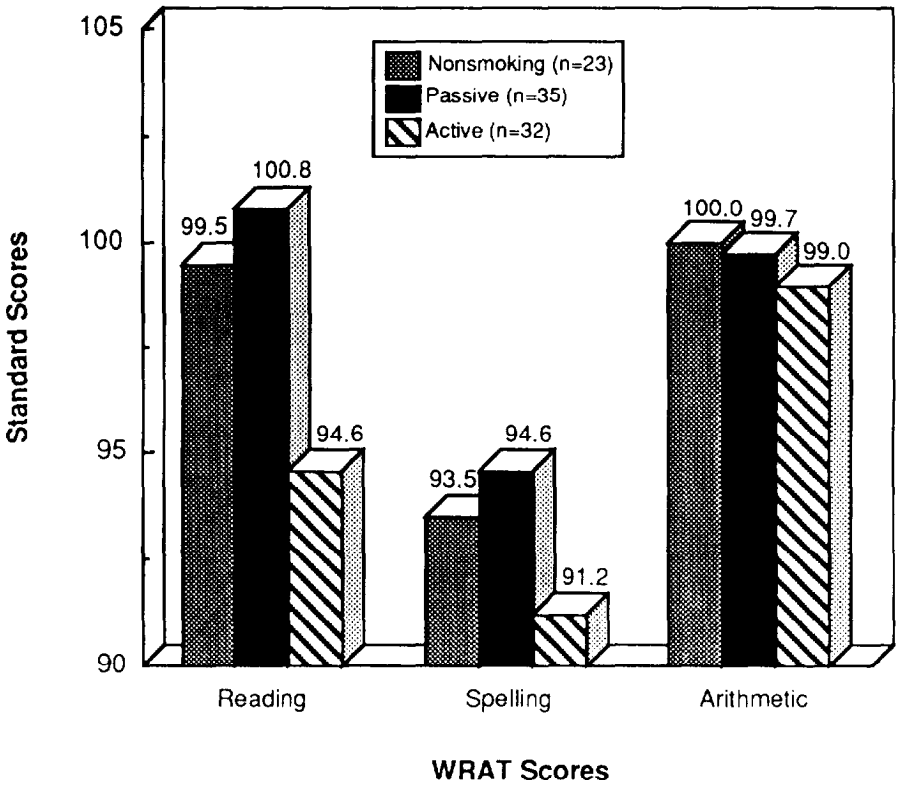

FIGURE 2. *Academic achievement scores of 6- to 9-year-old children of active and passive smokers*

OUTCOME AFFECTS DECISION OF RETENTION OF SUBJECTS

The selection issue continues beyond the choice of which mothers-to-be to retain for followup. It extends after the birth of the infant and may be contingent upon parameters associated with the offspring. There are some instances in which circumstances make it obvious that, beyond basic birth data, outcome variables at a later age would not be useful. One example would be the untestable baby (e.g., an infant with cerebral palsy). However, many less clear cases frequently come into play in the area of prenatal drug exposure.

Confounding Data

Certainly, it is not possible to consider all such variables, but a discussion of a few that have arisen in OPPS and other longitudinal prospective studies will serve to indicate the problem. Many drugs, when used during pregnancy, are associated with reduced birth weight and/or prematurity (Fried and O'Connell 1987). These birth parameters have effects on a host of outcome measures as the child develops. Should a low-birth-weight child or a premature subject be dropped from a longitudinal study? This would appear unwarranted as it is possible that one essentially is eliminating a subject that has shown a drug effect measured at one stage of development. If the subject is retained, then the issue moves to a question of statistical treatment of a related variable-not unlike that mentioned above with respect to potentially confounding variables. For example, when a regression model is used, one approach is to examine the unique contribution that the drug in question makes on the offspring's behavior once the possible confound of birth weight has been considered (Mau 1980). An alternative approach involves a chronological, causal chain rationale in determining what variables should be considered as potentially confounding factors (e.g., Sampson et al. 1989). In this approach, it is concluded that if birth weight, for example, is affected by use of a particular drug during pregnancy, then that should not be controlled statistically in an examination of a relationship between the drug in question and a later outcome measure. The statistical arguments are beyond the scope of this chapter (for a discussion, see Fried and Watkinson 1988), but the relevant point is that no matter how the data may be treated statistically, the low-birth-weight and premature subjects should not be eliminated from the followup phase of the work. Thus, in cases in which the drug being investigated may have a particular effect at birth, that effect may serve as a mediating variable for an outcome at a later age, and it would be inappropriate to exclude those subjects in the prospective study.

The decision to retain subjects in the above example is fairly obvious, However, in OPPS, somewhat more difficult decisions had to be made with respect to offspring selection and retention. The use of multiple offspring of the same mother is one such example. Because possible entry into OPPS was over several years, several participating women had two or even three children eligible for inclusion. Whether they should be included was not a straightforward issue. On the one hand, using siblings appears to violate the assumption of independence on which statistical tests are based. However, considering the child as the unit of analysis, each has a unique prenatal history. Although type of prenatal drug use is often consistent across several pregnancies, it is rarely consistent in quantity or pattern. The potential problem with independence includes such possible confounding variables as the mother's gene pool, her education, her medical conditions, the family

income, the home environment, and her childrearing practices. A factor in the decision to include multiple offspring is the need to have as large a sample as possible (nearly always a problem in research dealing with illegal substances). Finally, there is the important empirical opportunity to investigate the question of the degree of similarity or dissimilarity among siblings, although because of sample size, findings remain at almost anecdotal level. In OPPS, data are collected from all eligible subjects, and the outcome measures are analyzed with the random selection of one offspring's data and with all the offsprings' data. To date, both approaches have yielded similar results.

An extension of this issue is the question of dealing with multiple births. Here, however, the issue of lack of independence is more problematic, with much less variance between the siblings. That plus the few such cases have dictated that, although the subjects are followed, for publication purposes, only singleton births have been reported. Nevertheless, collection of parallel data on multiple birth siblings is not an opportunity to be missed.

Missing Data

An inescapable problem with longitudinal, prospective work is the issue of treatment of missing data. Any cases with missing data on the primary drugs of interest clearly must be deleted from the analysis. Dealing with cases with missing data on the outcome variables is dependent on several factors and involves several steps. The initial question is whether the missing dependent variables occur randomly or systematically across groups. If differential loss across groups is noted, the underlying reasons for loss should be investigated as they may be important in understanding differences among the groups. For example, some children may be uncooperative for some tests. If this behavior were to occur more often in one of the drug groups, this should not be overlooked as a potential consequence of maternal drug use.

With random or minor loss of data, several options are available. The case can be dropped if the sample is large. However, if the sample is small, mean values for the variables affected may be substituted. Within OPPS, the strategy is to use the overall means of the variables as substitutes, which is a more conservative approach than substituting the means for the variables for each group.

If missing data occur with the control variables, the first step would be to examine the proportion of cases missing the relevant data. If the percentage is less than some predetermined value (the OPPS figure is 15 percent), then the group mean is substituted as a score. If the proportion of missing cases is greater than the a priori cutoff figure, one of two approaches may be

appropriate. The variable may be dropped if it is highly correlated with another control variable that has few or no missing data. If this is not possible, the mean value for the missing scores is substituted and the analysis is run with all cases. The analysis then is repeated omitting those with missing data, and the two analyses are compared. If the results are similar, the larger sample with the substituted values may be retained. If they are dissimilar, a decision must be made as to which result is more valid.

Outliers

A related problematic issue pertains to the distribution of variables and the influence of outlying cases. For distributions that are skewed, appropriate transformations have been described in the literature. For example, log (for extreme positive skewness) or square root (for moderate positive skewness) transformations will reduce the influence of outlying cases, but all interpretations of the results then must be in terms of the transformed variables. If this approach is employed with the major independent or dependent variables in the study, problems may well arise with the interpretation. On the other hand, transforming control variables in this manner is not as problematic.

An alternative strategy is to change the extreme scores to one unit larger than the next score. Finally, deleting the outlying case may be considered, but if the sample size is of concern, analyses can be run with and without the offending **case** to ascertain the influence of the outlier.

LIMITING SUBJECT ATTRITION

Up to this point, the issues discussed pertain to the experimenter's decision as to whether to retain or reject subjects. However, how does the researcher keep subject attrition to a minimum over a considerable length of time? There is no one technique that is uniformly appropriate for all types of studies, but a common element is that extensive outreach activities are essential. Two approaches are described below. One is employed in OPPS, a highly motivated predominantly middle-class sample, whereas the other has been used by Day and coworkers (N. Day, personal communication, November 1989) with a sample of low-socioeconomic status (SES) women,

Low-Risk Sample

In OPPS, techniques to enhance the retention of subjects are initiated at the point when women enter the study. The interview during each trimester of pregnancy is conducted by a trained female interviewer at the place of choice of the mother-to-be, usually the participant's home. The same interviewer is

involved with each of the interviews (up to three) during pregnancy. The interviewer is skilled in establishing rapport with a range of people—from "straight" to drug-using subjects.

Once the baby is born, testing is carried out at the hospital, then up until 3 years of age at the mother's home, and later at university facilities. In all cases the same staff, blind to the drug history, "followed" the infant/child during his or her entire participation in OPPS. These staff members were competent in being able to advise the women, if asked, on general parenting issues.

However, the key aspect contributing to a high retention rate among the women participating in OPPS is the method of feedback. Two forms of feedback are given. Within 2 weeks of testing, a telephone call from the principal investigator to the family is made and a detailed description is given with respect to strengths and weaknesses observed in the child. No attribution to drug use is made in the feedback and, if necessary, an emphasis is placed on the impossibility of assigning such a cause-and-effect role in a single subject.

The second form of feedback has been altered over the years. Initially, a general letter was sent each year describing the basic findings, again presenting the results in terms of risk factors. Recently, because the test battery has become so extensive once the child reaches 4 years of age (Fried 1989), get-togethers have been undertaken to which the mother and father are invited via a mailing. At this session, data are presented via slides, and an extensive question-and-answer period is encouraged. Tokens of appreciation are given to the attendees (e.g., buttons with the OPPS logo imprinted are given to all, and some T-shirts with the logo are presented as door prizes).

The comments received either during the telephone feedback or at the annual get-together leave little doubt as to the importance of these approaches in maintaining continued participation. Aside from individuals moving from the Ottawa area, the retention rate of the study cohort over the past 8 years is more than 95 percent.

High-Risk Sample

A somewhat different approach to maintain contact and foster continued participation has been used by Day and coworkers (N. Day, personal communication, November 1989) with a less motivated, low-SES sample. At the initial interview that took place in an outpatient clinic during the mother's fourth month of pregnancy, names and telephone numbers of the mother-to-be

and the people she designated as significant others were obtained. Contact was maintained by telephone at least every 6 months. If that was not successful, attempts were made to contact the subject by mail. A newsletter (written in a chatty manner) was sent every 3 months informing the mothers of the study results. This procedure fulfills a dual purpose of maintaining subject contact and updating address files. If the post office returns the letter or if the woman cannot be located by telephone, local contacts (including significant others identified earlier), medical records, and a reverse telephone directory (listing the address of a particular telephone number) are used. Finally, a professional tracking system that identifies individuals through social security and credit data can be employed.

If, after being contacted, subjects are reluctant to come for a scheduled appointment, additional information is given to the participant with respect to the content of the upcoming interview for which she had been scheduled. If necessary, taxicab vouchers, pickup by the staff, reimbursement (above the scheduled amount), and small gifts for the children are added inducements in this work. In the study, the women were reimbursed financially with a nominal amount ($15) for participating beyond the initial intake to defray various costs and to serve as an incentive for continued participation. Together, these procedures were successful in retaining these relatively difficult subjects for the duration of the work.

It is appropriate to raise here the issue of payment of subjects. For some samples, this is clearly not necessary; for others, payment must be deemed appropriate and necessary. One cannot expect a low-SES individual to, in essence, pay to participate in a longitudinal study in which expenses are bound to be incurred. The issue of payment as incentive to continued participation is more problematic. Should the payment be in cash or is it more appropriate to give particular goods (e.g., food, toys, books)? The obvious problem with cash is how it may be used subsequently. Giving goods, however, is not an automatic solution as they can be bartered for whatever the cash might have been used to purchase. There is no clear solution to this dilemma, but the researcher must be aware of the appropriate amount within the subject's environmental circumstances to compensate the subject for the participation. The more the payment can be connected to continued participation, the better (e.g., giving a sum at each testing session and a bonus for complete participation). The details of the remuneration should be outlined in the informed consent that the subject signs before entry into the study.

INFORMED CONSENT

The informed consent merits comment from an additional point of view with respect to subject selection issues. The purpose of an informed consent is to inform the subject about aspects of the study and rights of the participants (i.e., process for withdrawal if she chooses; repercussions, if any, of both participation and withdrawal; form of feedback; availability of counseling; degree of confidentiality; remuneration, if any). These elements must be presented in a form that can be understood by the participant. As obvious a point as this may seem, the written consent is frequently couched in language that requires an advanced degree to understand. It is not sufficient to have a sentence at the end of the informed consent stating that "I have read the above and understand the contents." An additional aspect of the informed consent should be a series of oral questions asked by the researcher that would ascertain whether the participant really understands the content and the implications of the form. For example, one might ask: "When are you allowed to withdraw?" or "What happens if something is found to be wrong with the baby?"

The informed consent should include a clear statement of the researchers' legal obligations. For example, if abuse is noted by the research team, most (if not all) State and Provincial governments require that it be reported to appropriate authorities. A parallel obligation exists when continued maternal drug use is noted. These aspects of the consequences of participating in the longitudinal study must be part of the information dispensed to the individual.

CONCLUSION

This far-from-inclusive chapter has highlighted areas of subject selection ranging from initial screening of potential subjects, choice of the followup cohort, decisions pertaining to the retention of subjects within the followup cohort, and factors that may enter into the retention of the cohort over an extended period. It is rare that within any of these topics there is a simple, universal answer or approach that can be applied in a "cookbook" fashion. However, by using the experience of workers in the area of longitudinal consequences of maternal drug use, research design (as it pertains to subject selection) has steadily become a more sophisticated facilitating process in this fundamental phase of prenatal drug exposure research. Continued and possibly accelerated progress in this methodological area will occur if researchers are encouraged by reviewers and editors to provide more detailed information about subject selection procedures within their publications.

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Subject Recruitment and Retention for Longitudinal Research: Practical Considerations for a Nonintervention Model

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INTRODUCTION

Recruitment and retention of subjects are the two most crucial aspects of longitudinal research. The success of the entire project hinges on whether the appropriate subjects can be convinced to participate at the outset and made to feel it is worth their while to continue over the many years it often takes to complete the study. In this chapter, the authors draw on personal experience with five longitudinal prospective studies over a 30-year period.

Prospective longitudinal research is not new; in fact, it has been the backbone of child development research since the late 1920s when the Berkeley Growth Study (Bayley 1949) began. How else would one be expected to understand normal child development without systematic observational studies that tracked the child into maturity? In the early 1960s the prospective longitudinal method was used on a grand scale to determine the causes of disease and impairment in young children. The Collaborative Perinatal Project involved a national sample of more than 53,000 pregnant women from 12 centers and a cohort of more than 34,000 children followed through the age of 7 years (Broman et al. 1985; Niswander and Gordon 1972). These pioneering studies have served as models for the authors' approach to longitudinal prospective research on the prenatal environment as it influences postnatal development of the child.

This methodologic chapter draws most heavily on three large-scale studies that have been initiated over the past 16 years: (1) the Seattle Longitudinal Prospective Study on Alcohol and Pregnancy (the alcohol study), which was designed to examine the long-range effects on children of their mother's social drinking during pregnancy and the possibly exacerbating or ameliorating effects of tobacco, caffeine, drugs, medications, diet, and/or the postnatal environment

(Streissguth et al. 1981, 1989a, 1989b); (2) the Seattle Longitudinal Prospective Study on Maternal Iron Deficiency During Pregnancy (Streissguth et al. 1983); and (3) the Seattle Cocaine and Pregnancy Study (the cocaine study) (Streissguth et al. 1989c). Each study began with a cohort of approximately 500 subjects. These studies differed not only in their targeted agents and populations but also in their year of onset—1974, 1980, and 1989, respectively.

We have learned that what works for one time in history may not work for another. Times change, motivations change, populations change. Unless longitudinal prospective studies can be flexible and creative in meeting these changes, their success will be limited-not by lack of worthy hypotheses but by the mechanics of subject recruitment and followup. In this chapter, the authors urge investigators not only to learn from the past but also to be flexible in planning for the future. Moreover, funding agencies and review committees are urged to respect and encourage flexible approaches to this essential and expensive aspect of successful longitudinal research.

Careful attention to recruitment and retention of subjects is important for several reasons: (1) maintaining sample size and power to detect effects if they are present; (2) avoiding bias in sample selection and data collection; and (3) generalizing the findings to larger populations (Cox 1958; Harway 1984). Although the focus of the studies described in this chapter is on pregnancy followup, many of the techniques will be useful for longitudinal research in general.

This chapter deals with the population-based study that uses a nonintervention followup model. In the drug and alcohol field, the nonintervention model, which historically has been used widely in the field of child development, is useful for answering basic questions relative to human behavioral teratology: What are the long-range effects of prenatal alcohol exposure (or cocaine exposure) on the neurobehavioral development of the child. A companion chapter by Howard (this volume) describes recruitment and retention issues in longitudinal prospective studies using a referral model of recruitment and a clinical intervention followup. The two types of designs require different approaches to recruitment and followup because direct service to subjects is not an explicit aspect of the nonintervention model study design. Whichever model one chooses, careful attention to recruitment and retention sets the stage for successful longitudinal prospective research.

CONSIDERATIONS IN PLANNING THE STUDY

Prenatal vs. Postnatal Recruitment

For population-based pregnancy outcome studies, it is essential to estimate at which point the population best can be approached in full and in a standardized manner. How this question is answered depends on the goals of the study. In the social drinking study, the authors hypothesized that timing of exposure was critical, so enrollment was demanded at a standard time during pregnancy to optimize self-report of alcohol consumption. The pilot studies had shown that most of the women in the study population would be in prenatal care by the fifth month of pregnancy. As we were not interested in alcohol-abusing problem drinkers who might deliver without prenatal care, it was of no concern if they escaped the study net. We opted for a more homogeneous, low-risk group of mothers who were not engaging in other high-risk behaviors and who had adequate prenatal care. In this study, the standard interview was conducted during the fifth month of pregnancy, regardless of when the women entered prenatal care, and all women who were not in prenatal care by midpregnancy were purposely precluded from participation. This served the dual needs of a standard interview time and a population that was generally low risk and had adequate prenatal care.

In the cocaine study, it was recognized that many potential subjects would not be receiving regular prenatal care; therefore, to standardize the self-report period, the authors opted for an inhospital postpartum interview. From the standpoint of study design, it is a less expensive, less complex design to recruit at delivery. Possible disadvantages, such as a more retrospective recall of drinking and drug use during pregnancy, can be dealt with by procedures that maximize recall for the period before pregnancy as well as for the different trimesters of pregnancy (e.g., see Giunta et al. 1987; Day et al. 1985; Streissguth et al. 1989c). In the alcohol study, about 10 percent of the prenatal sample failed to deliver at the hospitals at which they had been recruited prenatally. This precludes neonatal assessments of the infants and makes obtaining uniform medical records data difficult. Restricting the sample to those planning to deliver at the study hospitals and to remain in the area for at least 1 year targets subjects most likely to be available for followup.

Short-Term vs. Long-Term Followup

It is wise to build in tracing procedures that will permit long-term followup even though the immediate commitment and funding may allow for only short-term followup. Although subsequent consents must be obtained for later phases, if the subjects cannot be found they cannot be asked to participate. For example,

in the alcohol study, 66 percent of the original followup cohort was examined at 7-1/2 years of age using the tracing procedures described here. When the investigators went back to the original screening sample and tried to locate additional control subjects after 7 years, only 20 percent were found because adequate tracing information on noncohort families had not been obtained.

Frequent vs. Occasional Followup

The decision to employ frequent vs. occasional followup hinges primarily on the type of subjects being examined, the overall resources for the study, and the outcomes to be obtained. Experience has shown that middle and upper class mothers (particularly volunteers) are busy and are not eager to commit themselves to a frequent followup schedule. On the other hand, in following high-risk populations from lower socioeconomic backgrounds, it would be virtually impossible to follow them without frequent contacts due to their transiency, their lack of familial and employment stability, and their general lifestyle.

Maintaining the "Blind" Examlner

Although it is clearly less expensive to send an examiner to the home to examine the baby, it is preferable to examine children in the standardized laboratory situation (with which all children are unfamiliar) and to employ an outreach worker to locate the subjects, set up the appointments, and transport the subjects as necessary. This maintains the examiners "blind" to many aspects of the family environment that might bias their impressions of the child and also permits a supportive relationship to develop between the mother and the outreach worker, which facilitates further followup. In the authors' study design, the outreach workers are the key to successful subject retention.

Human Subjects Considerations

It is desirable to obtain the consent for the entire funded study at the outset. This way the parents know from the start what is expected of them, and the study does not waste precious resources on subjects who may decline to participate in later components. The authors were surprised to discover that some things that were presumed to be objectionable to mothers (like taking a brief IQ test or allowing us to take a small sample of their infants' hair for drug screening) were not protested once the feeling of trust was established. On the other hand, compliance decreased when the protocol called for infant blood samples in the iron study.

Special precautions are necessary in studies involving questions about the use of illicit drugs. To protect the study records from subpoena, a Certificate of Confidentiality should be obtained from the Secretary of the Department of Health and Human Services, US Public Health Service. Recruitment also is improved by disassociating the project staff from the usual hospital staff and assuring the subjects that data are not entered into the medical records of either the mother or her baby. Human subjects restrictions on recruiting unemancipated teenage mothers (below age 18) without consent from their parents makes it especially difficult to include young mothers without a special protocol. (For these younger teenagers, it is also important to assure them that the information will not be released to schools or parents without their permission,)

Despite the focus on subject retention implicit in outreach activities, it is important to note explicitly that subjects do have the right to withdraw from a study, and this right must be respected.

Special Problems With Illicit Drug Use and Research in the 1990s

Fear of losing their babies is a paramount concern among women who use illicit drugs during pregnancy. Fear of disclosure of information on illicit drug use is a frequent reason for refusal to participate in followup studies, particularly as voiced by a spouse or boyfriend. Media flurries about “crack babies” and prosecuting mothers for child abuse often can have a direct and immediate effect on the rate of enrollment at any point in time. The outreach worker should be apprised of current State law so that proper reassurances can be given to women at recruitment. For example, at this time in the State of Washington, prenatal use of illicit substances is not considered child abuse; knowing this provides additional reassurance to the mother who is considering enrolling in the study and divulging information about illicit drug use. (Besharov and Weber, this volume, discuss the legal aspects of this complex problem in greater detail.)

Additional problems associated with studying mothers who take illicit drugs during pregnancy involve their frequent lack of a stable social support system and the overwhelming problems with day-to-day survival that many of these women face. The authors found that these factors necessitated a much more active role on the part of the cocaine study staff than had been assumed in the social drinking study. These activities are described in greater detail in succeeding sections.

Screening To Optimize Subject Recruitment

In the two major drug outcome studies, a screening device was used to optimize selection of the followup cohort, Screening produces a more generalizable sample (as needed for behavioral teratology studies) compared with recruiting directly from drug treatment populations or accepting only referred patients, As the use of alcohol and illicit drugs is not reliably reported in medical records, the authors prefer the screening method to the medical records surveys for recruiting a more representative sample of users. Recruitment from a screening instrument can greatly reduce the cost of the study design. In the alcohol study, the investigators felt it was essential to optimize the honest reporting of drinking during pregnancy. At that time, drinking was common (81 percent of the pregnant women). Private interviews were given in the home to 1,529 mothers who met the study criteria for being in prenatal care by the fifth month of pregnancy, who were not planning to immediately move out of the area, and who lived within a 20-mile radius of Seattle. It took six full-time interviewers to accomplish this in 1 year. From this screening cohort, a computerized priority score was developed based on 19 different drinking patterns and control features: it was used to select the approximately 500 infants who were examined neonatally and for succeeding postnatal exams (Streissguth et al. 1981). This was an effective strategy for optimizing recruitment of the followup cohort when studying a relatively frequent phenomenon.

For the cocaine study, in which pilot studies (Streissguth et al. 1989c) indicated that only 15 percent of the inner-city mothers and only 3 to 5 percent of the suburban mothers reported use during pregnancy, a more efficient screening device was needed. To meet this need, a one-page Hospital Screening Questionnaire (the HSQ, also called the “Purple Screening Form”) was developed that is distributed to all mothers delivering babies each day at each study hospital. (This form, which elicits recall of alcohol and other drug use before pregnancy and during pregnancy, is available from the authors on request.) The HSQ is self-administered, but any woman who has difficulty filling it out can be helped by the recruiter, It is also confidential; subjects are asked not to put their names on it and the mother puts it in a special envelope for returning it. Reading the form at the time it is picked up permits the recruiter to target for the followup study those mothers who have reported cocaine use during pregnancy as well as appropriate controls, This reduced the number of women getting 30-minute personal interviews on alcohol and other drug use during pregnancy from 8,000 to 500. Only the 500 women who met the intake criteria according to the HSQ were asked to be in the followup study and given the personal interview on alcohol and other drug use during pregnancy. For this study, two half-time recruiters could screen 4,000 mothers per year delivering at

two hospitals and could enroll and interview 250 mother/baby pairs for the followup study. (This includes weekdays only; additional staff would be necessary to cover weekends.) Thus, the specialized screening procedures appropriate to each study enable the staff to recruit a population-based cohort that most precisely meets the needs of each study.

RECRUITING SUBJECTS

Settlng the Stage for Success

Naming the study appropriately is important for the subjects as well as for staff members, The authors use a positive-sounding name originally borrowed from Little (1977), the Pregnancy and Health Study, which reflects the broad goals of the projects. As new studies evolve, they become P and H-2, etc. because it would jeopardize children and mothers, both users and controls, to be identified with a "cocaine study." As the children in the alcohol study have grown up and themselves become the primary focus for outreach, an additional name change has become necessary because Pregnancy and Health Study is not an attractive study name to teenagers. The new name, the "Seattle 500," has a sense of collegiality and solidarity that appeals to teenagers and does not embarrass them.

The people who do the recruiting are the most important ingredient in successful recruitment. In the alcohol study, six young women who were similar to the study mothers in age, race, and social class served as recruiters. Recruitment was solid at 86 percent. Each interviewer was carefully screened in terms of openness of attitudes about drinking (none were in recovery or thought to be judgmental about drinking), and the mothers seemed to relate easily to them. In the cocaine study, similar criteria were used in selecting the primary interviewers; however, without considerable additional inducement, recruitment of cocaine-using mothers was originally steady at only 58 percent. Obviously, what worked for a licit drug at one time did not work 16 years later for an illicit drug at a time when considerable media hostility was being directed toward mothers using drugs during pregnancy. When inducement was changed (see "Positive Inducements" below), 84 percent of these same women were recruited.

Constraining Recruitment To Enhance Followup

At the time of recruitment, with its pressure to enroll as many women as possible within the specified period, it is often difficult to remember that decisions will constrain the followup for years to come. Enrolling only mothers who live within a narrow radius of the study site will minimize followup costs.

This is possible when studying a substance that is widely used. On the other hand, the rarer the behavior, the more widely afield one must go for subjects and the higher the followup costs. Likewise, enrolling only mothers who had telephones and cars would reduce the need for scheduling and transportation but would bias generalization to only one type of mother. The investigators try to constrain the subjects geographically at the outset and target only women who plan to remain in the area for at least 1 year. On the other hand, they do not constrain for telephones and automobiles but rather develop outreach procedures to deal with each type of family enrolled, preferring to have a more broadly representative cohort.

Positive Inducements

In the alcohol study, the sample was predominantly white, married, middle class, and well educated. Mothers agreed to two followup exams of their babies within the first 18 months after birth, without payment or material reward. They were told that they would be reimbursed for transportation costs and, occasionally, for sibling child-care costs. The staff and subjects believed that by enrolling in this important study of prenatal influences on child development they would help other mothers have healthier babies. No other positive inducements were necessary.

Additional positive inducements were necessary, however, to enroll mothers in the cocaine study. The pilot studies had shown that subject remuneration was essential. During the first 3 months of the study, mothers were offered $10 for each of the four visits. Enrollment was flat at 58 percent, a figure that was considered inadequate for the type of generalizations the authors wanted to make. A review of the literature revealed that other longitudinal investigators (Capaldi and Patterson 1987) found $50 per visit to be a minimal amount to ensure adequate compliance. In fact, this is a figure commonly cited for adults who are asked to come in for various types of laboratory assessments, Why should mothers get less for bringing in their babies? The recruitment rate rose immediately upon raising the remuneration, and it has remained stable at 84 percent,

Types of positive inducements offered by some studies include well-baby checkups, medical care, baby photographs, and baby presents. The authors' studies used none of these, but in the alcohol study, the children were given coloring books at age 4, fancy balloons at age 7, and $20 at age 14.

Project outreach workers also help the mothers solve whatever obstacles stand in their way in terms of bringing their babies in for examinations, be it transportation, child care, scheduling flexibility, etc. In the cocaine study,

outreach workers have helped mothers solve many other types of problems such as buying diapers, getting baby furniture, getting breakfast the morning of the examination, obtaining referral for counseling, getting medical care for themselves and their families, getting into alcohol and other drug treatment programs, and getting help for their friends. These activities helped bond the mothers to the study but are not interventions in the sense that they directly interfere with the baby or the mother's interactions with her baby.

TRACING SUBJECTS

General Philosophy

The authors agree with Showstack and colleagues (1978) that losing track of subjects is a much more common cause of subject attrition than are refusals or withdrawals. Therefore, successful tracing activities devoted to keeping track of the cohort over time become essential.

Throughout all contacts with study mothers and their families, the project staff maintains a nonjudgmental manner, communicating a willingness to act as advocates for the women if needed. The staff is friendly and open in relationships with the mothers and their families and is respectful of them as individuals.

As a general philosophy, staff members also continue to correspond with and trace every subject enrolled in the study, even though they may have moved out of the area or missed an individual exam. Some subjects move back into the area at a later date or contact the staff for an exam when they return to town on vacation or to visit relatives. Even mothers who have refused one exam often participate in the next. Thus, the denominator is kept constant across exam ages, and compliance is often better when children are older and mothers are less pressured.

In the alcohol study, after 14 years, contact still is maintained with almost all the subjects, even those out of state and out of the country. By the time the children were 7-1/2 years old, 20 percent had moved outside the original 20-mile radius of Seattle. The number who can be brought back for followup exams in the laboratory depends on available funding.

Specific Techniques

Over the past 16 years, the investigators have gradually improved the tracing techniques to ensure even more successful followup. At the time of enrollment, subjects are asked specifically about plans to move and for the

names, addresses, and telephone numbers of three family members and/or friends to whom the project staff may turn for help in the event that the mother cannot be located. The staff also asks each mother for the name under which her telephone is listed, for her authorization to contact the telephone company for an unlisted number, for her social security number, for permission to obtain her address changes from social welfare agencies, and if applicable, for the name of her social worker. For mothers with frequent home changes, current addresses also can be obtained (for a small fee) through national credit check agencies. The mother's birthdate also is obtained for tracing addresses through government agencies. This information has proven useful in overcoming most barriers that were previously encountered in tracing women who remained in the community but moved so many times that the staff could not find them.

Some women are designated "special-care mothers" for whom the outreach worker needs to establish immediate contact after recruitment, without waiting for the next scheduled appointment. Special-care mothers are defined as women who are so socially isolated that they have no one to list as "references," who have no stable housing, and who have immediate needs that the staff can help with (e.g., bassinets, diapers, housing, legal aid).

Periodic written communications also are mailed to the families, with the envelopes marked: "Address correction requested." This allows the staff to immediately begin tracing mothers who have moved, even though it may be months or years before their next appointment. Annual custom-designed birthday cards are sent to the children in the alcohol study. Custom-designed Mother's Day cards are sent to the cocaine study mothers as well as newsletters every 3 months. The newsletters have a chatty, upbeat tone; they include pictures of the outreach workers and examiners, news about how the study is progressing, tips on baby care, recipes, and notes about community resources and activities. They encourage mothers to give out our telephone number to any friends who have concerns about alcohol and other drugs and pregnancy. The newsletter also reminds mothers to notify us if they change their address or telephone number. These communications are sent even to mothers who have moved out of town so that contact with them can be maintained. (For additional information, see Giunta et al. 1987.)

Other useful techniques involve using the reverse telephone directory and driving out to a mother's last known address (in a State car, in pairs) and talking with neighbors. A pleasant, positive approach and conveying the idea that this a health-related issue (the baby's clinic appointment) often can lead to success. In talking with a mother's references, it is often necessary to take time to establish a feeling of trust before the forwarding address can be obtained. Occasionally, after a negative contact with one outreach worker, it

is useful for another worker to be the main contact with the family for awhile. Certain public records, such as death certificates and local court records for both civil and criminal offenses, also can be useful for tracing mothers who are lost to followup.

Staffing Needs

In the alcohol study, one full-time outreach position is needed just for maintaining the sample, scheduling appointments, transporting subjects, and doing mailings for 500 subjects per year. During the 1983 wave of data collection, this outreach worker scheduled and brought in 40 to 45 children per month (Giunta et al. 1987). The study averaged a 4-percent "failure" rate for appointments and a 15-percent cancellation rate. A few subjects needed repeatedly rescheduled appointments but finally were brought in. For this 7-1/2-year followup examination, staff members saw 95 percent of the subjects who had been seen at age 4, and over the 7-1/2-year period, study subjects demonstrated an 85-percent followup rate without any differential loss of more highly exposed subjects.

In the cocaine study of very high-risk mothers and babies, a different half-time outreach worker is responsible for bringing subjects in for each of the closely spaced infant examinations. Each one sets the stage for the next, The study has a 93-percent rate of followup at 4 months and a 94-percent rate at 6-1/2 months; the 12-month exams are in progress. However, inclusion of a suburban hospital has escalated transportation costs and outreach worker time. Each outreach worker brings in 20 to 23 mother/baby pairs per month over a 2-year period for each exam phase.

RETAINING SUBJECTS

Bondlng to the Study

The authors believe that this is the single most important feature of subject retention. Even in the cocaine study, where a larger monetary remuneration was necessary to recruit mothers, what keeps the subjects returning for repeated exams is the positive feeling of support that they get from participation. Mothers express this to the outreach workers in a variety of ways.

Each Encounter a Positive Experience

It is the authors' philosophy that each encounter with the study should be a positive experience. The staff communicates feelings of respect and support

and the willingness to help. Participation in the study enhances feelings of self-worth, and this becomes particularly important among women whose experiences with institutions are primarily as recipients and are often negative. The mothers seem happy to know that the staff believes they are contributing something very important to the project and to other mothers by participating in these studies.

Personalized Communications From the Study

Each communication from the study is thought of as not only a manifestation of the staff's interest in the mothers but also a manifestation of the importance of the study. A special color stationery is used for each study. Each study has its own logo, which appears on the envelope and letterhead. Stamped self-addressed envelopes of the same color are enclosed for easy returns. Important communications are addressed by hand rather than on the computer; attractive postage stamps rather than postage metering machines are used. These small tokens appear to be most meaningful in the cocaine study, in which a larger proportion of the mothers are single and have little social support. Those who are estranged from their own families seem particularly needy and responsive to personal touches, which they say they view as a measure of the staff's concern.

Although the examiners remain "blind" throughout the study in terms of prenatal exposures and home environments, the outreach workers have access to this information. In dealing with mothers who have used illicit drugs during pregnancy, it is useful to have the new outreach workers acknowledge to the mothers that they have this information when they interview mothers at followup visits regarding postnatal drug use. Mothers thus are spared from having to use denial in dealing with new outreach workers to "save face." Mothers were less willing to admit to illicit drug use postnatally when the outreach worker did not indicate that she knew about their prenatal use.

Remuneration and Feedback

In addition to the $50 remuneration for each visit (see "Positive Inducements" above), the mothers are either driven to and from their appointments or reimbursed for transportation costs. About 40 percent of the cocaine study mothers need to be transported. Mothers are not given specific reports on their babies' exams but are given the measurements, if they wish to have them, to chart their babies' growth over time. Examiners answer the mother's questions in general terms, focus on positive aspects of the child's performance, and suggest that a mother discuss special concerns with her baby's doctor or nurse. Families without a source of well-baby care are given referrals for such care.

Mothers are not given advice about how to parent or interact with their children nor are they treated differently according to exposure history. Specific referrals are made for any serious medical problems observed in the course of the examination. After a study has been ongoing for many years, some mothers want to know what has been learned. Mothers requesting this information are sent occasional letters describing the findings in general terms.

STAFF RECRUITMENT, TRAINING, AND INSPIRATION

Project outreach workers from many different backgrounds have proven to be equally effective. What the authors look for is not a particular academic degree but a type of person who communicates concern without being condescending and who cares without being judgmental. The outreach workers are open, straightforward, efficient, and, above all, good problemsolvers. They are flexible in meeting the needs of individual mothers but determined in their efforts to locate each baby for examination and to leave each mother feeling good about her participation in the study. Outreach workers often give mothers their home telephone numbers and strive continually to reduce barriers to communication. They are trained in-house by previous outreach workers through the use of our outreach manual (Giunta et al. 1987) and by what they learn from the mothers, Some outreach workers feel that a social work background helps them listen with an “educated ear” and that a feminist perspective is a useful orientation. Others are able to use their own life skills as a basis for concern and understanding.

Although no special degrees are required for outreach workers, they should not be poorly paid. Writing job descriptions with adequate outreach salaries is important for staff stability, which, in turn, enhances subject retention. The outreach worker often must work irregular hours to accommodate the needs of mothers; compensating for such services can be difficult on restrictive budgets. Planning for sick leave and vacations also is complicated when outreach workers are employed over long periods.

Outreach work is so demanding and intense that it is essential to provide support for staff members in this position. Brainstorming sessions in which they share experiences and ideas are particularly useful to get a new slant on hard-to-trace mothers. Various types of in-service opportunities, such as child abuse conferences and programs about female drug and alcohol abuse, are also helpful for outreach workers. Budgeting for these costs in advance is important.

MAINTAINING CONTINUITY THROUGH TIME

No matter how dedicated the outreach staff, changes in personnel are inevitable. Thus, successful longitudinal prospective studies will need to devise ongoing systems for maintaining continuity through time despite personnel changes.

The availability of computer systems has improved the project outreach service greatly compared with what was available 16 years ago. The outreach files utilize a database management package with a mail manager and a word processor that produces personalized confirmation letters and facilitates labeling newsletters. This system permits the outreach worker not only to update name and address information for each subject as it is available but also to schedule each baby's appointment according to his or her adjusted age as necessary for many infant examinations conducted during the first few years after birth. Thus, by entering the birth date and the gestational age at delivery, the outreach worker can schedule the followup exam at the correct time even before all information is available in the main database from the medical records or maternal interviews.

Outreach workers also keep systematic notes on their attempts to contact each mother. A "Subject Contact Sheet" is filled out for each contact and filed in the locked tracing files, arranged alphabetically by mother's last name. The sheet is accessible only to the outreach staff. Thus, all old contact sheets are available to each new outreach worker at each new examination phase. Individualized outreach notes on each subject provide invaluable information to the outreach worker who finds the trail cold on a particular mother.

BUDGETING FOR SUCCESS

Outreach costs are not cheap. They often are undervalued in peer review compared with the unquestioned costs of instrumentation for data collection. Yet, without adequate outreach, the most precise outcomes will not yield results. Review committees and agencies accustomed to dealing with short-term projects usually have no idea about the skill involved with successful outreach and the attendant costs.

The direct relationship between the budget and the followup rate becomes accentuated as the children get older and more dispersed from the target area. The older the subjects and the longer the interval between exams, the higher the outreach costs. The task is not impossible, but it is expensive. Capaldi and Patterson (1987) described a longitudinal study in which families were paid up to $300 per year plus bonuses for three 1-hour home visits and a half day of

office tests. They concluded that high pay for subjects, highly trained home visitors, and written materials targeted to the subjects were the key to doubling recruitment and a followup rate of 100 percent,

Finally, the authors note again the importance of budgeting appropriately for each study at the outset. Agencies are urged to be responsive to the unanticipated outreach needs of longitudinal prospective studies (due to changing times and populations) and the tremendous resource represented in studies that have been ongoing for many years. Experience with long-term studies has led the investigators to believe that some of the most important outcomes are measurable only later in the child's life (Streissguth et al. 1989b). Yet, to track the child and his or her family over those years, some contact is necessary, which costs money even when it does not involve major data-collection phases. When dealing with issues of such major significance to the population as the impact of prenatal alcohol and drug exposure on the health and functioning of the next generation, it seems imperative to take a long-term rather than a short-term view. High recruitment and retention rates are essential for successful longitudinal prospective research.

IS THERE A CONSENSUS?

In preparation for this chapter, a brief questionnaire was sent to colleagues experienced with longitudinal prospective studies of children whose mothers used alcohol and/or other drugs during pregnancy. Responses were received from eight investigators, representing a total of 12 such studies. The factors most frequently noted or associated with successful followup were the quality of the subjects' personal relationship with the staff, adequate remuneration, and the services provided by the study. The biggest problems the investigators encountered in such studies were obtaining sufficient money for recruitment and retention, finding suitable subjects, motivating subjects from low socioeconomic backgrounds, and dealing with lifestyle factors of drug-abusing mothers (such as transiency and dangerous neighborhoods). When asked what longitudinal researchers might like to communicate to government agencies, the responses focused on three topics: (1) the amount of money it requires to recruit and follow up mothers in these projects and how labor-intensive this process is, (2) the amount of time necessary to run these studies and to analyze the data, and (3) the difficulty in maintaining an operational study and retaining key staff during periods in which the project is not refunded or when negative results are obtained during certain periods.

CONCLUSIONS

For longitudinal prospective studies, successful recruitment and retention of subjects over long periods is essential and expensive. It is essential because without successful recruitment and followup of subjects no outcome could be evaluated, and it is expensive because the creative task of motivating, tracing, and transporting subjects for repeated examinations over long periods is extremely labor-intensive. Outreach activities represent a far greater part of the successful research budget than most nonlongitudinal researchers realize. The essential ingredient for successful recruitment and retention of subjects in longitudinal research is the personal commitment of each subject to the project. The expense of obtaining this goal covers both the imaginative resources of the research team in determining how to inspire and maintain this commitment and their continual evaluation and upgrading of their outreach efforts. Although costs will vary greatly depending on the goals of the project and the type of subjects needed, recruitment and retention costs (including subject remuneration for some types of studies) are a valid and important component of the budget for longitudinal research. Without successful followup there is no study.

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Subject Recruitment and Retention Issues in Longitudinal Research Involving Substance-Abusing Families: A Clinical Services Context

Judy Howard

INTRODUCTION

The professional literature contains little information describing successful and unsuccessful methods for recruiting and retaining subjects in research projects dealing with chemically dependent women and their children. Although the *Handbook of Longitudinal Research* (Mednick et al. 1984) addresses methods for conducting longitudinal studies of birth and childhood cohorts in general, it does not include information specific to this population. This chapter reports some strategies that have proven effective during two 3-year longitudinal studies of substance-abusing families.

Recruiting and retaining chemically dependent families in research projects requires familiarity with the lifestyle of this client population and knowledge of their complex needs. Unlike families who have participated in prior studies of preterm infants (Parmelee 1977; Siegel 1984) or children from disadvantaged backgrounds (Lazar and Darlington 1982; Weikart 1989), chemically dependent families have unique characteristics that profoundly affect the recruitment and retention plan. These characteristics include (1) intermittent altered mental status secondary to the acute effects of alcohol and/or other drugs, (2) the effects of chronic alcohol and/or other drug use upon cognition, (3) the often untreated health care problems inherent in this population (e.g., sexually transmitted diseases, hepatitis, acquired immunodeficiency syndrome [AIDS]), (4) the violence associated with the drug lifestyle, (5) the "high-roller" economics of the drug culture, and (6) the disease of addiction and its implications (e.g., chronicity, recidivism). Ongoing professional interaction with these families demands that members of the research team be aware of these factors to help them maintain the professional objectivity necessary for conducting longitudinal research with this difficult population.

RECRUITMENT OF STUDY POPULATION

It is imperative that any recruitment strategy be designed with the specific study population in mind (Capaldi and Patterson 1987; Howard et al. 1986; McCorkle et al. 1984; Young and Dombrowski 1989). Furthermore, the recruitment process requires a bidirectional focus-on the referral sources and on the subjects. If the research design entails a population with specific attributes (e.g., subjects who are both pregnant and substance abusing), referral sources where such individuals may be identified have to be located, and their cooperation with research staff must be solicited. Following this, the subjects have to be recruited in such a manner that they will be motivated to participate in the project.

Referral Sources

In initiating the recruitment process for the 3-year study at the University of California, Los Angeles (UCLA) School of Medicine, Department of Pediatrics, my colleagues and I first established collaborative relationships with **a** variety of referral sources. A common referral source for chemically dependent subjects, for instance, would be a health or treatment center that identifies and provides services to substance-abusing individuals. In States where infants exposed prenatally to drugs are reported as being at high risk for child abuse and neglect, an additional referral source would be the local child protective services agency and/or the family court system.

Following identification of potential referral sources in reasonably close proximity to the research center, the research team must devise the appropriate "invitation" for use in recruiting subjects into the study. Such an "invitation" should include a clear description of the research project as well as of the participants' role. Also, it should convey an attitude of sensitivity to the subjects' life situations and needs.

Subject Recruitment

With chemically dependent families, a recruitment approach must allow more flexibility than would be necessary with families who are not involved with illegal activities. This flexibility enables project staff members to meet with subjects "on their own turf." The illicit nature of substance-abusing families' activities and their frequent changes of address necessitate a personal, one-on-one approach; furthermore, the project staff must be available to conduct intake interviews on weekends and during the evenings.

Although financial incentives have proven effective in recruiting and retaining subjects in some studies, particularly in the case of lower income families (Capaldi and Patterson 1987) our experience with incentives has focused on the provision of individualized services rather than payment to clients. Both approaches are costly but seem to be effective.

INHERENT VALUE OF CLINICAL SERVICES IN RESEARCH

My colleagues and I believe that provision of services in conjunction with conducting research is critical for subject retention and for ethical reasons. Thus, we maintain two separate staffs: The clinical staff provides ongoing services to project families, and the research staff is responsible for conducting the evaluations in the home and in the laboratory. These two staffs work separately to guarantee that research staff members remain "blind" to the experimental and control groups.

As data collection progresses and findings are analyzed, the work of the research staff may appear to be increasingly important-sometimes seeming to tip the balance between the two staff components. Exacerbating this, in certain academic settings, research in general may *seem* to be valued over provision of clinical services to families. Therefore, the clinical staffs role in client retention-and, thus, in ensuring that research data can be collected-may need to be accentuated as a critical project element. Just as research staff members may feel a sense of accomplishment when they are able to report their findings, the clinical staff also can experience such professional satisfaction when given opportunities for conference presentations and development of products such as informational brochures, manuals, and educational audiovisual materials.

RETENTION OF SUBJECTS

Strategies Used With Non-Substance-Abusing Clients

One longitudinal study conducted at UCLA that began in 1972, and focused on the developmental outcome of preterm infants, initially recruited 135 subjects, retaining 100 through the 12th project year (Cohen et al., in press). The first 2 years of the project emphasized individualized health care provided by a clinic-based pediatrician and a public health nurse who made home visits. During the remaining 10 years, project intervention was far less intensive but remained consistent. During this period, a psychologist and a pediatrician conducted periodic testing of the children and were available for consultation with families as needed.

Subjects were tracked over this 12-year period through four different means: (1) parents' employers, (2) parents' driver's licenses, (3) names of three family members or friends, and (4) records of ongoing health care at UCLA Medical Center. Maintaining contact with the subjects involved a tremendous amount of effort on the part of research staff members. However, it is the staffs impression that the intensive early intervention provided the foundation for the ongoing willingness of subject families to continue with a 10-year schedule of testing procedures (S. Cohen, personal communication, 1990).

Strategies Used With Chemically Dependent Subjects

Unlike the families served in the preceding longitudinal project, chemically dependent families present even more problems in tracking subject whereabouts. Furthermore, the chaotic lifestyle associated with alcohol and other drug abuse puts these families at particularly high risk for attrition. Many of them do not have driver's licenses, for instance. They tend to be unemployed; relatives and friends may not be willing to tell researchers where a family is located; and their health care is often sporadic. Thus, subject retention has become a primary focus for our staff. We have used a strategy that focuses on the family as a whole, which we feel has contributed to subject retention.

Based on the experience with families of preterm infants described above, as well as on our experience in working with chemically dependent families, we have combined two approaches in our research projects. In providing intensive, individualized services that include both clinic-based and in-home assessment and intervention, an interdisciplinary team is used to ensure that health and psychosocial issues as well as concrete concerns, such as finances, housing, food, legal problems, respite, and child care, are addressed. Along with conveying an attitude of concern for the participants' well-being and respect for their worth as human beings, the staff has approached each subject with consistency, reliability, flexibility, and honesty, while maintaining a professional role.

The research staff also needs to develop relationships with extended family members and any other individuals who may be providing care for the research subjects. Thus, it is helpful if project staff members can help facilitate appropriate services and referrals for other family members when indicated. For instance, if a newborn is the identified subject and the project staff observes that an older sibling has a health or developmental problem, it demonstrates concern for the family if the staff is able to assist this child in obtaining needed services.

Retention of Subjects and Collaboration With Community Agencies

Continued relationships with community agencies are essential in retaining research subjects. As a project progresses, community agencies not only can help secure services for families (such as financial assistance, help with food and housing, and legal consultation) but also can assist the research staff in tracking family movements. Because a chemically dependent parent may engage in illegal activities, family members, friends, and neighbors may withhold information about a family's whereabouts from the research staff if they suspect that the family is in trouble with the legal system. Thus, without the assistance of those community agencies with sufficient "clout" to maintain contact with these families, research staff members may not have access to records that identify changing addresses and telephone numbers. Furthermore, the coordinated advocacy on behalf of these families that results from ongoing collaborative intervention among research staff members and community agency personnel can greatly enhance services to this population.

Erratic Caregiving

Complicating this type of family focus in working with chemically dependent clients is the fact that children with substance-abusing parents frequently have multiple caregivers, including biological parents, extended family members, and foster caregivers. If a child is in temporary out-of-home placement, for example, the project staff needs to sustain relationships with the biological parents while continuing to provide services to the other caregivers.

The situation can be compounded further by the special issues surrounding each group of caregivers. For instance, biological parents who are chemically dependent require an intensive focus to address their own personal needs. Although extended family members may be reluctant to request help for themselves, they may require assistance in dealing with their own feelings of anger and grief and with their concerns regarding the addicted parent (who may be a son or daughter) as well as the child's health and development. Likewise, foster parents have issues that are different from those of biological parents and extended family members. These usually are less focused on personal feelings about chemical dependency and more directed toward organizing daily schedules for the children who may be under their care, including coordinating home visits by involved professionals and biological parents, keeping the children's health care appointments, and participating in evaluations that are part of the research project. Thus, maintaining a family focus in work with chemically dependent clients involves far more than assessing the child's development and health status.

Age and Subject Retention

The age of a subject at the time of his or her enrollment in a research study also may be a factor in determining attrition rates. For instance, Capaldi and Patterson (1987) and Ellickson and coworkers (1988) report that older children enrolled in a study that spans several years may be harder to retain once they become adolescents. This may be due to a lack of intensive family intervention early on in the study to ensure parental commitment to the project and/or the increasing independent behavior of the older child as he or she becomes an adolescent.

RETENTION OF PROJECT STAFF

It is our impression that staff continuity relates directly to subject retention. Thus, measures for preventing staff burnout are an important aspect of the research plan in work with chemically dependent families; examples of these are described below.

Staff Training and Support

The tone for program operation is established by the director of the research project. Identification of staff members who have the range of necessary professional backgrounds and experience, as well as interest in the research area, is critical to the success of any project. However, once the staff has been hired, the project director is responsible for arranging inset-vice training, staff support, and opportunities for innovation within the framework of the project design to ensure effective services and reliable findings and to promote retention of project staff members.

A Common Knowledge Base

As a basis for providing informed services, interdisciplinary research and clinical staffs need to establish a common knowledge base in a variety of areas related to the research focus. In serving chemically dependent families, we have found it critical to update the staff regarding the latest findings on the backgrounds, lifestyles, and health problems of substance-abusing parents; the disease of addiction; cultural issues; and community resources. It is also important for the staff to be familiar with child health care issues (including symptoms of pediatric AIDS, hepatitis, congenital syphilis, and other health problems that have been noted in children who were prenatally exposed to alcohol and/or other drugs) and with areas of developmental assessment and their implications for future functioning.

Knowledge About Communlty Agencies. Furthermore, because chemically dependent families may have frequent interactions with child protective services, family court systems, criminal court systems, and law enforcement agencies, it is necessary for staff members to learn about the specialized roles of these various organizations and the relationships among them. It is also important that the project staff be familiar with the expertise, responsibilities, and limitations of the multiple professional disciplines of the team that is involved with these families.

Knowledge of Family Systems. In addition, we have found that the clinical staffs knowledge of family systems and family functioning is essential as research data regarding caregivers and the effects of the environment on child development are collected and interpreted. An infant may be placed in the care of a maternal grandmother, for example, but the biological mother also may reside within the home. Although child protective services may identify the maternal grandmother as the primary caregiver, in reality the biological mother may be spending the most time caring for this infant. Thus, in assessing attachment behaviors, it is the biological mother, not the maternal grandmother, who should be involved with the laboratory evaluation. Accordingly, one feature of staff development programs must be to alert the clinical and research staffs to the importance of clearly identifying the roles of various family members so that a consistent interpretation of collected research data is possible.

Nature of Addiction. Another focus for staff development programs relates to the nature of addiction, which can impair an individual's ability to behave in a controlled fashion and to make sound decisions. It is not uncommon for chemically dependent parents to be neglectful and/or abusive toward their children and each other. In two of our longitudinal projects, for instance, in spite of less than 5-percent subject attrition and provision of intensive, home-based intervention, suspected child abuse and/or neglect was reported in several cases. These reports included failure to thrive on the part of the infant; child neglect due to a mother's absenteeism while on a "binge"; cigarette burns, sexual abuse, and school truancy in connection with older siblings; and domestic violence. Thus, the clinical and research staffs need to be aware of their mandated responsibilities with respect to reporting cases of suspected child abuse and neglect.

Assessment of Danger. Finally, just as intrafamily and community conflicts arise around alcohol and other drug abuse, project staff members must learn how to assess situations that potentially may be dangerous for them during home visits and while transporting clients to and from appointments. Staff safety is an additional issue that needs to be highlighted when dealing with chemically dependent subjects.

Staff Attitudes

In conjunction with this common knowledge base, project staff members need time to focus on their own attitudes, emotions, and biases in working with this complex population. In our experience, some professionals who choose to work in this field come from backgrounds in which there was alcoholism, substance abuse, physical abuse, or neglect, whereas others who may not have experienced this type of family dysfunction also may require time to come to terms with their views about substance abuse. Therefore, opportunities should be available for staff support, venting of feelings, and exploration of how a professional's attitudes can affect his or her intervention with these families.

Staff Differences and Cooperation

To further promote a supportive and productive working environment in dealing with these complex families, there must be respect among team members for individual skills and different styles of approaching clients and a provision within the program design for a certain degree of staff autonomy. Over time, this can be facilitated through regularly scheduled meetings that incorporate case presentations and group case discussions. In addition, it is helpful when project directors can set aside time for individual case consultations with project staff members. Finally, both research and clinical staffs can benefit from access to interdisciplinary supports such as drug treatment counselors, pediatricians, and hospital Suspected Child Abuse and Neglect Team coordinators.

Fostering a work environment that provides opportunities for individual staff members to develop and implement creative approaches to intervention and research not only encourages staff "ownership" of the project but also can enhance significantly individualized services provided to clients. For instance, in connection with one of our projects, research staff members were responsible for interviewing chemically dependent parents regarding their childhoods and experiences with family members, Clinical staff members were apprised that sensitive issues (e.g., a history of physical or sexual abuse) might be uncovered during these interviews and, in response to staff members' suggestions, made themselves available to clients following these sessions to assist as needed. In another case, a staff member was able to arrange, through local churches, delivery of Thanksgiving food baskets to needy program participants. Sending birthday and holiday cards or taking clients to lunch are additional efforts staff members have made to enhance both project services and their own positive feelings about working with these families.

Caseloads

It is particularly significant in the area of staff support to ensure that caseload sizes are manageable, since this benefits clients and helps prevent staff burnout. It has been our experience that a chemically dependent family generally includes more than three individuals, all of whom require attention from the project staff. On average, four community agencies are involved per family-representing at least two individual staff members each. Thus, a caseload of 20 to 25 families can entail more than 75 family members, with an additional 8 community agency representatives for each family. When a project has a home-based component, which is critical for effective intervention with chemically dependent families, caseloads not exceeding 25 to 30 families are sufficiently manageable to permit effective tracking, home visitation, and coordination of center-based appointments and activities.

Administrative Support

Finally, the role of an administrative and support staff in ensuring that project activities can be conducted with minimal complications is also significant. Procedures that promote effective communication among staff members as well as practical systems for recordkeeping, appointment scheduling, and notating completed or failed laboratory and in-home evaluations can greatly enhance project operation. Thus, “front-line” staff persons who answer telephones and interface with clients, community agency representatives, and even grant agency staff must be incorporated as part of the research team.

CONCLUSION

Research in general is essential to increase knowledge. Informed research is based on a rudimentary understanding of the subject to be examined. To study the development of children who have been exposed prenatally to drugs, we need to be able to conduct longitudinal research. This chapter attempts to highlight the types of activities and programs that have proven successful in retaining substance-abusing parents and their children in research projects.

The study of chemically dependent families is obviously complex, not only because of the seriousness of the problem of addiction but also because of lack of information about these clients’ chaotic lifestyles and the effects of polysubstance abuse. Because of the nature of illicit substance abuse, some professionals may conclude that retention of these subjects in a longitudinal study is not feasible. However, such a study is possible given the provision of informed, individualized services and an interagency approach that often includes the legal and child welfare systems.

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Perinatal Substance Abuse and AIDS: Subject Selection, Recruitment, and Retention

Kenneth C. Rich

INTRODUCTION

Perinatal acquired immunodeficiency syndrome (AIDS) is now a major focus of attention in the field of chemical dependence research. Illicit drugs are being used in a high proportion of pregnancies (Chasnoff et al. 1990), and the occurrence of human immunodeficiency virus-I (HIV-I) infection has a close association with substance abuse (Guinan and Hardy 1987). As many as 4 percent of deliveries have been reported to be from HIV-infected women delivering at hospitals serving high-risk populations (Nicholas et al. 1989). However, despite the importance of this problem, knowledge of the consequences of perinatal substance abuse and HIV infection is inadequate due, in part to the difficulty in performing studies in a population with major psychosocial and medical needs. The execution of studies on perinatal AIDS requires a careful integration of the medical and psychosocial needs of the study subjects with the scientific design. This chapter discusses some of the problems of scientific design, particularly subject selection, in association with issues of recruitment and retention.

PERINATAL HIV INFECTION

The increasing prevalence of HIV infection in chemically dependent women and the widespread consequences of HIV infection in their infants is forcing the reassessment of study design in the field of perinatal chemical dependence. Therefore, it is important to determine the magnitude of the problem of HIV infection at any potential study site and to understand the impact of HIV infection on chemically dependent women and their offspring. Although excluding HIV-infected subjects from perinatal substance abuse studies may be appropriate now, as the epidemic spreads, the omission of a substantial minority of potential subjects may result in unacceptable bias of the outcome in future studies.

Seroprevalence

Quality information on the background seroprevalence of HIV in infants is difficult to find. The incidence of AIDS among pediatric patients that is reported by the Centers for Disease Control (CDC) is biased by an inefficient reporting system and stringent diagnostic criteria that may underestimate the incidence by as much as fiftyfold (Nicholas et al. 1989). Some of the best data that are available are those from the anonymous HIV screening of newborns that is being conducted by State health departments through funding from CDC. In this surveillance study, samples are collected from all newborns at the time of phenylketonuria (PKU) screening and tested by techniques described by Hoff and colleagues (1988). The data have the advantage of having a useful denominator that has minimal ascertainment bias. The data are usually available from State health departments, but whether the hospital providing the sample can be identified depends on the policies of the individual State health department.

The seroprevalence of HIV infection among pregnant women has been found to vary considerably throughout the country. It ranges from 4 percent in high-prevalence areas, such as parts of New York City (Nicholas et al. 1989), to 0.8 percent in moderate areas, such as inner-city hospitals in Massachusetts (Hoff et al. 1988). A majority of cases are associated either directly or indirectly with substance abuse. There is some suggestion that the overall occurrence of symptomatic AIDS in high-prevalence areas is now leveling off (Thomas et al. 1990). In other areas where the epidemic is less mature, a continuing increase in prevalence is being observed. In Chicago, repeated studies of a cohort of female intravenous drug users from March 1988 through June 1990 showed a surprisingly high seroconversion rate of 7.67 percent per person-year (Wiebel et al. 1990). In view of these data, careful consideration must be given on whether to screen all women and infants who enroll as subjects in studies of chemical dependence since HIV infection can have direct or indirect effects on many of the commonly used outcome indicators. Whether screening needs to be performed in all parts of the country is debatable, but not doing so will potentially leave a study open to retrospective criticism if the local seroprevalence increases during the life of the study.

Transmission Rate

Of the infants born to HIV-infected women, approximately 18 to 30 percent eventually will be found to be infected (Mok et al. 1987; Blanche et al. 1989). It remains unclear whether infection occurs at the time of delivery or at some point earlier in the pregnancy. There is evidence that infection can occur as early as

8 weeks of gestation (Lewis et al. 1990). It is likely that some cases also become infected intrapartum, although definitive proof is lacking.

The role of the placenta in transmission is poorly understood. It may become infected or simply may serve as a conduit for transmission of infected leukocytes (Lewis et al. 1990). Substance abuse also may affect the integrity of the placenta. Cocaine use is associated with *abruptio placentae* (Chasnoff et al. 1985), but it is not known whether this disruption of the placental barrier increases the risk of transmission.

Other factors also may play a role in determining which infants become infected. Candidates include intercurrent cytomegalovirus infection or sexually transmitted diseases or the immune-depressing effect of some substances of abuse. However, despite considerable interest in a theoretical manner, there have been remarkably few published data to document the true role of cofactors, which suggests that the studies are negative or that unexpected difficulties have been encountered.

Diagnosis of HIV Infection In Infants

The difficulty in identifying HIV infection early in life is based on the fact that infected infants often have negative HIV cultures and p24-antigen assays (Nicholas et al. 1989), and the antibodies present in the infant may be of either maternal or fetal origin. Transplacentally acquired maternal IgG anti-HIV antibody decays slowly and becomes undetectable in 75 percent of infants by 1 year of age, although infants can lose antibody and still be infected (Mok et al. 1987). Other techniques, such as polymerase chain reaction assay, show promise in the early identification of infection in infants (Rogers et al. 1989), but they are not routinely available or have significant technical problems.

Clinical Consequence of HIV Infection

The overall clinical course of pediatric HIV infection has been reviewed (Falloon et al. 1989). The median age of presentation of symptoms is 8 months and median survival is 77 months (Scott et al. 1989). There appear to be two groups of infected infants: those who become ill and succumb within the first year of life and those who remain only mildly affected for years. In the long-term survival group, one sees such clinical symptoms as lymphoid interstitial pneumonitis and, in the short-term group, encephalitis and *Pneumocystis* carinii pneumonia (Scott et al. 1989). Severe neurologic disease occurs in 16 percent of patients and can become the dominant feature of the chronic course.

It should be remembered that the immunologic and infectious consequences of pregnancy and substance abuse, irrespective of HIV infection, are essentially unknown. It has been reported that immunologic abnormalities occur in infants of HIV-negative mothers (Culver et al. 1987). Rich and colleagues (1989) have found that there is a correlation between maternal and offspring immune function in HIV-negative subjects that suggests an influence of the prenatal maternal environment on the infant immune function, irrespective of HIV infection. Thus, one might expect an increased number of infections due to a variety of social and environmental reasons, although definitive proof is lacking.

Another clinical factor that enters into the design of studies is treatment of HIV infection. Zidovudine now is approved for children, and some of its most apparent effects are on the neurologic disease. As time goes on, the ethical demands of patient care will require more patients to be on Food and Drug Administration-approved drugs or treatment research protocols. It is apparent that these treatments will have profound effects on subject selection and study design.

Additional Factors

The actual or intended identification of HIV infection status in subjects of research studies brings into play a watershed of new problems that are not seen in many other types of perinatal studies. Some of these are social, whereas others are realities of the disease process that is occurring simultaneously in the mother and infant.

HIV Fear and Bias. Fear and bias against HIV-infected patients is extensive. It is common for HIV-infected women to refuse to tell family members or others, such as babysitters, of their HIV status or that of their infant. This is based on a bias perceived by infected women against HIV-infected individuals that might result in the loss of lodging, social support, or employment. The maintenance of secrets isolates the patient, interferes with the psychological processing of the disease, and hampers attempts at improving social supports.

The bias continues through other parts of daily life. For example, enrolling an HIV-infected child in an enrichment program at a public school, such as a 0-3 program, requires special procedures. It requires special permission and education of the staff and the parents of other children and may be accompanied by media coverage. The medical establishment also is not immune to the fear and bias. In addition to the few well-publicized cases of physicians refusing to care for infected patients, patients report numerous instances of small perceived slights that they interpret as the result of the bias. The author and colleagues at the University of Illinois at Chicago have found

that patients understand the need for universal precautions and, indeed, are uncomfortable if a phlebotomist does not wear gloves. However, they also know that mask, gown, and gloves are not necessary for routine care. As the staff on a given unit experiences more patients with HIV infection and becomes better educated, the bias diminishes. However, it is likely that any study that identifies HIV-infected mothers and infants for the first time will find a previously unexpected wellspring of staff concern and bias. The amount of time and effort necessary for the study leadership to deal with the HIV fear and bias should not be underestimated.

Effect of Medical Status on Study Participation. The mother's clinical status helps determine the degree to which she can have her infant participate in studies. The course of HIV infection tends to be shorter among substance-abusing minority women than in other groups, most likely because of such factors as diminished access to medical care, poor nutrition, chaotic lifestyle, and the immunologic consequences of intravenous substance abuse (Rothenberg et al. 1987). As the mother becomes more ill, medical care and study participation become more problematic and practical issues of daily living assume greater importance and become a limiting factor in study participation. Some of the issues include difficulty in using public transportation, the need for frequent, intense medical visits and hospitalizations, and the need for sophisticated in-home medical care. If the mother experiences central nervous system (CNS) disease, the unique problems of studies in HIV-infected populations become even more acute. The mother may not be able to participate in the care of her child due to memory lapse, decreased cognitive function, or decreased motor ability. The study team also may experience the tragedy of helping plan for the death of both participants or for the continuing care of one after the death of the other.

The infant's clinical state also complicates study participation. As the infant becomes more ill, frequent medical visits and hospitalizations become necessary. In studies requiring frequent blood drawing or large amounts of blood, there is competition between clinically indicated studies and those indicated for research due to the real limitations of the blood volume of infants. Furthermore, neurologic and developmental studies may be invalid due to intercurrent illness. Therefore, the study must have the flexibility to deal with intercurrent illnesses.

Consequences to Chemical Dependence Programs. HIV infection in the mother also has implications for chemical dependence programs. Chemical dependence treatment is complicated by a diagnosis of HIV infection, especially when newly established. It can be viewed as an intruding factor by staff

members who already have a full agenda in handling the dependency needs As a consequence, the staff may resist performing HIV screening.

SUBJECT SELECTION

The selection of experimental subjects for perinatal AIDS and substance abuse studies depends not only on the object of the study but also on the limitations imposed by the biology of HIV infection, the limits of the state of the art of the diagnosis of infants, and the treatment of HIV infection, For studies intended to be more than descriptive studies, the selection of controls is critical and must take into account several factors. However, despite the complexities, the biology of the infection provides opportunities along with the potential pitfalls.

Staging of HIV Illness

A problem in study design is appropriate controls for the huge spectrum of the effects of the HIV illness per se. Because of this spectrum, if the focus of the study is not on HIV infection, the presence of this infection could be considered a confounding variable and the subjects excluded. If HIV-infected infants are to be included, it will be necessary to classify the HIV infection on the basis of the stage of disease since the clinical state may range from virtually asymptomatic to overwhelming illness.

The stages of HIV infection can be categorized by widely used standardized classification schemes. For infants, **the most** commonly used scheme is the CDC classification of pediatric HIV infection in which patients are classified **as** being in the indeterminant (P-O) category-during the first few months of life when it is unclear whether infection has occurred because of the presence of passively acquired maternal antibody-or in the infected but asymptomatic (P-l) or the symptomatic (P-2) category. Within the latter two categories are subgroups that describe the immunologic function (P-1A or -1B) and clinical categories (P-2A through E) (Centers for Disease Control 1987a). For women, the most widely used classification scheme is the CDC system in which class II patients are asymptomatic, class III have persistent generalized lymphadenopathy, and class IV have symptomatic disease (Centers for Disease Control 1987b). For patients who have progressed beyond the asymptomatic stage, the effects are likely to be so profound that the HIV infection will need to be handled as an independent variable. The classifications are likely to be revised and updated in the near future.

Use of Indeterminant Illness Infants as Controls

Since fewer than one in three infants born of HIV-infected mothers are infected, the uninfected infants can be used as the controls for the infected. Their use as controls has an advantage in that the infected infants usually are identified retrospectively as they become older and, therefore, there is less bias in their care and management compared to an identified control group. The theoretical disadvantage of using this control group is the possibility that there may be some as yet unidentified difference in those who ultimately become infected compared to those who do not.

HIV-Induced CNS Disease

HIV-induced CNS disease deserves special mention. Many studies of perinatal substance abuse examine development and cognitive function in the infant as an endpoint. Studies using the Bayley Scales showed that definitely infected infants had significantly worse function, particularly in the motor area, than those who only had passively acquired maternal HIV antibody or than unexposed controls (Hittleman et al. 1990). A progressive encephalopathy **may** develop, with tragic consequences of developmental delays and loss of previously acquired skills (Belman et al. 1988). The neurologic process can become a dominant part of the clinical syndrome. The symptoms can be subtle or progress rapidly to a full-blown state over a period of a few months,

The mother can develop a host of neurologic abnormalities as well. These range from AIDS dementia complex-with its early loss of memory, apathy, and changes in motor function and later major intellectual and motor dysfunction-to peripheral neuropathy and myelopathy and chronic meningitis (reviewed by Michaels et al. 1988). The mother's CNS disease may secondarily affect her ability to care for and nurture the infant, which further compromises the development of the infant and underscores the need for appropriate controls.

Effect of HIV Treatment

Another confounding factor in HIV infection is the effect of HIV treatment. Zidovudine, a purine analog with antiretroviral activity, has been remarkably successful in temporarily slowing the progression of adult HIV infection from asymptomatic to symptomatic AIDS (Volberding et al. 1990). The effects of zidovudine are to reduce symptoms of HIV infection, such as fever and weight loss, to improve T-cell counts, and to reduce the occurrence of secondary infections. However, the effect is temporary and disease progression eventually continues.

Few pediatric patients have been examined in depth. It has been reported that a major effect of zidovudine is increased verbal and performance IQ in patients with encephalopathy as well as in some with no overt evidence of encephalopathy (Piuo et al. 1988). Other effects of antiretroviral treatment only now are being reported in pediatric patients. In the future, combination drug regimes are likely to be used. Each of these schemes will have varying consequences as treatment schemes move toward the ideal. The consequence to studies of perinatal HIV and substance abuse is to make treatment effects a major independent variable. Since each drug or combination is expected to have varying degrees of success, it will not be legitimate to lump the effect of treatment into a single variable.

Additional Biases In Subject Selection

Obtaining appropriate subjects and controls for studies can be biased by several factors. Of these, some of the most important are that (1) subjects frequently give inaccurate information about risk factors for HIV infection; (2) the referral patterns of HIV-infected patients may be different than those of noninfected patients; and (3) the intervention of State child protection agencies may result in an inadvertent bias.

Patients frequently give inaccurate information about risk factors during the initial encounter with the investigative team. As a result, if patients are screened for HIV serostatus only on the basis of admitted risk factors alone, many will be missed. The experience of the author and colleagues is that even with trained, sensitive female interviewers, many potential subjects deny the presence of any risk factors on first contact, even if they are not being asked to specify which risk factors they have. However, after the patients have become more comfortable with the study personnel, all readily participate in long, detailed interviews about risk factors, which frequently contradict the results of the original screening. Therefore, laboratory screening of only those patients who admit to having a risk factor is inadequate.

Another source of bias comes from two factors: There are many more chemically dependent women than HIV-infected women, and the source of HIV-infected and uninfected women may be different. A prescreening mechanism that keeps the number in balance and reduces the potential bias may be needed. One possible mechanism would be to base the entry of uninfected women on the recruitment of an infected one. All women at risk in a population would be listed consecutively as they come to the attention of the study. After identification of an infected woman, only the next predetermined number of uninfected controls on the list would be asked to participate in the study. This mechanism helps keep the time of enrollment of the infected women and their

controls similar so that unintended “creep” in the diagnosis or management of the groups does not occur.

SUBJECT RECRUITMENT

Since the potential subjects for these studies are a disenfranchised group who often are hidden from the medical system, the study design must recruit from the points at which patients are likely to surface. At these locations, special efforts will be needed to identify appropriate subjects rapidly and efficiently. In addition, the recruitment strategy will need to be tailored to the type of subject and the frequency of the occurrence of the condition that is the object of the study. For example, a study interested in young infants of HIV-infected women will need to cast a wide, shallow net due to the low number of women who are both infected and pregnant or newly delivered. A study interested in HIV-infected nonpregnant women and their offspring of any age can afford to work more intensely with a few sources.

Possible Sources of Subjects

One of the most fruitful sources of subjects for perinatal AIDS studies is obstetric prenatal clinics and delivery rooms. Although many women in the target population elect not to receive prenatal care, strong consideration should be given to establishing a routine voluntary screening system for those pregnant women who want to receive prenatal care. A program could be justified in medium- to high-seroprevalence areas on the basis of good clinical care alone because of the high risk to the infant of the disease. Prenatal screening is routine for such disorders as PKU that have a miniscule prevalence in comparison with HIV infection. For those women who do not receive prenatal care, a system for rapid screening for HIV antibodies could be established. As in any diagnostic procedure for HIV infection, informed consent needs to be obtained with pretest and posttest counseling. Since locating patients for giving results and conducting posttest counseling is labor-intensive and inefficient, immediate feedback of the results is useful.

Another potential source of patients is drug treatment programs. Again, in medium- to high-seroprevalence areas, the prevalence in a chemical dependence program may be sufficiently high to warrant screening on the basis of sound medical practice as well as research potential. Resistance may be encountered among staff and patients if screening is not currently a routine part of care. However, identification of HIV disease has treatment potential, particularly at the conclusion of the pregnancy, and the pregnancy may be the only “handle” that is effective in bringing the women into the medical system.

Another potential source of referrals is the State child protection agency. Although several ethical dilemmas can be encountered in this source of patients, our experience has been that the agency is eager to develop a working relationship with potential sources of quality medical and psychosocial care for HIV-infected infants.

At the University of Illinois, investigators also have found a fruitful network of recruitment possibilities among those who work in the numerous small social agencies that abound in large metropolitan areas. Networking at the level of the social worker or nurse may be more successful than at the physician level. Some of the practical concerns of recruitment and retention of a similar program have been described (Young and Dombrowski 1989).

Problems and Pitfalls In Subject Recruitment

In addition to the problems of identifying a source of subjects, a number of other problems are likely to be encountered in enrolling subjects. One of these is the lack of efficacy in identifying women on the basis of admitted risk factors. An anonymous seroprevalence survey at the University of Illinois found, that 1.1 percent of women delivering were HIV-infected. When simultaneous confidential (nonanonymous) screening was done using the same sample, the seroprevalence among those who agreed to testing was only 0.6 percent. Fewer than half admitted to having risk factors usually associated with HIV infection (Wenstrom and Zuidema 1989). This suggests an active refusal process among those who knew or suspected they were infected. We have since found that, as expected, the refusal rate depends greatly on the technique of the person seeking permission, At the University of Illinois, approximately one-third of women accept screening if asked as part of the routine prenatal clinical process. However, if a member of the study team seeks approval, the acceptance rate increases to approximately three-quarters. Obviously, care must be taken to ensure that the consent is without coercion and that options are presented.

Ethical Dilemmas In Subject Recruitment

Several ethical dilemmas come up in the recruitment of women and their infants into studies of HIV infection and substance abuse. Some are universal to all perinatal substance abuse programs, whereas others are unique to HIV seropositive women and infants.

One of the dilemmas is the concern for confidentiality. In view of the adverse social and economic consequences of unauthorized knowledge of HIV status, the dissemination of information on patient HIV status is held to a higher

standard of confidentiality than most other medical information and, consequently, should not be released without legal authorization. On the other hand, knowledge of HIV status is a key piece of medical information and does need to be known by caregivers. Furthermore, notification of sexual partners is required by some States and some intramural Federal programs, and notification of the local health department usually is required. These requirements can complicate the sense of trust between the investigative team and the patient. In our experience, these conflicting needs are accepted if patients are notified at the time that informed consent is obtained for the study.

Another ethical dilemma is the payment of subjects in money or in services, Participation can become a financial burden. Payment of large sums may be a form of coercion of the infant under the theory that the mother may not be an advocate for the welfare of her infant. However, some reimbursement for costs encountered seem reasonable. The question also has been raised about the ethics of providing higher quality services to patients in return for study participation than is customary for the community. This also could be considered a form of coercion although the solution of making the services of similar high quality for all patients in the population is generally not under the control of the study team.

Ethical conflicts also arise because of the need for involvement of State child protection agencies. As in any perinatal chemical dependence study, subjects must be monitored for abuse and neglect. This can confuse the role of the scientific observer with the role of the caretaker and must be discussed with a potential study subject in a forthright manner. Paradoxically, in Chicago more services are available for HIV-seropositive infants under the protection of the State than the “routine” cases that are not infected. A close working relationship with the agency may allow careful monitoring of borderline cases of child neglect and abuse and the building in of services that may keep the family intact.

Finally, there is a dilemma in the decision to approach a patient for enrollment in one of several competing studies. There is no dilemma if study objectives do not overlap and one does not affect the outcome of the other and does not require excess testing. However, in the study of HIV infection, treatment protocols do provide a dilemma. For example, should an experimental HIV treatment protocol in which some amelioration of symptoms can be expected take precedence over an epidemiologic study in which treatment is a major confounding variable? At this time, we submit that the opportunity for “pure” epidemiologic studies untrammeled by the effects of treatment is past. Therefore, an epidemiologic study will require careful crafting and attention to sample size and statistical power to take into account the effects of treatment.

In addition to the design problems, the study also must take into account the need for laboratory samples that may exceed the safe amount of blood that can be drawn.

RETENTION OF HIV-INFECTED SUBJECTS

Special efforts often need to be made to retain appropriate subjects for studies. The target population is distinguished in being a hidden, disenfranchised group with few of the usual social supports and access to medical care. They tend to come to the attention of the medical system for crises and then disappear until the next crisis. They are highly mobile, and locating them for continued care may be a challenge. Therefore, retaining subjects for longitudinal studies must take into account the labor-intensive challenge and problems of continuing followup and appropriately plan and budget for it.

As in any program targeted to this group, the definition of retention must be flexible. Patients may not keep appointments but will nearly always maintain contact with the study team and will return, even if not at the time originally expected. Given this flexibility, we have found that more than 85 percent of patients can be retained over a 1-year period for epidemiologic studies and an even higher proportion can be retained for other types of studies such as treatment protocols.

A key to retention is the provision of services to the subject that gives them something in return for the effort that it takes to participate in the study. The system of care can be thought of as a “seamless” system that provides medical and social care while collecting the data necessary for the study.

Provision of Services: Medical

Many mothers fail to obtain care for themselves, but with encouragement they will do so for their infants. Therefore, providing well-rounded pediatric care (acute as well as preventive) has value. The care can be provided by qualified nursing personnel or by physicians. It further has the advantage that the study protocols can be incorporated into an integrated system of care and service. This allows the objective collection of longitudinal data from reliable sources, Furthermore, it cuts down on the burden of multiple visits and increases efficiency of patient tracking. Disadvantages of this system are that it is expensive and may complicate the blinding of observers if blinding is necessary to achieve the study objectives.

Care for the mother also can be provided as part of the system. The mother’s care is often sporadic and triggered by acute illness. If objective longitudinal

data are needed on the mother's health, consolidating care to one location is essential due to the unreliability of retrospective data collection from **a** variety of nonstandardized sources. A particularly well-accepted format is the provision **of** care for the mother and infant by a physician qualified in internal medicine and pediatrics. It is efficient and reduces the number of visits necessary.

Specialized HIV-related care also can be included in the program. In the past, much of the care of HIV-infected pediatric patients has been provided by specialists. The expected clinical course now is becoming sufficiently well understood that, throughout much of the course, day-to-day direct care by a specialist is not necessary. HIV treatment, especially with zidovudine, is becoming generally accepted and can be managed by an internist or pediatrician. As the mother or infant becomes more ill, greater input will be needed on the part of specialists, and it will become more complex to dovetail study and patient needs. It is also important to provide access to treatment research protocols should the patient desire them. In our system, the care by specialists and the access to treatment protocols are included in the package.

Provision of Services: Psychosocial

The provision of psychosocial services is another incentive for continuing participation. Several services can be provided that demonstrate the value of the study to the patient in a manner useful to the patient. These services are expensive but have high value in patient retention, ranging from concrete services to coordination with drug treatment programs to provision of counseling and group therapy.

Concrete services include intercession by the study personnel to obtain services that patients are eligible to receive but are having difficulty in obtaining. For example, transportation assistance is often necessary but is difficult to obtain. This was found to be a major problem in Chicago because of the wide catchment area from which patients are drawn and because many subjects do not own cars. Transportation can be provided by the study in the form of taxicab vouchers or subway/bus tokens. Another useful aid to the patient is acting as a spokesperson with the public aid system, a bureaucracy that is often overwhelmingly complex for the unsophisticated patient. Another essential service is coordination of complex medical and psychosocial care. This coordination of services may require multiagency team meetings, coordination of skilled in-home medical services, child protection agency services, and so on.

Individual and group therapy also assists in retaining patients. Since HIV infection has multifaceted consequences, numerous preexistent psychological problems become exaggerated and new ones appear. It has been observed

that substance abuse may increase transiently after the diagnosis. There is also a high risk of attempted suicide around the time the infection is diagnosed; therefore, access to treatment services within the context of the study is a key retention technique.

Access to chemical dependence programs is also important. Access may be limited, particularly for pregnant women. Once enrolled in a program, considerable effort must be expended to ensure that the goals of the study and the chemical dependence program are complementary.

SUMMARY

Studies that involve subjects who are HIV infected as well as chemically dependent present special challenges to the study team. HIV infection is now so common in many parts of the country and infection can potentially influence so many commonly used endpoints for perinatal chemical dependence studies that HIV must be considered in these studies. Some of the factors that need to be taken into account in the design of studies include the staging of HIV illness, the consequences of HIV-induced CNS disease, the effects of HIV treatment, and the biases in subject selection that arise due to inaccurate information about risk factors and imbalance in sources of subjects and controls. In addition, the study team needs to remember the community and staff fear and bias that are often encountered in the care of HIV-infected patients. Fruitful sources of subjects for perinatal studies include prenatal clinics and delivery rooms, chemical dependence programs, and the network of community social agencies. Retention of this challenging group is strongly aided by the establishment of a seamless system of services that includes all aspects of general medical care, HIV specialty care, access to treatment protocols, and psychosocial care.

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Discussion: Subject Selection, Recruitment, and Retention in Longitudinal Studies Involving Perinatal Substance Abuse and Human Immunodeficiency Virus Infection

Emmalee S. Bandstra

The acute and long-term effects of *in utero* alcohol and other drug exposure have been a subject of intense investigative interest for at least three decades. However, the epidemics of so-called "cocaine babies" and "AIDS babies" have necessarily turned the eyes of the country (government officials, health care professionals, educators, and the lay public) on perinatal drug research. They want to know the number of affected infants and answers to probing questions regarding projected outcome. Scientific scrutiny and appreciation of the complexity of the issues are lacking. Cocaine may be the current target in the "war on drugs," but the underlying issues relevant to conducting longitudinal followup studies are similar to those faced in past studies involving other substances such as alcohol and marijuana. However, difficulties in selecting, recruiting, and retaining subjects for current studies of perinatal substance abuse are exacerbated by the illegal nature of cocaine use and its related lifestyle of criminal activity, violence, and sexual abuse and by health care issues concerning human immunodeficiency virus (HIV) infection and other sexually transmitted diseases. Furthermore, efforts at constructing careful study designs and maintaining control of identified cohorts of study participants can be thwarted or enhanced by the evolving community "support" systems (Bandstra 1990). This monograph wrestles with the intricacies of prospectively planning quality longitudinal research that will yield meaningful data. Much is to be learned from the distinguished investigators who share their formulae for successful subject selection, recruitment, and retention in four other chapters of this monograph (Streissguth and Giunta; Fried; Rich; Howard).

Embarking on longitudinal research into perinatal substance abuse requires gathering the resources to select, recruit, and retain subjects. The studies usually involve interfacing numerous collaborators within an interdisciplinary

team who must learn to overcome barriers to recruitment, guarantee confidentiality, secure informed consent, obtain objective and blinded observations, provide necessary services to drug-exposed and control infants and their families, and retain cohorts over considerable time.

The issue of subject selection is more complex than it may at first appear. Which subjects to select depends on the scientific question to be addressed. Selection also is limited by the practical matter of whether appropriate subjects using the drug or drugs in question are available in the investigative team's community. One of the first questions posed by reviewers of research proposals is the feasibility of recruiting a sufficient number of subjects over the specified enrollment period to address the research hypotheses adequately. It behooves each investigative team to explore thoroughly the patterns of substance abuse within the proposed recruitment catchment area before initiating costly and cumbersome prospective longitudinal followup studies. Shifts in drugs of choice within a community can wreak havoc on a tightly designed study attempting to recruit subjects over time. With careful monitoring, astute investigators can anticipate shifts and launch pilot studies to assess the impact of newly introduced substances. In South Florida, the Dade County Medical Examiner's Office, the Metro-Dade Police Department, the Jackson Memorial Hospital Emergency and Trauma Units, and private and public drug rehabilitation centers have assisted University of Miami investigators in tracking community trends in drug usage.

Decisions regarding subject selection necessarily involve criteria for subject exclusion. The other chapters in this monograph acknowledge that polysubstance abuse confounds nearly every study. For example, the use of caffeine, tobacco, alcohol, and marijuana is nearly impossible to eradicate from a cocaine-using study population. However, it may be possible in a single-site study of perinatal drug abuse to exclude exposure to opiates, methadone, amphetamines, phencyclidine (PCP), and sedatives/hypnotics without significantly jeopardizing the number of eligible subjects. In other words, the investigation probably can successfully recruit adequate numbers of subjects who have used cocaine in combination with the so-called "gateway" drugs. However, the permutations on the varying combinations of drug type, dose. and duration are still numerous.

Time of recruitment significantly affects study design. Prenatal studies as previously conducted in Seattle and Ottawa are more difficult to implement with cocaine-abusing women (Streissguth and Giunta, this volume; Fried, this volume). Prenatal care may introduce bias since drug-using women who do seek and comply with prenatal care demands may have better outcomes than those who fail to do so. Recruitment at delivery is fraught with obvious

difficulties, including maternal fear of legal retribution, mistrust of confidentiality pledges by the investigative team, and physical and psychologic discomfort associated with labor and delivery. These difficulties notwithstanding, the delivery hospitalization may be the only window of opportunity for recruitment and evaluation of adverse perinatal outcome of *in utero* drug exposure.

Correct identification of race/ethnicity is essential to defining the population under investigation. Cosmopolitan centers must cope with considerable cultural diversity, which may complicate the scientific aspects of the study as well as the efforts to recruit and retain subjects. It may be necessary to provide ethnically sensitive professional staff fluent in English, Spanish, and French (or Creole), unless the investigation specifically excludes certain groups or mandates that the study participants be fluent in English. Assigning race/ethnicity is not always an easy task. A classification scheme limited to "black," "white," "Hispanic," "Oriental," and "other" is inadequate to describe the racial/ethnic diversity (e.g., Caribbean-born black individuals) in certain study populations. Infants resulting from biracial unions generally are assigned the same race/ethnicity as the mother. Specifically questioning the mother regarding self-identified race/ethnicity, country of birth, and primary and secondary languages (of both parents) significantly enhances the ability to recruit the desired target population and to determine the generalizability of the outcomes noted.

Fried (this volume) notes analytical difficulties associated with inclusion of multiple births and subsequent births from the same mother. He appropriately suggests that only singleton births be reported or that only one randomly selected member of a twinship be included in the analysis, Multiple births exceeding twins are so rare that they probably should be excluded at the outset. Investigators choosing to include only one twin in the analysis should nonetheless perform all studies on both twins to allow random selection of one twin for data analysis, to foster maternal-infant bonding to the twinship, and to enhance compliance with the appointment schedule. Subsequent pregnancies are also problematic. Even if subsequent drug-exposed siblings are not enrolled, the research team often must cope with the additional needs of older and younger siblings to retain successfully the original cohort. The number of siblings may be quite large over the course of a longitudinal study. At the University of Miami/Jackson Memorial Hospital, a preliminary tracking survey was conducted of 240 cocaine-using women who delivered during the 6-month period January through June 1989. The mean maternal age was 26 years, and the mean parity was 4. By June 1990, 44 of the 240 women had a repeat pregnancy. Twenty-nine of the women had delivered live-born infants, of whom 14 were documented at delivery to be cocaine exposed.

Fried also cautions against excluding infants with adverse outcomes such as intrauterine growth retardation or prematurity from longitudinal perinatal drug

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studies. In large study populations, controlling statistically for the independent contributions of birth weight and gestational age is feasible. However, in smaller study populations a disproportionately high number in the drug-exposed group of small for gestational age or preterm infants, some of whom may have suffered severe neurodevelopmental handicaps due to central nervous system hemorrhage or ischemia, may produce uninterpretable results. An alternative or complementary approach might be to focus separately on the outcome of *in utero* drug exposure within specified birth weight and gestational age categories while matching or controlling statistically for confounding variables contributing to intrauterine growth retardation or prematurity.

Preterm infants, especially very-low-birth-weight infants, deserve special attention in future research programs. Few institutions have sufficient numbers of very-low-birth-weight, preterm, cocaine-exposed infants to conduct meaningful large-scale longitudinal followup. The University of Miami and the other participating centers of the National Institute of Child Health and Human Development Collaborative Neonatal Research Network are planning a multicenter study to assess the outcome of very-low-birth-weight, preterm, cocaine-exposed infants. A multicenter study would allow enrollment of larger numbers of subjects in a shorter time span than a single-site investigation. The individual sites would benefit from a well-planned cohesive study protocol drawing on the expertise of internationally known consultants; a centralized database; a consulting biostatistical center to facilitate quality control, data entry, and analyses; and referral laboratories for performing assays unavailable onsite at the participating centers. The funding institute(s) would benefit from the enhanced generalizability of the results due to the ability to examine intersite variations in outcome.

The chapters by Streissguth and Giunta, Fried, Rich, and Howard proffer vastly different philosophies regarding subject selection, recruitment, and retention. Each style has worked well in its own setting and in its own era.

The Seattle studies over the past 17 years (Streissguth and Giunta, this volume) have emphasized volunteer recruitment utilizing a screening questionnaire followed by an intensive interview. Positive-sounding project titles have fostered a nonjudgmental approach. By study design, no specific developmental feedback or interventions have been given. Streissguth and Giunta emphasize the need for monetary inducement in the current population of cocaine-using women in contrast to previous study populations. Participants in the ongoing cocaine study are paid well ($50 per visit) for their involvement and are given transportation and extensive social service support. Although this model might be termed a “nonintervention” model, participation probably has some therapeutic value for study and control families. It should be

remembered that subjects soon discover the local rates for research participation in various studies and within a study. Even-handed distribution of inducements and services is vital to retaining subjects and especially controls, In the oral presentation of her chapter, Streissguth also mentioned “E” for evangelism. An investigative team without at least an altruistic atmosphere probably is doomed to failure. Substance-abusing women are unlikely to comply unless study demands are complemented with convincing, heartfelt sensitivity.

The Ottawa Perinatal Prospective Study (Fried, this volume) also used a self-initiated volunteer recruitment, but significant feedback was given as an incentive for remaining in the study. Disclosure regarding the findings on the individual child was coupled with explanations of the findings of the overall study at group parties and in an annual letter. Fried indicates that incentive monies, small gifts, and a bonus for complete participation also were given.

The Los Angeles-based studies (Howard, this volume), recruited from a referral base of social service agencies and the Child Protection Team, hava extensively used the support of the community agencies to facilitate compliance and have exhaustively provided concrete resources, but not money, to the participating families of substance-exposed infants. Howard asserts that the program relies heavily on the “clout” of legal authorities to maintain contact with the families. She notes the increased complexity of studying substance-exposed infants within their extended families. Multiple caregivers, shifts in family dynamics, and psychiatric problems of the substance-abusing parents and other family members pose considerable study design difficulties. Furthermore, foster families add a new dimension to perinatal substance abuse research. Family case management is successful when caseloads are small and manageable and when well-trained staff know how to access community resources. Separate clinical and research staffs are maintained to guarantee “blinded” observations by the research staff.

In today’s era of cocaine-using women, it is evident that social service providers are so overwhelmed that scientific investigators routinely confront numerous unmet needs in terms of food, shelter, transportation, clothing, health care, day-care for the infant and siblings, drug rehabilitation, vocational rehabilitation, and legal aid-all of which interfere with a family’s ability to comply with research expectations.

Networking with other professionals within the institution, community, State, and Nation is essential to successful research and service endeavors in the field of perinatal substance abuse. The most formidable barriers to longitudinal research are imposed by philosophical differences and “turf protection” among

professionals and agencies. Even the nomenclature symbolizes the problem. Drug-using pregnant and postpartum women are referred to as "patients" by health care professionals, "clients" by social service providers and drug rehabilitation specialists, and "subjects" by scientific investigators. Unfortunately, health care professionals often fail to acknowledge social and substance abuse problems of their patients, whereas drug rehabilitation specialists often avoid health care issues in their clients. Investigators conducting longitudinal research on perinatal substance abuse and HIV infection must address the "patient" and "client" needs of their "subjects" if the scientific objectives are to be met.

How to interface with State and local agencies without breaching confidentiality regarding substance abuse issues is extremely problematic. Obtaining a Department of Health and Human Services Certificate of Confidentiality may alleviate some, but not all, of the legal concerns surrounding these issues. When a scientific study also identifies HIV-infected women and children, the confidentiality issues escalate further. The Chicago experience (Rich, this volume) with recruiting and following HIV-infected mothers and their offspring emphasizes how intricately interwoven are the issues relevant to perinatal substance abuse and HIV infection.

In planning any prospective study of perinatal substance abuse, HIV screening is an essential element. The relationship of substance abuse, especially nonintravenous cocaine abuse, to HIV infection in women of childbearing age is an important consideration in its own right. However, even if epidemiology is not a specific objective, conclusions regarding neonatal and infant outcomes of perinatal drug exposure cannot be interpreted fully without assessing HIV status concomitantly. Difficulties exist with ascertaining the ultimate HIV status of the neonate due to interference from transplacentally acquired maternal antibodies. The need for prospective assignment of infants to study and control groups in controlled studies of *in utero* exposure often necessitates excluding infants of HIV-infected mothers from participating.

HIV seropositivity and HIV infection in drug-abusing mothers significantly complicates the assessment of pregnancy outcome and long-term followup of the mother/infant dyad. The long-term neurologic sequelae of HIV infection in infants is under intense scrutiny in numerous institutions. A research question not yet explored is whether *in utero* drug exposure exacerbates the adverse neurologic consequences of HIV infection in young children. Children with HIV infection generally develop normally in the first months of life but either fail to progress or experience developmental regression thereafter (Epstein et al. 1985, 1986). Problems with perceptual motor function, expressive speech, hyperreflexia, increased tone, spasticity, bilateral pyramidal tract signs, paraparesis, spastic-ataxic gait, seizures, acquired microcephaly, and

neuropathologic findings, including diffuse calcification of the cerebrum, cerebellum, and pons; reduced brain volume; ventriculomegaly; and vacuolar degeneration of the spinal cord have been described in the literature. Newer antiviral agents, used either prophylactically or when symptoms of HIV-associated encephalopathy are apparent, may offer hope but introduce an unavoidable bias in followup studies.

One of the more successful mechanisms to retain subjects for longitudinal research in perinatal substance abuse and/or perinatal HIV exposure is to provide opportunities for combined maternal and infant health care visits. Rich (this volume) points out the advantages to HIV-infected mothers and their infants of such a concrete service by a family medicine specialist or general practitioner trained in obstetrical and pediatric care.

At the University of Miami/Jackson Memorial Medical Center, Drs. Gwendolyn Scott, Celia Hutto, and Mary Jo O'Sullivan are conducting longitudinal studies on perinatal HIV infection using a combined Special Immunology Clinic attended by pediatricians and obstetricians. The mother's routine postpartum and interconceptional gynecologic examinations and study-mandated clinic visits are scheduled to coincide with the infant's comprehensive pediatric health care and developmental assessments. Dr. Gene Burkett and I also have found the format of a combined mother and infant clinic attended by an obstetrician and a pediatrician extremely beneficial in fostering compliance with scheduled visits within a followup program dealing with postpartum substance-abusing women and their offspring.

Successful teams are usually multidisciplinary and include physicians, psychologists, nurses, social workers, case managers, and related professionals to render diagnostic and interventional services as dictated by the study protocol. There is no substitute for personal contact by the scientific investigators in the patient process.

The most stressful component in any longitudinal research program is subject retention. The value of case managers who are known by the mother and/or alternate caregiver and who maintain regular and intensive telephone and home visitation contacts with the family cannot be overemphasized. The brunt of the responsibility for subject retention is felt by the case managers, who often are undercompensated due to lesser educational achievements, although they may have "life experience" credentials far superior to other professional team members. The University of Miami has relied heavily on an intense medical center-based case management system for tracking and coordinating social and health care services, but the investigators have found it optimal tc limit caseloads to approximately 35 per case manager. Attention to the morale and

esteem of individual team members, especially those who operate independently during outreach visits, is vital. Adequate salary increases, appropriately timed promotions, incentive pay, comfortable workspace, congenial team interactions, and frequent investigator-led organizational meetings facilitate retention of staff members and study participants.

One approach to improvement of staff morale is seeking assistance from experts on stress management and group dynamics. At the University of Miami, the number of investigators and support staff dealing with various aspects of perinatal addiction is growing exponentially. Researchers studying perinatal HIV infection at the university are undergoing a similar growth phenomenon and have begun to take advantage of stress management techniques offered by seminars and individual counseling when appropriate. The resources for the acquired immunodeficiency syndrome programs have been provided through a National Institute of Mental Health grant to the Department of Psychiatry. Similar programs dedicated to professionals in perinatal substance abuse research would significantly enhance an institution's ability to conduct productive longitudinal investigations without costly personnel turnover or unproductive phases of depression or burnout among key personnel.

Prospective longitudinal studies as described in this volume necessitate gathering extensive tracking information at the outset. Streissguth and Giunta suggest planning to track for 10 years or more even if funding is not available currently. Successful tracking may include frequent family contacts, newsletters and holiday greeting cards with "address correction requested," and such personal touches as handwritten envelopes and attractive postage stamps. Prospective and ongoing efforts are absolutely critical to successful subject retention.

This section of the monograph deals with subject selection, recruitment, and retention in labor-intensive prospective longitudinal studies. Today's computer-driven society offers innovative opportunities for tracking research subjects. One method of tracking long-term outcome of birth cohorts is to link hospital records with later school records using identifiers common to both sets of records (e.g., child's name, gender, and birth date and mother's name and birth date). The methodology, known as database linkage, has been used in health and consumer research (Scott et al., in press). There are two main classes of database linkage research designs, historical prospective and historical retrospective. In a historical prospective study conducted at the University of Miami, infants within three birth weight groups (≤1,500, 1,501-2,500, and >2,500 grams) were identified from Jackson Memorial Hospital birth records for 1975-76 (Carran et al. 1989). Using a relational database, the birth records

were linked to computerized school records during 1986. Successful tracking of 70 percent was obtained in this inner-city research population. In a historical retrospective study, Shaw (1989) has studied all children receiving special education services during 1988 in 52 Dade County inner-city schools and has compared them to two groups of normal-achieving classmates born during the same month In 1978.

Prospective studies also can be facilitated by sophisticated database networking such as the Dade County Birth Registry (figure 1). The registry is a computer-based case management system for all high-risk and handicapped children up to 5 years of age who receive services from any agency in Dade County. The registry data also can be linked to hospital and school records, Similar registries will be mandated in 1992 by Public Law 99-457. The implications for tracking many identified drug-exposed infants through school age are obvious. Of course, careful strategies for maintaining confidentiality must be implemented.

Funding agencies can facilitate prospective longitudinal research studies by allowing simultaneous enrollment of subjects in service demonstration projects. Such a mutually supportive endeavor would enhance subject retention in research investigations while improving the objective assessment of service delivery.

CONCLUSION

Subject selection and retention are two of the most challenging aspects in longitudinal studies involving perinatal substance abuse and HIV infection. Today's researcher in perinatal substance abuse must be well versed in basic sciences, medicine (including pediatrics, obstetrics and gynecology, and psychiatry), psychology, social services, public health policy, and legal issues. The topics of perinatal substance abuse and HIV infection have given new dimensions to the concept of "networking," which no longer means simply establishing a "referral" system for "patients," "clients," or "subjects" (depending on one's perspective), but now means attempting to break down the turf-protection barriers that cause agency gridlock and impede successful study implementation and service delivery. Networking also means implementing "user-friendly," but "access-limited" database linkages to ensure confidentiality. With careful prospective study designs, nonjudgmental approaches to subjects and their families, adequate monetary and social service incentives, and the use of sophisticated computerized databases for tracking subjects, clinical studies in perinatal substance abuse and HIV infection should yield meaningful long-term followup data well into the 21 st century.

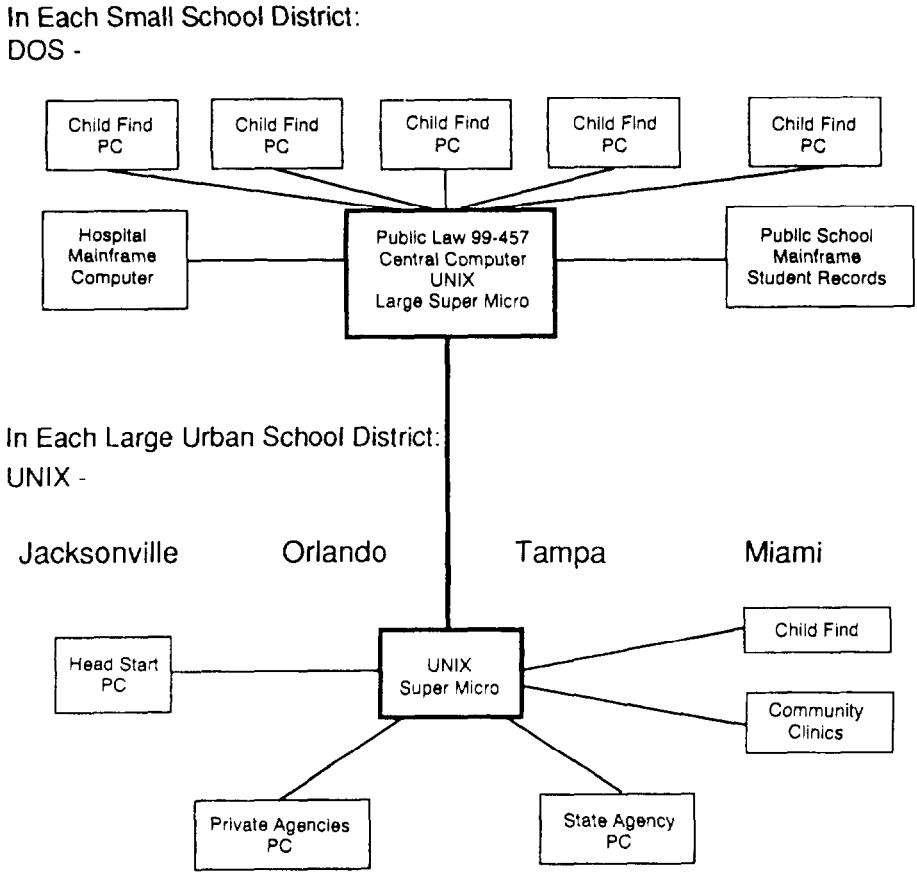

FIGURE 1. *The Florida Handicapped and At Risk Demonstration Project links all providers with a distributed computer network that supports (1) case management with an agency or between agencies, (2) a registry of all children who are screened or referred for special preschool services, and (3) tracking of all services received from birth through high school. Personal computers (PCs) are used at individual sites using the disk operating system (DOS). DOS will operate under UNIX, which is functional at multiuser sites.*

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Measures of Pregnant, Drug-Abusing Women for Treatment Research

Anne M. Selden

INTRODUCTION: MAGNITUDE OF THE PROBLEM AND SOME CAUTIONS

Increasing numbers of pregnant, drug-abusing women are reported today, a problem some people call an epidemic. To compound the problem, there are severe shortages of treatment programs for pregnant, drug-abusing women, with the general shortage of treatment slots exacerbated by the fact that some drug abuse treatment programs specifically exclude pregnant clients (Cole 1990). Wisely or not, program directors may fear that they lack the expertise or resources to address the special obstetric and psychological needs of this population, or they may fear liability for the child if treatment fails with the mother or fails to avert damage to the child.

There are no accurate epidemiologic data to indicate if the numbers of pregnant, drug-abusing women are increasing or if the apparent upswing is caused by increased reporting and awareness of the problem; obtaining such data is a clear research need.

Several known trends indicate that at least part of the increase is real:

- High school surveys show that although the casual or experimental use of some drugs may be dropping, the frequent use associated with or predictive of addiction appears to be increasing (Adams et al. 1989).

- Licit and illicit drugs of abuse are used in all social classes, and women who as a group were previously thought to use less are increasing their use of several substances to the levels previously seen only in men. For at least some substances, such as tobacco, women are showing greater difficulty in quitting than men, even when they want to (Office of the Surgeon General 1988). These trends may be related to the observation that depression is associated with use of substances and with difficulties in quitting (Covey et al. 1990) and that diagnosable depression is more prevalent in women than men (Weissman and Myers 1978).

- As smaller families and planned pregnancies become the norm among those who have their lives well organized, it is entirely possible that unplanned pregnancies will be increasingly concentrated in the drug-using segments of the population. Therefore, the incidence of drug-exposed pregnancies could continue to rise even if some parameters of drug use decline.

There are four major public health rationales for emphasizing treatment of substance abuse or dependence during pregnancy even more than at other times: (1) the hope of decreasing damage to the developing fetus by arresting or diminishing drug use during the remainder of a pregnancy; (2) the hope of enhancing childrearing by providing the newborn with at least one drug-free parent; (3) the opportunity for case finding based on the fact that many pregnant, drug-abusing women seek prenatal care and, thus, come to the attention of health care providers; and (4) the possibility that pregnancy represents a time of heightened motivation for decreasing drug abuse for at least some women. Unless the fourth rationale is supported by research, the mounting evidence for fetal damage early in pregnancy could suggest that scarce resources for treatment should be devoted to women before they become pregnant. An obvious approach to this problem is to obtain the best possible data on women's spontaneous changes in drug use after pregnancy occurs and after women become aware of pregnancy. This would help target which patterns of drug use, if any, spontaneously improve with pregnancy (suggesting the use of supportive treatments that enhance the spontaneous effect). Such research also could identify drug-use patterns that are predictably resistant to spontaneous change with pregnancy and, therefore, require vigorous intervention if any intervention is to be of help. In addition, intervention in any pregnancy, if effective, not only serves as secondary or tertiary prevention of damage to the index pregnancy but also could serve as primary prevention of potential damage to future pregnancies,

Prospective studies of cohorts of drug-abusing women who are not yet pregnant might yield useful information, but ethical issues and observation effects are likely to limit the information that can be obtained. Given that it already is known that use of at least some drugs can be damaging to the fetus and that others appear to pose risks, it is difficult to continue to observe drug-using women who are at risk of pregnancy without intervening to discourage drug use, encourage prevention of pregnancy, or both. Also, because information about drug hazards during pregnancy is broadly available and increasingly disseminated, it is difficult to imagine that even asking the necessary questions to conduct prospective research would not affect either drug use, contraception, or both. The populations of women who would be least susceptible to such deterrent effects probably are the same women who are most difficult to capture for longitudinal research.

EFFECTS OF PREGNANCY ON DRUG USE

Pregnancy is often a time in which women report heightened motivation to cease drug use. At the simplest level, the physiology of pregnancy occasionally makes some drugs less attractive: Nausea or fatigue in early pregnancy may make sedative drugs less appealing or make abstaining from them a little easier.

More poignantly, many women state quite strongly that, however willing they were to abuse their bodies with drugs, they fear damaging the baby and cannot bring themselves to do to the baby what they were doing to themselves-not only a telling comment on the depths of their self-esteem but also a useful motivator for entering treatment. Many women identify with the baby, want to provide a better life for the baby than they had themselves, or recognize that a drug-using lifestyle that they had accepted for themselves is not the context in which they wish to parent. (Anecdotally, one also hears of some expectant fathers who share this maturational motivation: wanting to revise their lifestyles to be a better parent. Although the frequency of this motivation may be less in men than women, when present it would be of obvious potential benefit both to the individual men concerned and to their partners and children).

Of course, this heightened motivation is not present in all drug-abusing women, and when it is present, it is not always strong enough to bring about abstinence in the absence of treatment and/or other supportive factors.

It also is known that the physiology, discomforts, and circumstances of pregnancy can engender influences or motivations that are associated with *increased* drug use-influences such as anxiety, fear, depression, and/or guilt; situations of partner or family conflict; or frank desires to end the pregnancy by attempting to induce abortion or premature labor with, for example, cocaine.

WHAT HAPPENS TO DRUG ABUSE WHEN WOMEN BECOME PREGNANT?

Some women stop drug use as soon as they become pregnant or even in preparation for pregnancy. Some would like to stop but do not or cannot; they presumably would seek and welcome treatment if effective and user-attractive treatment is available. Some would not seek treatment on their own but can be persuaded to seek it by pressure from family, friends, and health professionals. Some would not accept treatment on their own but may accept it if the alternative were criminal sanctions and/or loss of custody of children.

Loosely, the first category above may more often correspond to the Diagnostic and Statistical Manual III, Revised, category of psychoactive substance abuse and the other three to that of psychoactive substance dependence (American Psychiatric Association 1987). At present, there are few data on the proportions of pregnant women falling into these four groups, even though such data would be important in health care planning and resource allocation and even for planning rational, fair, and effective use of legal and child protective service strategies.

Treatment planning is further complicated by lack of information about the incidence of dual diagnosis (substance abuse complicated by coexisting psychiatric and/or medical diagnoses) and the incidence of complicating life circumstances (such as homelessness, isolation from extended families, and adverse family situations, including partners who physically or sexually abuse the women as well as partners or children who abuse and/or deal in drugs). Although drug abuse occurs in all social classes, the family chaos frequently engendered by parental drug abuse is likely to be compounded where other resources are lacking and women must obtain drugs through criminal activities or by remaining dependent on a partner who supplies the drugs. All the above factors can (1) complicate treatment, (2) require more extensive treatment for those least able to afford it, and (3) contribute to treatment dropout, failure, or relapse. As discussed more fully below, information about the incidence of these complicating factors in a treatment sample is essential if the extent to which outcome data can be validly compared across treatment settings is to be known.

GENERAL LOGIC AND MEASUREMENT STRATEGIES: WHAT WE WANT TO MEASURE AND WHY

For this chapter, it is assumed that, in general, treatment of pregnant drug abusers is a good thing if the treatment is sufficiently effective, *if* it does not backfire and make things worse, and *if* effective treatment is not too costly to be feasible. The problem of potential negative effects of treatment so far has received more attention in the general psychotherapy literature than in the chemical dependency treatment literature (e.g., Strupp 1977). Thus, measures in several domains need to be considered.

Sample Selection and Eligibility Criteria

Is the woman pregnant? Are there any characteristics of the pregnancy or her plans for it that should exclude her from a given study? Is she too far along in pregnancy or not planning to maintain the pregnancy or retain custody of the child-factors that might create a poor match between a woman and a program that heavily emphasizes preparation for motherhood?

Does the woman use drugs? If so, does her use meet the study's criteria for substance abuse and/or dependency? Are there any characteristics of her drug use pattern or of her goals for modifying it that should exclude her from a given study? Are there concomitant medical or psychiatric diagnoses whose treatment is so imperative as to take priority over drug abuse treatment (or render meaningful participation impossible)? Can she give informed consent and be an active participant in her own care? Should a given study accept a patient whose housing arrangements, transportation needs, or other life circumstances make regular and meaningful participation in care and treatment unlikely?

Ethically, excluding a woman from a treatment program, even a research one that requires such exclusion, imposes an obligation to make every effort to refer the patient for more suitable treatment elsewhere, since these exclusionary criteria are disturbingly reminiscent of some of the reasons cited by other programs for excluding all pregnant women.

Measures of Maternal Motivation for Treatment and Predictors of Sustained Motivation

What characterizes women who (1) seek treatment on their own; (2) can be persuaded to accept treatment by pressure from family members, referring health professionals, or other community resources; or (3) accept treatment only if compelled by legal sanctions? How do these groups of women differ in what they want out of treatment and what they fear from it? How does their motivation change over time?

What evidence can be found of the intensity of a woman's motivation for treatment and of the strength of the ambivalence that is almost universally present? What goals does she have from treatment, and how realistic are they? Is she there only to please others, to avoid criticism or sanctions, or to protect her baby (and perhaps even that only during the pregnancy); or can she see a drug-free lifestyle as a more satisfying choice for herself? Does she seek a drug-free lifestyle or only a reduction in dose or in use of certain drugs? How committed is she to a process of setting her own goals or complying with program goals? What other potentially useful and/or competing goals does she have for her life besides a drug-free lifestyle? In what other ways (besides modifying drug use) might she want to use treatment to enhance her lifestyle?

Other Maternal Characteristics

What is the woman's history of drug use? What is her family and personal history, including past or present sexual and physical abuse and neglect? Is

there a history of prior drug abuse treatment? Is there a dual diagnosis or complicating physical illness and life circumstances?

Characteristics of the Treatment Program

Which ingredients are provided in the treatment package? Are they standard or individualized? For a given patient, what was the quantity and quality of her utilization of each ingredient? Levels of training, experience, and personal characteristics of treatment personnel may be highly pertinent to a full description of the ingredients they provide.

Outcome Measures

In-treatment outcomes may include mastery of specific treatment elements offered. (Not all programs will offer all elements nor will all generally successful participants necessarily succeed in every single element.) Examples include participation and progress in treatment elements for which she has contracted, cognitive mastery of cognitive components, emotionally meaningful participation in therapy sessions, verifiable progress toward attaining any coping skills for which training is offered, participation and progress in 12-step groups, and maintaining clean urines during treatment.

Posttreatment outcomes may include maintaining clean urines; maintaining aftercare as contracted; maintaining active participation in 12-step programs (which appear to be an economically feasible way to provide needed aftercare for prolonged periods, perhaps for a lifetime); learning from any lapses or relapses, with maintenance of or quick return to aftercare and/or 12-step programs; and improving one's quality of life. In the case of women treated during pregnancy, improved obstetric outcomes and infant health are additional positive outcomes, as is quality of parenting, especially where parenting education is a specific program component.

Long-term outcomes need to include general quality-of-life measures, with particular emphasis on psychological constructs such as self-esteem, self-confidence, and self-efficacy, and realistic optimism for the future as well as effective coping with the inevitable negatives, since sustained recovery is less likely without ongoing progress in these areas. Educational-vocational habilitation or rehabilitation, normally a major long-term outcome, is a salient need for women who start with educational and job skill disadvantages; yet its timing for women who are already responsible for the care of several small children may be difficult. Taking on too many responsibilities at once can be a source of stress and, therefore, a trigger to relapse. Program and outcome measures in this area need to fit the realities of women's lives.

Since chemical dependency is by nature a chronic and relapsing disease, realistically, treatment programs should look for more than complete sustained abstinence as a positive outcome. Successful treatment outcomes can include lapses and even relapses if the patient is able to be candid about them, take them seriously, look for triggers and learn something from them, and follow them with intensified participation in aftercare and/or 12-step work.

Combined, Interactive, and Second-Level Measures

Comparison of specific entry characteristics of the women, specific in-program outcomes, and specific long-term outcomes permit the formation and ultimately the validation of several hypotheses important to treatment improvement. For example, what patient and treatment characteristics, alone and in interaction, predict risk of a patient's losing her motivation, or conversely, predict the likelihood of developing her own motivation after entering treatment under duress? Can these predictor variables be validated by using them to modify programs or individual treatment plans to enhance retention? Can they be used to rationally assign patients to different programs (e.g., inpatient vs. outpatient, women-only vs. mixed-gender programs, and different types of programs)?

What baseline variables characterize women who benefit from treatment, and what are the kinds or elements of treatment? Are there different predictors for early dropout, for late dropout, and for achieving and maintaining abstinence during the pregnancy vs. avoiding relapse later? Are dropouts always treatment failures? An important and often neglected question is: Do characteristics of women or programs that avoid one kind of adverse outcome increase the risk of others? For example, could excessive emphasis on abstinence during pregnancy encourage postpartum relapse? Could facilitating entry into the program and preventing dropout sometimes result in a less strongly motivated cohort for whom a lower percentage of long-term success might be predictable? And if so, is this always bad or unmodifiable?

Could there be different intake predictors of what kinds of outcomes constitute success? For example, does the diagnostic distinction between substance abuse vs. dependence (or any other cluster of characteristics) differentiate between a group of women who must permanently avoid any addictive psychoactive substance to prevent full relapse and a group who could use alcohol socially and moderately? What predictive power, if any, does the abuse vs. dependence diagnostic distinction confer? How must success criteria be modified for the dual-diagnosis patient?

Under what circumstances are elements of treatment helpful vs. harmful? For example, could the confrontation that helpfully challenges one woman to break through her denial cause another woman lasting damage to self-esteem with increased depression and drug use, perhaps even suicide? Can a program that insulates a woman too much from the environment to which she will return after initial treatment result in enhanced risk of relapse when she does return to it? Could a program that is too intensive be as harmful as one that is not intensive enough (Miller and Hester 1980)? When Is it beneficial for a woman to defer her other responsibilities (such as work or child care) in favor of a focus on treatment goals, and when does that cause harm by disrupting what may be the healthiest areas of function in her life? When is it helpful for a marginally motivated patient to be in a group with more motivated ones, and when does such a patient suffer alienation, lose self-esteem, drag down the other group members, and perhaps incur their wrath?

Treatment Cost-Benefit Considerations

Can it be demonstrated that treatment programs, perhaps even costly ones, pay for themselves in terms of reducing high costs associated with premature births or otherwise damaged babies? If they pay for themselves with some patients, but not with others, how well can it be predicted which patients? Can costlier treatments, such as inpatient treatment, be justified if the indications can be refined so as to use these costly treatments sparingly, when they are most needed?

Research Cost-Benefit Considerations

In searching for the above predictor variables, it is easy to get lost in a costly and unproductive "fishing expedition." All possible maternal variables cannot be measured against all possible outcome measures to produce interpretable data. Guidance from theory is needed. In complex treatment strategies, a careful search must be made for active ingredients, specific indications, and measurable intervening variables.

A simple-minded example suggests a general strategy: If, for example, it is believed that assertiveness training might help in relapse prevention, either alone or as part of a social skills training package, it probably would be predicted that it helps some patients more than others, Those who already display adequate assertiveness might not need it, and those who are the least assertive may be unable to learn it in the time available. It might be predicted to be an active ingredient only for those who, at baseline, have a moderate assertiveness deficiency: of those, it may be effective only for the ones who demonstrate that they can acquire the skill, maintain it, and generalize it appropriately to real life.

If studies are to be as comparable as possible, similar inclusionary and exclusionary criteria should be used across studies. However, depending on the specific research questions asked, there is a potential conflict between the goals of isolating variables and producing generalizable results.

Studies whose aim is to verify effects of a particular drug on the developing human fetus ideally would hold other factors constant. For example, if researchers want to determine what lasting fetal consequences result from first-trimester cocaine use, they would seek a sample of women who can be proved to have used cocaine during the first trimester, and not later, and they would want to eliminate such potential confounds as use of other drugs, exposure to other toxins, and potentially complicating maternal medical problems and life circumstances. Such a sample, if located, would be ideal for isolating effects of first-trimester cocaine use on the fetus.

However, any findings about treatment approaches that help stabilize cocaine abstinence for the balance of pregnancy in such a sample would have limited generalizability to the bulk of drug-abusing pregnant women because the majority use more than one drug, seek prenatal care after the first trimester, have at least some complicating medical and/or psychosocial conditions, and have at least some lapses or relapses before achieving abstinence, if indeed they achieve it at all.

Therefore, a sample that is most generalizable to the drug-abusing pregnant population will not be ideal from the standpoint of isolating specific effects of specific drugs in specific doses or at specific times in pregnancy. Nor will it be likely to be ideal from the standpoint of partitioning out which adverse fetal effects occur as a result of the pharmacologic or toxic effects of the drugs in question vs. which occur as a result of other circumstances of a drug-using lifestyle, such as poor maternal nutrition and weight gain, delayed and/or sporadic use of prenatal care, increased incidence and delayed treatment of infections and other medical complications of pregnancy, and increased incidence and severity of maternal psychosocial and biological stress. It would be more ideal if these problems could be reduced by providing excellent prenatal care even in the face of continued drug use-a formidable challenge.

DISCUSSION OF SPECIFIC MEASURES

Meaning/Context of Pregnancy to the Women

If a drug-abusing woman is pregnant, what does she intend to do about the pregnancy? Answers include a continuum ranging from “end it,” to “do just

about nothing" in terms of health care or lifestyle modification, to "make an all-out effort" in terms of seeking every possible enhancement to the pleasure and health of mother and developing fetus as well as every possible enhancement of the lifestyle in which the pregnancy is occurring. Answers may affect eligibility for the study and may serve to describe the subjects further. Almost certainly both the place on the continuum from "end it" to "enhance it" and the content of what forms of ending or enhancing were contemplated would vary among groups of newly pregnant women and for women with different pregnancies. "Ending it" could mean suicide for one woman, abortion for another, giving a child up for adoption for another, and for yet another, chemical forms of Russian roulette. Thus, paradoxically, knowledge that certain drugs are risky to the baby can increase their use, and—for a woman who wants to let fate decide whether she carries a baby to term—knowledge that prenatal care can save babies' lives can decrease the chances of seeking that care.

Similarly, "enhancing" a pregnancy for one woman may mean entering or strengthening a marriage or partnership, but for another woman it may mean finally deciding to throw out an abusive partner. For one woman it may mean furthering her career; for another it may mean dropping out of school or a job. For one woman it may mean continuing in dietary or drug indulgences (which are her current version of "the good life"); for another it may mean ritualistic and even superstitious abstention from many usual pleasures. For one woman it may mean assiduous compliance with whatever her chosen advisers recommend during pregnancy; for another it may mean adopting a perceived "adult" status that includes a declaration of independence from (or opposition to) any form of compliance.

Simple tallies of engagement in healthy prenatal behaviors may fail to capture important dimensions of the meaning of a particular pregnancy to a particular woman; conversely, simple measures of the degree to which the baby is planned or wanted, while important, should not be expected to predict the content of the mother's conscious or unconscious pregnancy-ending or pregnancy-enhancing behaviors, either in the realm of drug use or of other behaviors that may affect pregnancy outcomes and either alone or in conjunction with drug use.

Similarly, simple measures of the extent of attachment to the developing baby probably are not going to be linearly related to healthy relationships once the babies are born. There is undoubtedly such a thing as too much attachment as well as too little. Furthermore, attachment may be based on realistic or unrealistic hopes for what the baby will do for the mother's life and well-being.

An obstetric history scale for pregnant drug abusers ideally should include not just the number and obstetric outcome of previous pregnancies but also a scaling of past emotional responses to past pregnancies and their outcomes (Raskin, in press), consideration of life events at the time, and coping methods used, including drug use.

Measures Confirming Pregnancy

Standard obstetric examination is sufficient and is confirmed by standard pregnancy tests (which in general measure hormones of pregnancy and only indirectly indicate the presence of a viable fetus).

Gestational age and the absence of major anatomical abnormalities can be assessed through ultrasonography. Estimating gestational age through menstrual cycle history is frequently inaccurate in drug-abusing populations for a host of reasons: Drug use, malnutrition, and gross stress all are associated with a higher incidence of menstrual irregularity, and maternal recall may be less accurate under chaotic life conditions. Ultrasonography around 16 to 17 weeks is considered most accurate for determining gestational age and still is pertinent for detection of major abnormalities in time for abortion if that is being considered. However, early ultrasound can be done only in the subsample of women who present early for prenatal care. Self-report data on date of last menstrual period should be gathered in the usual way because they are available to some extent from all women and are therefore more generalizable to future clinical samples. Such self-report data should be supplemented with whatever other cautionary data the woman can give, such as prior menstrual irregularity, and with more objective data available during pregnancy (ultrasound) and from neonatal examination after birth.

Measures Confirming Drug Abuse

Biological Measures, Retrospective and Concurrent. The advantages and disadvantages of particular methods will not be discussed here, since other chapters in this monograph address these issues.

Biological measures of past drug use have potential prospective psychological consequences. If an accurate record of what a woman has ingested in the past can be established through, for example, a highly accurate hair analysis—and if the drug use can be pinpointed in relationship to onset of pregnancy by measuring, for example, a progesterone surge in the same hair sample—and if this were done routinely, it could result in more accurate information on the timing of drug effects in specific developmental stages and determination of whether pregnancy was followed by increased, decreased, or unchanged drug

use. However, some women might be deterred from entering treatment by fear of such a record of past behavior that could be used against them or, at least, that could enhance guilt. The woman entering treatment hopes to modify her current and future behavior; there is nothing she can be offered with regard to past behavior other than help in dealing with guilt or the hope that future technology will permit reversal of consequences of past behavior.

Biological measures of current drug use have psychological consequences. Ongoing monitoring of current drug use permits validation of ongoing self-report measures, Therefore, it encourages honesty in self-report by removing any motivation to give a misleading optimistic report. Ongoing monitoring permits early detection of relapse and allows modification of treatment. Since few if any patients will be monitored for the rest of their lives, the goal of relapse prevention includes engaging the patient in ongoing self-monitoring. Therefore, in treatment it seems best to use biological monitors as a backup and validity check on self-report measures rather than as a substitute for the latter.

This may be particularly feasible during pregnancy, because urine samples are obtained regularly at prenatal visits for medical checks, With the patient's advance permission, toxicology screens could be done on these urines at any time. The focus in the drug treatment program then could be on the ongoing self-report. Urines could be used as backup to the veracity of self-report, at reduced cost, by running only a random sample of them for toxicology (the so-called Bogus Pipeline technique); however, if this technique is used during pregnancy it means that the routine samples used obstetrically must be specimens obtained under observation. Otherwise, the patient who is tempted to use someone else's urine to escape drug detection also could avert detection of obstetrically important evidence of bacteria, protein, or sugar in the urine.

Where there is a choice, the use of a method that gives immediate feedback offers significant clinical advantages. A delay of even several days in detecting a discrepancy between self-report and urine results makes it easier for the patient to forget what she was experiencing psychologically at the time of use and makes it easier for her to elaborate defensive mechanisms.

Self-Report Measures of Drug Abuse History. The Addiction Severity Index (ASI) provides comparability of data with that obtained from other drug abuse treatment programs (McLellan et al. 1985). However, the ASI references self-report of past use to standard time intervals, which are not keyed to the duration of a pregnancy. Therefore, when used to measure self-reported drug use in relationship to a pregnancy, the ASI drug use items should be cast in time intervals related to landmarks of pregnancy: the time when conception most probably occurred, the time when the woman first suspected pregnancy, and

the time when she was first certain she was pregnant. Differences in drug use around these three landmarks reflect not only the potential impact of the drugs on the fetus but also the impact of the pregnancy on the woman's drug use.

It is also useful to know the extent to which common symptoms of pregnancy (e.g,, fatigue, nausea) and psychological responses to awareness of the pregnancy (e.g., pleasure, displeasure, anxiety, depression) were associated with either spontaneous decrease of drug use or increased use as an attempt to cope. Concurrent life events (emotional and/or physical abuse, moves, increased or decreased closeness with sexual partner and significant others, and illness in self, children, and other family members) should be recorded along with drug and nondrug coping attempts and their success,

Informant Histories of Patients' Drug-Using Behavior. Self-report measures are limited by patients' ability or willingness to give an accurate history. Reports from close friends and/or family members have their own inaccuracies but do provide another source of information. Using an ASI-Informant version would help eliminate differences related to format.

Measures of Psychiatric Status

Individual differences in patients in the somewhat overlapping areas of psychiatric diagnoses and personality characteristics are important to measure for at least three reasons.

First, there is no point in providing a standard drug abuse treatment protocol if the patient is too disabled by a concomitant psychosis or too immobilized by a concomitant depression to participate meaningfully in the treatment.

Second, a coexistent and possibly preexistent psychiatric diagnosis is common and has been associated repeatedly with poorer response to drug abuse treatment and greater risk of relapse (e.g., Kosten and Kleber 1988). These conditions deserve treatment in their own right. Furthermore, the success of drug abuse treatment applied to a sample with a higher prevalence of these poor prognostic indicators cannot be compared readily with the outcomes of a different treatment applied to a sample in which these conditions are less prevalent.

Third, the triggers associated with relapse for different patients are highly individual but appear to be associated with personality characteristics. Thus, information about personality characteristics as well as lifestyle vulnerabilities and support system strengths and weaknesses could be incorporated meaningfully into individual and group treatment for relapse prevention. Plausible examples include the following:

- Individuals with shyness or social phobia often use drugs in an attempt to cope with social situations, and they may have difficulties in refusing social encouragements to use drugs.

- Individuals with high degrees of depression or generalized anxiety often give a history of short-term relief of these affects by drug use, and they may fail to notice that long-term use generally increases the frequency and intensity of these affects. The reinforcing effect of the drug in short-term relief of painful affect is far more strongly learned and therefore more enduring than is the potentially punishing effect of the drug in long-term exacerbation of affect—immediate effects are almost always more strongly learned than remote ones (Wikler 1971).

- Self-esteem, which is frequently impaired in drug abusers, typically rises with effective treatment and falls with relapse. The fall may antedate the chemical relapse, but there are not enough careful prospective studies of relapse to establish this point firmly. Most experienced clinicians believe that a state of falling self-esteem in an abstinent recovering patient indicates risk of relapse. "State vs. trait" self-esteem has not been as clearly differentiated. There is a general clinical belief that high usual levels of self-esteem are protective against momentary blows to self-esteem, but this has not been effectively disentangled from the fact that high self-esteem usually is associated with more effective social interactions, lessening the occurrence of damage to self-esteem.

- Closely related to self-esteem but distinguishable from it is self-efficacy or locus of control. Successful rehabilitation from several disabling medical conditions and successful achievement of educational and vocational advancement, all have been associated strongly and persistently with individuals' beliefs that their actions rather than uncontrollable fate determine their lives (Strecher et al. 1966). On the other hand, there have been some indications that individuals who expect to control their life circumstances may be particularly vulnerable to events that shatter that expectation. Locus of control appears to be related to self-esteem in that individuals with external locus of control attempt to regulate self-esteem by attaching themselves to powerful others and esteeming themselves insofar as they succeed in pleasing the significant other, whereas individuals with internal locus of control are vulnerable when their expectations of control are thwarted such that they can blame only themselves. Women as a group are more likely than men to have external locus of control, as are persons of lower socioeconomic status.

- Stressful life events are of obvious importance as contributors to exacerbation of ongoing psychiatric illness and as potential triggers for drug abuse relapse.

- Support systems, when adequate, are major buffers in dealing with stressful life events (Lin et al. 1966).

These variables, if measured at intake, may need to be repeated after a period of active treatment and again in aftercare. Depression, anxiety, and other symptoms observed at intake may reflect drug use and/or immediate withdrawal states, and in such cases, the symptoms may diminish or dissipate with a period of abstinence. Measures taken between 1 and 2 months after beginning drug abuse treatment are usually more predictive of continuing problems.

A major unresolved problem in the diagnosis of psychiatric comorbidity is that current diagnostic instruments do not converge as much as would be desired, particularly in the area of personality disorders (Gaulier et al. 1990). Some reasons variance occurs are that self-report, informant report, and clinician data tap partially independent domains; different items and different cutoff points in different instruments may obscure real convergence; traits that conceptually make up different syndromes overlap to a considerable extent and may be measured more reliably as traits than as syndromes; and personality tests normed on non-drug-abusing samples may apply differently to drug-abusing populations. In addition, in the case of pregnant women, items that refer to somatic experience and identity may be affected by pregnancy in ways that are not yet fully studied. In the meantime, it is important to remember that psychiatric diagnoses arrived at with the use of different respectable instruments will not capture exactly the same patients, especially for Axis II diagnoses.

Obstetric Measures Related to Course and Progress of Pregnancy

Important areas to be measured include the following:

- Nutritional status: estimated by diet history at intake and at 28 weeks, compared with weight gain and other dietary outcome measures such as hemoglobin and folate levels at intake and 26 weeks

- Complications: incidence, severity, and timing of any complications (such as infections, increased blood pressure, diabetes, preterm labor, or anything else requiring hospitalization)

- Adequacy of prenatal care: gestational week of first visit, number and percent of scheduled visits kept by trimester, and extent of outreach required to achieve acceptable level of care

Group Measures of Treatment Efficacy

Progress of chemical dependency treatment for a group rather than an individual usually involves simpler measures recorded as percentages, such as percent of eligible patients who enter a program, drop out (defined as permanent cessation before achievement of objectives), "fade out" (absenteeism from scheduled sessions), or achieve such goals as 12-step group participation (e.g., percent attending a specified number of meetings per week during active treatment; percent selecting a home group and a sponsor, and percent completing specified steps). Progress also may be measured in percent of patients whose partners and/or other family members participate in the primary treatment program and/or outside support groups and percent achieving treatment outcome goals initially and maintaining them over followup.

CONCLUDING NOTE

Research demonstration projects are noted for designing programs that appear to work in the pilot or research phase but never get broadly implemented for a variety of reasons. Although there are many barriers to service implementation for noncost reasons that lie outside the scope of this chapter, it should be clear that any program recommended for large populations at mostly public expense must justify not only efficacy but also cost. In the case of chemical dependency treatment for pregnant women, even persons who do not give high priority to the well-being of the women may be persuaded to support treatment for them if costs of treatment can be favorably balanced against the costs to the public of not providing treatment. This again brings up the paradox with which this chapter started: Greater concern for the baby (and costs of the baby's care) than for the mother may motivate the public to fund treatment, just as it may motivate the pregnant woman to enter treatment. However, sustained abstinence will occur only as part of a lifestyle that is demonstrably preferable from the perspective of the woman.

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Assessing Acute and Long-Term Physical Effects of In Utero Drug Exposure on the Perinate, Infant, and Child

Emmalee S. Bandstra

INTRODUCTION

Perinatal centers nationwide estimate that in excess of 10 percent of all deliveries are affected by *in utero* exposure to illicit drugs as documented by maternal history and/or urine toxicology (Chasnoff 1989; Bandstra et al. 1989). Furthermore, a recent study by Ostrea and colleagues (1990) showed that 40 percent of the infants delivered at Detroit's Hutzel Hospital had meconium stools positive by radioimmunoassay for cocaine, heroin/morphine, or cannabinoids. Therefore, accurate identification of infants who have been drug-exposed *in utero* is essential to clarify perinatal mortality and morbidity trends. Although the longitudinal study design clearly is the most powerful tool in perinatal drug research, assessment of acute outcomes also may be valuable.

Collaborative relationships forged between clinical investigators of perinatal substance abuse and those skilled at assessing the pharmacology and physiology of various organ systems may be mutually advantageous. Clinical research into the prevention and management of numerous neonatal complications (e.g., perinatal asphyxia, intrauterine growth retardation [IUGR], prematurity, central nervous system [CNS] hemorrhage and ischemia, and cardiorespiratory disorders) may be seriously confounded by *in utero* exposure. Published studies on neonatal populations uncharacterized regarding *in utero* drug exposure therefore may be subject to significant retrospective criticism by reviewers within all disciplines.

This chapter focuses primarily on methodological issues related to *in utero* cocaine exposure, but the spectrum of polydrug exposure is always present in clinical studies. Special emphasis is given to the following adverse consequences: spontaneous abortions, stillbirths, congenital structural defects,

IUGR, and prematurity. Key points in establishing measurable endpoints with respect to the CNS also will be illustrated.

SPONTANEOUS ABORTION AND FETAL DEMISE

One of cocaine's devastating effects appears to be early labor and uncontrolled delivery. Pregnant, cocaine-abusing women may suffer spontaneous abortions or stillbirths. Furthermore, many drug-using women pay little attention to contraception and, thus, seek therapeutic or self-induced abortion, sometimes with cocaine as an abortifacient, as a remedy for an unwanted pregnancy.

Abruptio placentae was first mentioned as a cocaine-related complication by Acker and colleagues (1983). Bingol and colleagues (1987) showed a tenfold increase in the number of stillbirths, all of which were related to *abruptio placentae,* in pregnant cocaine-abusing women compared with a drug-free control group. No other series has yet confirmed fetal demise as a statistically significant complication among cocaine users. However, Critchley and colleagues (1988) reported a fetal death secondary to maternal cocaine abuse. At the University of Miami/Jackson Memorial Hospital, Burkett and coworkers (1990) also have reported a cocaine-induced fetal and maternal death.

The true impact of drug exposure on perinatal mortality may be related more to early pregnancy losses and third trimester stillbirths than to neonatal demise per se. Past pregnancy histories should be carefully analyzed for frequent or unexplained fetal losses. Screening for substance abuse should be an integral part of the obstetrical evaluation of spontaneous abortions or stillbirths. Gross and histopathologic examinations of postmortem tissues and organs in drug-related maternal, fetal, or neonatal deaths and in placentae from stillborn or live-born drug-exposed infants should be incorporated into clinical practice and pertinent research study protocols. Cocaine's propensity for causing spontaneous abortion and stillbirth may confound clinical studies of congenital malformations unless the fetal remains are examined carefully and subjected to toxicologic, morphologic, and chromosomal examinations.

CONGENITAL MALFORMATIONS

Investigations in mice show conflicting results regarding the effects of cocaine on the development of congenital malformations. "Nontoxic" doses of cocaine administered to gravid mice have been shown to be teratogenic (Mahalik et al. 1980). A subsequent paper in 1984 from the same investigators showed significant increases in the fetal resorption ratio and the rate of fetal anomalies compared to controls (Mahalik et al. 1984). The researchers reasoned that

cocaine-induced blockage of norepinephrine uptake is responsible for placental vasoconstriction and fetal hypoxia, which produce the defects.

Other reports conflict with the above findings, however. In the study by Church and coworkers (1988), subcutaneous cocaine injections in Long-Evans rats were shown to have adverse effects on maternal weight gain, maternal food and water consumption, fetal weight, maternal and fetal fatalities, fetal edema, *abruptio placentae,* and cephalic hemorrhage, but few congenital abnormalities were observed. Fantel and MacPhail (1982), using the Virgin Sprague-Dawley rat model, showed no increase in congenital defects but found fetal growth retardation induced by cocaine.

Chasnoff and colleagues (1988) compared 50 infants exposed to cocaine during the first trimester of pregnancy with 30 noncocaine polydrug-exposed infants and noted a significant increase in genitourinary tract malformations. Physical examination and renal ultrasound were employed in the diagnosis. Two cases of ileal atresia also were detected. Some of the cocaine-exposed infants also had been exposed to heroin, marijuana, alcohol, and nicotine. Chavez and coworkers (1989) also confirmed a relationship between cocaine use in early pregnancy and urinary tract defects in the population-based Atlanta Birth Defects Case-Control Study. Little and colleagues (1989) showed a significant difference between 53 cocaine-exposed infants and 100 unexposed infants with regard to congenital anomalies, specifically cardiomegaly, atrial septal defect, and ventricular septal defect. The cocaine-exposed group also had a higher rate of exposure to tobacco, marijuana, alcohol, and methamphetamines. In contrast, other investigators have not observed increased rates of congenital malformations in cocaine-exposed infants (Cherukuri et al. 1988; Hadeed and Siegel 1989; MacGregor et al. 1987).

Polydrug exposure confounds clinical studies attempting to relate cocaine exposure to congenital defects. Alcohol causes many of the same anomalies noted in cocaine-exposed infants, including microcephaly, cardiac defects, and genitourinary tract anomalies (Jones et al. 1973; Jones 1986). Mice exposed *in utero* to alcohol develop genitourinary anomalies, principally hydronephrosis (Boggan et al. 1972). Marijuana increases nearly fivefold the risk of delivery of an infant with features of fetal alcohol syndrome (Hingson et al. 1982).

Investigations also are hampered by the inability to ascertain the presence and magnitude of first trimester exposure due to lack of suitable biologic markers and inaccuracy of maternal self-report (Zuckerman et al. 1989). Maternal hair samples (Graham et al. 1989) may provide some insight into time course and quantification of *in utero* drug exposure and may permit better verification of drug-free comparison groups.

ABNORMALITIES IN INTRAUTERINE AND POSTNATAL GROWTH PATTERNS

The most frequently described consequence of *in utero* cocaine exposure is "low birth weight," a term commonly used by the lay public as well as scientific investigators. Many studies attempt to document an increased incidence of low birth weight in cocaine-exposed infants as a harbinger of the potential costs to society of dealing with their anticipated problems. However, confusion surrounds the term low birth weight. Low birth weight refers to infants weighing less than 2,500 g at birth; "very low birth weight" (VLBW) refers to infants weighing less than 1,500 g at birth; and "extremely low birth weight" refers to infants weighing less than 1,000 g at birth. Perinatal statistics rely heavily on these categories, designated regardless of gestational age, because birth weight (BW) is a more objective and measurable parameter than gestational age. Unfortunately, the categories make little sense without knowing the relationship to gestational age. Neonates should be classified by BW, gestational age, and a standard for intrauterine growth. The most commonly used standard of intrauterine growth is the University of Colorado Medical Center classification (Battaglia and Lubchenco 1967) despite the problem of applying high-altitude BW norms to sea-level populations.

Infants are classified as small for gestational age (SGA) if their growth parameters fall below the 10th percentile for the gestational age. SGA infants may be constitutionally small or "intrauterine growth retarded." Symmetrical growth retardation affects weight, length, and head circumference and suggests longstanding aberration of fetal growth; asymmetrical growth retardation involves sparing of head growth and denotes a late-onset compromise of the feto-placental unit (Gruenwald 1963).

Complete physical examination, including neurologic assessment, should be performed at birth and at each encounter during the longitudinal followup. Measurements of weight, length, and head circumference should be performed by a trained examiner. Dysmorphology examination formats with checklists beyond a "yes" or "no" for "normal facies" and "physical anomalies" enhance the physical examination. Photographs also provide a permanent record for review.

Standard gestational age assessment, such as the Ballard modification of the Dubowitz examination (Ballard et al. 1979), should be performed and interpreted in light of obstetrical parameters of gestational age, if known, A recent report (Constantine et al. 1987) from the Infant Health and Development Program revealed that Ballard estimates of gestational age based on physical criteria more closely correlated with dates estimates and yielded higher

proportions of correct classifications of prematurity and SGA than did estimates based on neurologic criteria or combined neurologic and physical criteria. The most consistent teratogenic consequence of *in utero* cocaine exposure is IUGR (MacGregor et al. 1987; Cherukuri et al. 1988; Chouteau et al. 1988; Hadeed and Siegel 1989; Fulroth et al. 1989; Zuckerman et al. 1989). The last study involved a prospective survey of 1,126 mothers receiving prenatal care in the Boston City Hospital clinic system. Maternal drug histories and urine toxicology screening for cocaine and marijuana were performed during the first prenatal visit and delivery hospitalization. The investigators found independent contributions of cocaine and marijuana with regard to decreased growth parameters of BW and length and an independent contribution of cocaine with regard to decreased head circumference. Multiple regression analysis, including prepregnancy weight and pregnancy weight gain, suggested that cocaine may have an indirect negative effect on fetal growth mediated by maternal undernutrition as well as an independent, direct negative effect. The observed negative impact on intrauterine growth was not apparent when infants were classified only by maternal self-report, thus underscoring the need for urine toxicology screening.

In future studies, emphasis should be placed on IUGR to determine whether *in utero* cocaine exposure further compromises neurodevelopmental outcome measurements beyond the anticipated adverse effects of impaired intrauterine growth (Smeriglio 1989). Such a study would require elucidation of other potential etiologies for IUGR (Gross 1989; Evans 1989).

For example, congenital infections must be extensively explored with respect to *in utero* drug exposure. Congenital syphilis and cytomegalovirus (CMV), the two most common entities to cause CNS injury, have been reviewed elsewhere (Prober and Arvin 1989). Congenital syphilis is on the increase in major metropolitan areas (Ricci et al. 1989). This reflects the surge in the incidence of sexually transmitted diseases in the general population and specifically in the drug-using culture. The pattern is exacerbated by pregnant substance abusers failing to seek prenatal health care. Fortunately, mandatory serology screening for syphilis facilitates identification. The current rates of seropositivity for syphilis, usually untreated, identified among cocaine-users in the University of Miami/Jackson Memorial Hospital delivery population is approximately 25 percent (unpublished data). The diagnosis of congenital syphilis should be considered in any neonate born to a mother with a reactive serology for syphilis. Congenital syphilis may be associated with the following findings: growth retardation, prematurity, bullous skin lesions, maculopapular rash, “snuffles,” skeletal lesions, jaundice, hepatosplenomegaly, lymphadenopathy, and CNS involvement.

CMV occurs in 1 to 2 percent of all live births, The incidence of CMV among cocaine-using pregnant women is not known. Congenital CMV infection can be confirmed by isolation of the virus from urine or saliva, ideally within the first postnatal week. Congenital CMV can result from either primary or recurrent maternal infection, but the majority of infants symptomatic at birth have been exposed to primary maternal infection. The clinical manifestations of CMV are as follows: prematurity, growth retardation, microcephaly, CNS involvement, chorioretinitis, hepatomegaly, splenomegaly, jaundice, and petechiae. Long-term sequelae include cognitive and developmental delays, learning and behavioral disorders, seizures, neuromuscular disorders, and sensorineural hearing loss. Approximately 10 percent of infants apparently asymptomatic at birth develop long-term sequelae (i.e., progressive sensorineural hearing loss, potentially impaired cognitive development, and behavioral problems) (Prober and Arvin 1989).

In addition to IUGR, postnatal growth patterns of drug-exposed infants also should be assessed. Attention should be paid to malnutrition and deficiencies in vitamins and minerals (e.g., iron deficiency anemia) and exposure to environmental toxins (e.g., lead). Landrigan and Graef (1987) termed childhood lead poisoning the “silent epidemic.” Shukla and coworkers (1989) concluded that high *in utero* lead exposure, reflected by maternal blood lead concentration, followed by a relatively high postnatal lead exposure, detrimentally affects an infant’s growth in terms of stature. Conversely, infants exposed to lead *in utero,* but not postnatally, experienced “catchup” growth. Lead may be dispersed in air, dust, and soil. Prevalence rates of elevated blood lead levels are highest in densely populated urban areas, the very dwelling places of many of the study participants in perinatal substance abuse programs. Childhood lead poisoning is defined as a whole blood lead concentration of 25 mg/dL together with an erythocyte protoporphyrin level of 35 mg/dL or above (American Academy of Pediatrics 1987). Neuropsychologic dysfunction, including cognitive impairment and behavioral disorders, may occur in asymptomatic children with elevated blood lead levels. The Academy recommends that all children at risk for lead exposure be screened at approximately 12 months postnatal age by means of the erythrocyte protoporphyrin test, which provides a sensitive and inexpensive screen for increased lead absorption and for iron deficiency.

PREMATURITY

The World Health Organization and many investigators set the dividing line between preterm and term birth at 37 weeks gestation. Neonatologists generally prefer to define preterm as less than 38 weeks and term as between 38 and 42 completed weeks of gestation (Lubchenco and Koops 1987).

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Cocaine has been recognized as a contributing factor in premature delivery, yet no studies thus far have focused on the specific consequences of *in utero* cocaine exposure on outcome of premature infants already predisposed to increased risk of death or long-term disability.

One of the most devastating complications of prematurity is periventricular-intraventricular hemorrhage (PIVH), which occurs in approximately 40 percent of VLBW premature infants (Volpe 1985; Shankaran et al. 1990). Hemorrhage originates in the capillary bed of the fragile subependymal germinal matrix and, in severe cases, fills and distends the ventricular system. Severe PIVH also may cause hemorrhage into the parenchyma and/or progressive hydrocephalus. Hambleton and Wigglesworth (1976) hypothesized that increases in arterial blood pressure, under conditions of maximal dilatation of the capillaries by hypoxia and hypercapnia, may be responsible for the hemorrhage. The observation by Lou and coworkers (1979) that failure of autoregulation occurs because of perinatal asphyxia in the premature infant emphasizes that PIVH may be evoked by fluctuations of blood flow within a pressure-passive cerebral circulation.

Cepeda and colleagues (1987) determined that VLBW infants delivered to opiate-dependent mothers had a significantly lower incidence (23 percent) of PIVH compared with infants of mothers who denied drug usage (52 percent), $p<0.05$. Wurtzel and colleagues (1988) noted neither an increase nor a decrease in PIVH in an uncontrolled study of 25 preterm cocaine-exposed infants with a mean BW of 1,560 g and a mean gestational age of 32 weeks. The PIVH rate was 16 percent, similar to the retrospective overall rate noted in infants <=36 weeks. However, few VLBW preterm infants were assessed.

Another entity, periventricular leukomalacia (PVL), occurring as an isolated finding or in combination with various grades of PIVH, is characterized by echodense lesions evolving over several weeks into echolucent cysts within the white matter adjacent to the ventricles. PVL, a predominantly ischemic lesion that may have a hemorrhagic component, often is associated with severe developmental delay, spastic diplegia, or quadriplegia. The lesion may result in myelination delay. Van de Bor and coworkers (1989) have shown that magnetic resonance imaging (MRI) is useful for detection of CNS myelination of preterm infants with PVL. Their investigation of 33 preterm infants of less than 30 weeks gestational age studied at 44 weeks postconceptional age showed significantly delayed myelination patterns in infants with PVL compared with those with PIVH or without PVL or PIVH. The latter two groups had myelination patterns similar to term infants at 44 weeks postconceptional age. DeVries and colleagues (1988) also reported that transient periventricular echodensities, even though unaccompanied by PIVH or periventricular cystic degeneration,

may herald neurologic abnormalities, especially dystonia, and may represent mild PVL.

Determining whether *in utero* cocaine exposure affects the risk of PIVH, PVL, or other lesions in VLBW infants is critical to understanding the pathogenesis and prevention of these entities. It is not unreasonable to expect that *in utero* cocaine exposure would have adverse CNS effects in VLBW infants due to its profound effects on uterine blood flow. A case report of a term cocaine-exposed infant alerted clinicians that cocaine could be responsible for neonatal cerebral infarction, seizures, cortical atrophy, and neurodevelopmental delay (Chasnoff et al. 1986). *In utero* stroke with resultant porencephaly in a term infant also has been described in association with maternal polydrug abuse (Tenorio et al. 1988).

Dixon and Bejar (1989) determined the incidence of CNS lesions detected by echoencephalography in a group of 74 apparently healthy term infants documented by urine toxicology to have been exposed *in utero* to drugs (32 cocaine, 24 methamphetamine, and 18 stimulant/narcotic). Forty-one percent of the 32 cocaine-exposed infants had abnormal echoencephalographic lesions, which included white matter cavities, acute infarction, intraventricular hemorrhage, subarachnoid hemorrhage, and ventricular enlargement. Similar results were described for methamphetamine-exposed infants, except for a significantly lower percentage of white matter cavities.

CNS ASSESSMENT

Most longitudinal neurodevelopmental studies have utilized physical and neurologic assessments in conjunction with standardized neurodevelopmental and neurobehavioral evaluations. Strict adherence to established norms, verification of interobserver reliability among examiners, confirmation of interpretations by reviewing videotaped assessments, and blinding of the observers to medical and substance exposure histories are critical to successful neurodevelopmental assessment.

Too little attention has been given to quantitation of neurologic examination results. Many investigators simply resort to recording the neurologic exam according to categorical representation of “normal,” “questionable,” “at risk,” or “abnormal.”

Prechtl’s neurologic examinations, standardized on a large sample of full-term infants, is a clinical and research instrument that is predicated on specifying the optimal behavioral state or states in which most of the test items must be administered and which of the infant’s responses are optimal. The examination

is lengthy and should be administered on a repetitive schedule (Prechtl and Beintema 1964).

The Dubowitz neurologic assessment, useful for evaluating preterm and full-term infants, also is recommended to be performed repetitively to determine whether initially abnormal neurologic signs persist (Dubowitz and Dubowitz 1981).

The Brazelton Neonatal Behavioral Assessment Scale (NBAS) using Lester's cluster scores provides the most comprehensive assessment of the behavioral repertoire of newborns (Brazelton 1976; Lester 1980) and is a useful tool in comparative studies. Specific scales for preterm infants have been designed (Brazelton 1984; Als et al. 1982; Korner and Tom 1990). Chasnoff and colleagues (1989) showed significant impairment of orientation, motor, and state regulation behaviors on the NBAS in infants who had been exposed *in utero* to cocaine even when the exposure only occurred during the first trimester. Eisen and coworkers (1991) documented abnormal habituation patterns in cocaine-exposed vs. drug-free control infants during the first postnatal week. Although early testing may be informative, performing the NBAS serially over the first month may be more illuminating.

The Bayley Scales of Infant Development consists of mental and motor scales as well as the Infant Behavior Record, which assesses the infant's characteristic behavior patterns during the assessment (Bayley 1969). Raw scores are converted to the Mental Development Index (MDI) and Psychomotor Development Index (PDI), respectively, which are standard scores based on a larger sample representative of the US. population within the age range of 2 to 30 months. To date no other measure has been as widely used as the Bayley Scales in this age range, and, thus, it may be the best tool for interstudy comparisons. Many study designs incorporate examinations at 6, 12, 18, and 24 months. The advantage of such a schedule is the frequent early contact, which fosters compliance for later evaluations. If attrition can be minimized without such a repetitive schedule, focusing on an examination at 8 months and at 18 to 24 months is logistically and financially advantageous. Preliminary data on Bayley Scales performance in a relatively few cocaine-exposed vs. control infants have not revealed significant differences in mean MDI or PDI scores (Chasnoff and Griffith 1989). New investigative initiatives may need to include more innovative measures of mental, psychomotor, behavioral, and special sensory performance.

The Motor Assessment Inventory (MAI) appears to be an effective instrument in evaluating muscle tone, primitive reflexes, automatic reactions, and volitional movement in the first year of life (Chandler et al. 1990). Although the MAI is not

normed, interrater reliability has been reported as 0.72 (Harris et al. 1984). A recent study found the MAI to be more than twice as sensitive as the Bayley Motor Scale in detecting early signs of cerebral palsy (Harris 1987).

The Fagan Test of Infant Intelligence (visual information processing) is a unique alternative to traditional assessments (Fagan and Shepard 1987). The test, a visual preference paradigm that relies solely on face recognition, has been applied to a variety of high-risk groups of infants. The equipment comprises a viewing stage and an online computer for accurate administration and automated scoring.

Long-term data on intelligence testing, special sensory assessments, and behavioral and learning disorders in cocaine-exposed infants are as yet unavailable. Controversy still exists regarding the use at age 3 years of the revised version of Stanford-Binet; many investigators still administer the previous version. One also could consider using the McCarthy Scales at age 3 years to provide more objective evaluation of motor performance and specific areas of strength and weakness than the Stanford-Binet, but the test is more time-consuming. The McCarthy usually is preferred by the children due to its more interesting performance tasks, Another approach is to assess IQ by the Stanford-Binet at age 4 years, although this becomes a difficult timeframe for 5-year grant cycles. All the tests should be interpreted in light of the socioeconomic and family circumstances that strongly influence child development.

Neurologic examinations and neurobehavioral assessments should be coupled to state-of-the-art neuroimaging and neurophysiologic assessments. Echoencephalography has become the mainstay of neonatal cranial imaging due to its lack of ionizing radiation, portability, rapid performance time, and reliability in detecting congenital structural anomalies, PIVH, periventricular and subcortical leukomalacia, calcifications, cysts, and ventricular dilatation. MRI now provides a safe, noninvasive, albeit expensive and time-consuming, method of diagnosing these lesions as well as being uniquely capable of delineating myelination patterns that could relate to neurologic function. Repeat scanning is possible after fontanelle closure. No clinical studies thus far have addressed the potential impact of cocaine on myelination patterns,

McArdle and coworkers (1987) reported MRI results of 51 neonatal brains (29 to 42 weeks postconception), which showed stages of progression of gray-white matter differentiation and myelination. Cerebral gray-white matter differentiation was graded on a five-point system (GW1 to GW5) and the distribution of myelin stages on a four-point system (M1 to M4). Delayed myelination in the neonatal period was defined as the absence of myelin in the corona radiata by 37 weeks

postconceptional age. Barkovich and coworkers (1988) described maturation "milestones" as follows: The splenium of the corpus callosum should be of low signal intensity by 8 months of age, the genu by 8 months of age, the anterior limit of the internal capsule by 11 months of age, the deep frontal white matter by 14 months of age, and the entire brain (except for some fine peripheral arborization) by 18 months of age. Myelination delay strongly correlates with abnormal motor tone and/or abnormal scores on the Bayley Scales in the first postnatal year.

In addition to neuroimaging assessments, one might consider near infrared oxygen sufficiency scope (NIROS-SCOPE) (Brazy et al. 1985), positron emission tomography (Volpe et al. 1983), nuclear magnetic resonance spectroscopy (Leonard et al. 1985), cerebral blood flow velocity measurements (Bada et al. 1979; Altman and Volpe 1987), and acoustic cry analysis (Lester 1987). These modalities and others beyond the scope of this discussion may expand research dimensions in the assessment of CNS structural anomalies and/or functional derangements associated with *in utero* drug exposure.

CONCLUSION

The measurement of adverse fetal, neonatal, and infant outcome associated with *in utero* drug exposure is fraught with difficulties, including misclassification of the exposure(s), errors in determining timing and quantity of exposure(s), numerous confounding variables, and inherent limitations of the measuring instruments. However, careful attention to ensuring confidentiality of maternal histories, utilizing state-of-the-art biologic markers, planning and executing complete prospective data collection, standardizing examinations, maintaining "blinded" observations, utilizing sophisticated technology appropriate for each organ system, and emphasizing rather than excluding such subpopulations as infants who are SGA or premature should yield valuable insights into the outcome of the offspring of substance-abusing women,

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Methodological Issues in the Assessment of the Mother-Child Interactions of Substance-Abusing Women and Their Children

Dan R. Griffith and Catherin Freier

INTRODUCTION

One research question in evaluating the long-term development of infants exposed to drugs *in utero* is the degree to which maternal behavior might exacerbate or compensate for the neurobehavioral deficits commonly observed in drug-exposed infants. To build an optimal maternal-infant relationship, mother and infant must have the behavioral repertoire and the adaptability to respond appropriately to the stimulation provided by the other. If the infant has difficulties responding to environmental demands in an organized fashion, then it becomes the responsibility of the mother to sustain the mother-infant relationship by modulating her stimulation to fit the information-processing needs of the infant (Horowitz 1984). When the mother is unable to fulfill this function, the infant is likely to be exposed repeatedly to experiences that overwhelm him or her and impede rather than facilitate development (Solnit 1984). When examining the relationship between substance-abusing women and their prenatally drug-exposed children, one must evaluate the behavioral characteristics of the infants (especially as these shape the mothers behaviors), the personality and behavioral characteristics of the mother, and the myriad of variables that affect both the infant's and the mother's behavioral repertoires.

One of the major variables that affects maternal behavior is the child (Sameroff and Chandler 1975). Many cocaine-exposed newborns, for example, have been described as having fragile, disorganized, easily overloaded nervous systems that leave them ill-equipped to organize and respond appropriately to information from their internal or external environments (Chasnoff et al. 1985, 1989; Griffith 1989). The caretakers of these infants are required to limit their interactions with the infants to those relatively few behaviors that do not exceed

the cocaine-exposed infants' low threshold for overstimulation. There is variability from mother to mother as to how they respond to this requirement. Some become increasingly frustrated with their failures to engage their unresponsive infants until they reach the point of emotional detachment from the infants and avoid any interactions with them. Other mothers continually overstimulate their infants as if to compensate with their own excessive activity for the infants' lack of responsiveness.

Beyond the impact of the infant on the mother's effectiveness as a parent, many drug-using women share several characteristics that researchers have found to interfere with the parenting abilities of drug-free women and may affect the long-term outcome of their children. In the authors' research population, for example, 65 to 60 percent of the women at any point in time can be classified as being of low socioeconomic status (SES). Researchers have indicated that non-drug-using mothers from low-SES backgrounds tend to provide less stimulation of an appropriate type to their infants. They vocalize to their infants less often than mothers from middle-SES backgrounds (Field 1980) and, as a group, decrease their interactions with their children as they grow into toddlers, whereas mothers from middle-SES groups tend to increase their interactions with their children (Farran and Ramey 1980).

Many of the drug-using women from the authors' research population live in high-stress environments. Many women are victims of sexual and/or physical abuse, and about 70 percent are single parents with few sources of social support. Crnic and colleagues (1983a) found that drug-free women experiencing high stress with few social supports had greater relational difficulties with their infants than mothers with either low levels of stress or high levels of social support. Crnic and coworkers posited further that relational difficulties experienced by mothers under stress may create greater stress, thus compounding the relational difficulties.

A final common characteristic shared by the drug-using women participating in the authors' research is a high incidence of psychopathology. Of the women on whom the authors have collected Minnesota Multiphasic Personality Inventories (MMPIs) during their pregnancies, 71 percent have had at least one clinical scale score greater than or equal to 70. These elevated scores have been shown to be predictive of poor interactive capabilities as measured by the Brazelton Neonatal Behavioral Assessment Scale (NBAS) (Brazelton 1984) in the cocaine-exposed infants at 1 month of age (Griffith et al. 1989). The authors found that 23 percent of the women completing the MMPI had depression scale scores greater than or equal to 70. Several researchers have linked maternal depression to poor-quality maternal-infant behaviors (Field et al. 1990; Cohn et al. 1990).

Unfortunately, relatively few research projects have provided systematic analysis of the relative contribution of maternal risk factors, child risk factors, and interaction among factors to the continued socioemotional, behavioral, and intellectual development of drug-exposed children. Studies that have looked at some of these variables are reviewed in this chapter following a discussion of the methods used and the methodological issues faced when assessing mother-infant interactions with any population.

METHODS AND METHODOLOGICAL ISSUES IN THE ASSESSMENT OF MOTHER-INFANT RELATIONS

A range of techniques has been used in the study of mother-child interactions. Maternal questionnaires have been designed to assess maternal attitudes toward the fetus (e.g., the Maternal-Fetal Attachment Scale [Cranley 1981]), the neonate (e.g., the Neonatal Perception Inventory [Broussard and Hartner 1971]), the infant, the child, the demands of childrearing/child care, discipline, and social support systems (e.g., the Maternal Social Support Index [Pascoe et al. 1987). Several maternal questionnaires and behavioral checklists have been developed to assess maternal perceptions of the child's temperament and characteristic behavior (e.g., the Infant Characteristics Questionnaire [Bates et al. 1979] and the Infant Temperament Questionnaire [Carey and McDevitt 1978]).

However, the method with the greatest potential to give information on how infant behaviors affect mothers and vice versa is the direct observation of mothers and infants interacting with each other. Direct observations of mothers and their infants have been made in the home and in the laboratory, in structured and unstructured situations, focusing on a range of maternal and child behaviors and using a variety of recording techniques. Regardless of the specific observational methods chosen by a researcher, there are numerous issues that affect the reliability and validity of the data collected.

Interrater Reliability During Mother-Infant Observations

The first research decision to be made when evaluating mother-infant interaction is which behaviors to observe. The specific behavior chosen will vary depending on the age of the infants or children being studied, which aspect of mother-infant interaction is being studied, and the theoretical model of the researcher. Regardless of the specific behaviors chosen, it is important to provide explicit behaviors that can be defined in precise terms to achieve acceptable levels of interobserver reliability (Ramey et al. 1978; Field 1977; Bakeman and Brown 1980a). To provide an adequate representation of behavioral differences among groups, one should select behaviors that are

likely to occur in the populations being studied (Field 1977; Bakeman and Brown 1980a). A final consideration is the degree to which observers can reliably score the behavior without extensive training. This has the practical advantage of saving time in the training of observers for the research team that has designed the system and also increases the availability of the tool for use by other researchers with other populations (Ramey et al. 1978).

The reliability of observational data can be affected by the method used to establish interrater reliability. Lytton (1971) and Ramey and colleagues (1978) cited research evidence that indicated that interobserver reliability dropped off rapidly in observation episodes where the observers did not expect their reliability to be checked. Ramey and colleagues (1978) suggested that perhaps the most efficient way to maintain vigilance on the part of observers and, consequently, high interobserver reliability would be to have observers score their observations from videotape while informing them that random reliability checks would be made of their scoring. Because of this potential loss in reliability, Ramey and coworkers (1978) urged researchers to exercise extreme caution when interpreting data that were scored during live observations. The interobserver reliability for data collected live may be improved by having two observers rate the behaviors simultaneously (Bakeman and Brown 1980a). However, this technique, in additlon to requiring increased demands on the observers' time, would seem particularly obtrusive, especially for in-home observations. An additional advantage of videotaping observational sessions is that the events are preserved as they occurred. This allows for the analysis and scoring of new behavioral dimensions as the researcher's focus changes or theoretical framework evolves.

A final issue regarding interrater reliability involves the statistical method used to calculate the level of reliability. According to Ramey and colleagues (1978), the two general methods for establishing interrater reliability are by (1) correlating the total scores obtained by independent observers for particular behaviors across observational sessions *or* (2) computing the percent of agreement between independent observers on the occurrence of particular behaviors. Ramey and colleagues (1978) stated that the preferred and most rigorous method of estimating Interrater reliability is to compute percent agreement by dividing the number of agreements between observers by the number of agreements plus disagreements. This is particularly true if one wishes to analyze the conditional probabilities of specific sequential relationships among different behaviors (Ramey et al. 1978).

Validity of Observations of Mother-Infant Interactions

One of the key validity issues for any observational study is the degree to which the behaviors observed are an accurate reflection of the usual or typical interaction between mother and infant. Perhaps the biggest threat to the validity of observational data is the alterations that occur in maternal and infant behavior because of the observer's presence. The effect on maternal behavior may be particularly significant if the mother knows or suspects which particular behaviors the investigator is interested in observing. Researchers have tried to deal with this issue by building a rapport with the mothers and visiting the observation site frequently (Lytton 1971) or for a long enough period of time (Thoman 1975) to habituate the subjects to the observers' presence. Thoman (1975), for example, began observing mother and infant separately and together in the hospital nursery and then continued her observations in the home where she spent 7-hour days with the family. She indicated that this type of intensive observation combined with explanations to eliminate any expectation on the part of the mother to interact with the observer seemed to be effective in making the mother comfortable in the observer's presence. Thoman (1975) further noted, however, that this was only effective in reducing the effects of observer presence up until the infant reached about 5 weeks of age, at which time the infant began to watch the observer as well as the mother. Beckwith and coworkers (1976) acknowledged and controlled for the presence of the observer by including infant responses to the observer in their scoring system.

Where the data are collected (either in the home or in the laboratory) and the degree of control the researcher has over the situation (from highly structured tasks to totally nonstructured situations) also affect the validity of observational data. In spite of the previously noted observer effects, the home is probably the best setting for deriving a sampling of maternal and infant behavior that most closely resembles their usual mode of interaction. Observations in the home allow the observer to gather firsthand information about the home environment in terms of roles and activities of other family members, existence of appropriate play materials, and the organizational level of the home, such as Caldwell's HOME (Home Observation for Measurement of the Environment) Scale (Elardo et al. 1977). The home is the only place where truly unstructured observations can take place. As soon as subjects enter the laboratory, they are exposed to conditions that do not exist in their homes and that most likely alter their behavior.

There are, however, several reasons why laboratory research is preferred. The major advantage to laboratory research from a purely methodological standpoint is the higher degree of control the researcher has over extraneous

variables that might affect the subjects behavior. This type of control is particularly important in studies where the researchers are attempting to experimentally manipulate the behaviors of the mother-infant dyad to gain information on cause-effect relationships between behaviors (Field 1977; Gusella et al. 1988). Because the stimulus conditions affecting mothers and infants vary from home to home, this type of control cannot be achieved even with the addition of a structured task into the home environment (Lytton 1971). One practical consideration in deciding where to observe the mother-infant interaction is the lower costs of the laboratory study in terms of research hours spent traveling from home to home as well as setting up and taking down such technical equipment as video cameras. This is not an expense that can be taken lightly when one considers the large numbers of subjects required to unravel the relationships between mother-infant interactions and the myriad of other variables that affect the outcome of the child. A second practical consideration should be the safety of the observers. Many of the drug-using women live in high-crime areas where a realistic assessment of the dangers to observers must be made and precautions taken to ensure staff safety.

The decision to use structured vs. unstructured tasks depends in part on the probability of occurrence of the behavior of interest. Structured tasks can serve to prompt the subjects into performing specific behaviors that are unlikely to occur otherwise. The structured tasks, however, do not allow one to draw conclusions about the usual incidence rates for the behaviors observed.

Predictive Validity of Mother-Infant Interaction

Observations of mother-infant interactions have been used with varying degrees of success to predict later mother-infant/child interactions (Crockenberg and McCluskey 1988; Bakeman and Brown 1980a; Crnic et al. 1983b), the intellectual development of the child (Watt 1988; Watt and Strongman 1985; Bakeman and Brown 1980b; Beckwith et al. 1976; Coates and Lewis 1984; Pettit and Bates 1989), and the social/behavioral outcome of the child (Jacobvitz and Sroufe 1987; Bakeman and Brown 1980b). Perhaps the major difficulty faced by researchers trying to predict later behavior from early mother-infant interactions is the ever-increasing and changing behavioral repertoire of the infant, which in turn demands changes in the mother's behaviors. Furthermore, those behavioral aspects of mother-infant interaction that may be important at one stage of development may have little importance later on (Thoman 1975; Watt 1986). In fact, variability in infant behavior and maternal behavior over time is probably the best sign of a healthy, fully functioning dyad.

Researchers have tried several solutions to the problem of predicting long-term outcome from discontinuous development. Many researchers have attempted to summarize the data collected on the incidence and/or duration of all discrete behaviors observed into relatively global categories representing different types of behavior. The decision as to which summary categories to create is often an intuitive one based presumably on the authors' hypotheses concerning mother-infant interactions. Coates and Lewis (1984), for example, in a study of full-term infants at 3 months of age and their mothers, summarized maternal behaviors observed into distal and proximal behaviors, vocal responsivity, responsivity to distress, tactile responsivity, total amount of stimulation, and interaction level (based on the total number of lo-second intervals where both maternal and infant behaviors occurred). Using regression analysis, they found significant relationships between maternal behaviors when the infant was 3 months old and the child's cognitive performance at 6 years. However, these results are difficult to interpret, in part due to the lack of any maternal-infant interaction assessment beyond the 3-month level and also due to their counterintuitive nature. Coates and Lewis (1984) found, for example, that there was a negative relationship between the amount of time mothers stimulated their infants vocally at 3 months and reading achievement tests at age 6 years. Credibility of such a finding would require much more information about what occurred between mother and child during the intervening 5 years, 9 months between assessments.

Jay and Farran (1981), in analyzing their observations of 3-year-olds and their mothers, used four summative measures of behavior: total time spent in mutual interaction, time spent in passive involvement, frequency of interactive behavior, and frequency of controlling behavior. Using a stepwise multiple regression, they found that each of the four summative behavior measures accounts for a significant portion of the variance in the children's 3-year Stanford-Binet IQ scores and their 5-year Wechsler Preschool and Primary Scale of Intelligence IQ scores. This study, however, only assessed children and their mothers at one point in time. Consequently, nothing can be said about the predictive validity of the mother-infant interaction.

The use of researchers' intuition to select summative behavioral categories makes it particularly difficult to interpret nonsignificant research findings. For example, if a researcher finds no difference between mother-infant interactions in preterm vs. full-term dyads, is it because there are no differences or because the researchers chose the wrong summative categories? A number of researchers have avoided this problem by allowing the behavioral data to select the summative categories through factor analysis. Beckwith and colleagues (1976), for example, observed and coded the behavior of premature infants and full-term infants at 1, 3, and 8 months from the expected dates of birth for the

preterms and the actual dates of birth for the full-terms. Factor analyses of behaviors at each observation period revealed five behavioral factors at 1 month of age (social interaction, responsive holding, verbal stimulation, mutual gazing, and stressful holding), five behavioral factors at 3 months of age (responsive social, mutual gazing, physical contact, control, and interference), and four behavioral factors at 8 months of age (responsive social, intellectual stimulation, control, and floor freedom).

It is important to note that the results of this study reflected the continuity and discontinuity of mother-infant interactions over time. The social responsiveness transcended all the observation periods, but the overall constellation of factors changed with the children's ages. Regression analyses revealed further that different factors at each observation age were significantly related to developmental outcome measures collected at age 9 months. Mutual gazing at 1 month of age was predictive of success on a series of Piagetian tasks at 9 months but not of Gesell Developmental Quotient (DQ). Control at 3 months of age was predictive of Gesell DQ at 9 months. For 8-month-olds the amount of floor freedom they were allowed was predictive of Gesell DQ at 9 months.

In addition to creating summative behavioral categories, several researchers have added global rating scales to their assessments of mother-infant interactions in an effort to increase predictability. Jay and Farran (1981) measured the overall impressions of observers about mothers interacting with their 3-year-olds on three five-point rating scales assessing degrees of maternal involvement with the child, maternal control of the child, and maternal acceptance of the child. They found these global ratings to be better predictors of the children's IQ scores at ages 3 and *4* years than were the summative measures of behavior that were generated during observation.

Crnic and coworkers (1983b) assessed the frequency, duration, and sequence of infant and maternal behaviors in preterm and full-term dyads at 4, 8, and 12 months following hospital discharge. They found little consistency in specific maternal behaviors or infant behaviors over the three assessments and were not able to differentiate preterms from full-terms in terms of specific measures. However, they were able to find significant results when using a summary measure of maternal behavior (total amount of maternal activity) and global ratings of maternal and infant affect collected at each assessment. These measures indicated that mothers of preterm infants, compared with those of full-term infants, were more active and displayed less positive affect when interacting with their infants across the first year. Similar to their mothers, the premature infants displayed less positive affect than the full-term infants across the first year.

Finally, Jacobvitz and Sroufe (1987) in a prospective study, assessed behavior of mothers toward their infants/children at 6 months, 24 months, and 42 months of age using global rating scales at each age. At the 8-month assessment they used a nine-point maternal interference rating scale estimating the mother's tendencies to disrupt the baby's ongoing activity with her activities or intrusions. At the 24-month assessment they used a scale rating maternal seductiveness. At 42 months they assessed maternal overstimulation while the children were engaged in a frustrating task. Mothers who provoked and teased their already frustrated children rather than providing calm reassurance were scored as overstimulating. At 6 years of age, 34 of the original 287 children who began the study were diagnosed with attention deficit disorder with hyperactivity (ADD-H) based on *Diagnostic and Statistical Manual III* criteria and were compared to a matched control group of non-ADD-H children from the original research population. Results indicated that the mothers of ADD-H 6-year-old children were significantly more interfering at the 6-month assessment and significantly more overstimulating during the 42-month assessment than were the mothers of non-ADD-H children.

A final method through which researchers have tried to capture the stable essence of mother-infant interaction and thereby improve long-range predictability is by assessing what Tronick and Cohn (1989) refer to as the coordination of mother-infant behavior. Watt (1986), for example, looked at the relationship between mother-infant interaction in premature infants at 2 to 3 months corrected age and the infants' Bayley Mental Development Indices (MDI) at 6 months corrected age. When looking at mother behaviors or infant behaviors in isolation, Watt found that, at 2 to 3 months, infant vocalizations were negatively related, whereas maternal vocalizations were positively related to 6-month Bayley MDI scores, This finding suggests a counterintuitive negative relation between early infant vocalizations and later cognitive development as well as a negative relation between rates of maternal and infant vocalization at 2 to 3 months of age. By looking at infant behavior and its synchrony to maternal behavior, however, Watt found infant vocalizations in the absence of accompanying maternal behavior to be negatively related, whereas infant vocalizations coordinated with maternal vocalizations were positively related to 6-month Bayley MDI scores.

Bakeman and Brown (1980a) studied maternal-infant interactions in full-term and preterm infants during feeding sessions at the time the infants were released from the hospital and 1 month and 3 months postdischarge. When analyzing the frequency and duration of discrete infant behaviors, they found a number of differences between preterm and full-term infants at discharge that had disappeared by the 1-month and 3-month followups. Persistent differences

were found, however, between preterm infants and full-term infants when interaction patterns between infants and their mothers were examined. Preterm infants were significantly more static in their patterns of interaction, more frequently required maternal initiation of interaction, and were more likely to be the ones to break off an interaction with their mothers. However, these differences did not prove predictive of either cognitive or social abilities of the infants when assessed at age 3 years (Bakeman and Brown 1980b). Bakeman and Brown (1980b) attributed this lack of predictability at least in part to the restriction of their observations to the feeding situation. They further posited that the size of their sample was probably too small to pick up whatever weak effects early interaction might have had on the child's behavior years later.

As mentioned earlier in this chapter, there have been relatively few published studies exploring mother-infant interactions within substance-abusing populations. Lief (1985) and Chasnoff and Griffith (in press) have presented descriptions of drug-using mothers based on clinical observations. A few additional studies have directly assessed the parenting abilities of drug-using women. Bauman and Dougherty (1983) assessed mother-child interaction in a group of methadone-maintained women and their 2- to 6-year-olds compared to a group of drug-free women and their similarly aged children. They found, using summative measures of behavior, that methadone-maintained women engaged in more aversive behaviors (i.e., provoke, threaten, and command) than did drug-free mothers. They also found significantly more aversive behaviors, especially complaining, emanating from the children of methadone-maintained women. Bauman and Dougherty further found the methadone-maintained mothers to be less adaptive as measured by their California Psychological Inventory profiles.

Jeremy and Bernstein (1984) and Bernstein and coworkers (1984) also found differences between methadone-maintained women and drug-free women on interaction with their 4-month-old infants and psychological resources. However, they carried their analyses a step further to examine the degree to which drug use per se vs. poor psychological and psychosocial resources were related to maternal interactive performance. Their findings indicated that it was not drug use but the level of resources that was most predictive of maternal interactive performance (Jeremy and Bernstein 1984). Bernstein and colleagues (1984) made another important point that is too often overlooked when substance-abusing mothers are discussed. They indicated that there was a range of differences in maternal interactive performances among the methadone-maintained women observed. About half the methadone-maintained women fell in the average range for interaction and about a third of these did so in spite of having poor maternal resources.

The data on the specific characteristics of mother-infant interactions among drug-using populations are still rather sparse. A recent symposium presented at the 1990 International Conference on Infant Studies, however, indicated that several researchers are in the process of studying this population. Hans and colleagues (1990) presented data indicating an interactive effect on maternal behaviors between methadone use and psychopathology in mothers. Mothers using methadone and diagnosed as having antisocial personality disorders were significantly more dysfunctional in their interactions with their 24-month-olds than were drug-free mothers. Mothers using methadone and having no significant psychopathology or having affective disorders did not differ from the drug-free mothers in their interactions with their children.

Rodning and colleagues (1990) presented data indicating that phencyclidine-using mothers and their extended family members demonstrated significant deficits in their interactive performance with their 3- and 9-month-old infants compared with drug-free mothers' interactions with their children at the same ages.

O'Connor and colleagues (1990) presented information indicating that maternal alcohol consumption during pregnancy and the mother-infant interactions between alcohol-using women and their 1-year-old infants both contributed significantly to the variance in infant attachment behavior at 1 year.

INFANT TEMPERAMENT

Perhaps the most neglected area of mother-infant interaction research is the contribution that the infants' enduring characteristic temperaments have on the relationship over time. Several approaches have influenced the manner in which temperament is measured. Thomas and Chess' (1977) approach to temperament is the most widely cited and defines temperament as a behavioral style or the "how" of behavior and rules out the content of behavior. It is seen as a "goodness of fit" approach that emphasizes an interactive orientation of the individual's temperament characteristics and the environment. Buss and Polmin (1975) divide temperament into four dimensions that are not specific to content: emotionality, activity, sociability, and impulsivity. Rothbart and Derryberry (1981) differ from this approach as they incorporate emotion-specific content. Although these theorists approach temperament from different angles, they all identify three major substantive issues for temperament research: (1) biological contributions, (2) stability, and (3) influence on interpersonal relationship.

Types of Instruments

Four methods have evolved for the measurement of temperament: parental interviews, parental questionnaires, structured professional observations, and home and laboratory observations.

Parent Interviews and Parental Questionnaires. Most temperament measures have been based on the nine temperament categories derived from the New York longitudinal study (Thomas et al. 1968). The most widely used infant-child temperament questionnaires are Baby Behavior Questionnaire (Bohlin et al. 1981) Infant Behavior Questionnaire (Rothbart 1981) Infant Characteristics Questionnaire (Bates et al. 1979), Infant Temperament Questionnaire (Carey and McDevitt 1978), Toddler Behavior Questionnaire (Hagekull and Bohlin 1981), Toddler Temperament Scale (Fullard et al. 1984), Behavioral Style Questionnaire (Hegvik et al. 1982) and Parent Temperament Questionnaire (Thomas and Chess 1977).

Structured Observatlons. Although sacrificing the depth of knowledge about the child that the parental report provides, structured observations made by trained examiners also provide measures of temperament. The most prominent instruments used are the NBAS (Brazelton 1984) and the Bayley Infant Behavior Rating Scale (Bayley 1969). These scales were not developed for the intent of temperament assessment, and thus, both have weaknesses when used for this purpose.

Home and Laboratory Observations. Laboratory and home observations as measures of temperament have become more widely used. These observations are typically done by observing certain specified interactions (e.g., playing games, doing measurements, interactions with mother, and interactions with strangers). These observations are videotaped frequently and then are rated by observers using rating scales.

Advantages and Disadvantages of Types of Measurement

Parental interviews and questionnaires offer the possibility of obtaining considerable data at low cost but have been criticized on several grounds. The mother's perception is seen to compromise objective determination of the infant's temperament. The mother's responses are affected by prior interactions between parent and infant. The psychometric properties of these measurements have received little attention. These measures are criticized most often as being colored by the personal involvement of the mother as the observer. In contrast to this is the argument that the strongest asset of parental reports is that they represent the distillation of innumerable observations

extended over time and events. As Carey (1983) points out, for the purposes of some studies, the caregiver's perception of the infant's temperament may be precisely the construct of importance.

Structured and observational laboratory and home assessments are relatively free of subjective influence: These observations by trained observers may yield more objective measures of temperament, but by necessity the periods of observation are short and the range of naturalistic situations is constrained. Consequently, the behaviors expressive of temperament may not be fully displayed within this narrow observation, If these observations are not structured so as to be common to all infants, the comparisons among infants may be limited. Another criticism of these measures is that they need to be modified to maximize individual differences.

Current Trend of Use In Research

Temperament research commonly focuses on certain mother-infant dyads that may be of special clinical need, such as adolescent mothers, single-parent mothers, twins, developmentally disabled infants, premature infants, small-for-gestational-age infants, and infants with minimal brain dysfunction (MBD). The authors are not aware of published studies of temperament with infants or children who have had perinatal exposure to illicit drugs.

Studies that have focused on stability of temperament have had difficulty with interpretation of results and predictability for several reasons: (1) The use of different temperament measures at different ages may reflect the measurement of different constructs; (2) in infants who have unique problems (e.g., motor abnormalities/drug exposure), temperament may be more difficult to test as the child gets older because such constructs as "activity" or "state regulation" may not be appropriately tested by current measures; and (3) infants mature at varying rates.

Recently, researchers have emphasized the need for multiple and even cross-method assessment of temperament within the research or clinical setting. This approach has been proposed to enhance predictability as correlations between questionnaires and direct observations fall within the 0.20-0.50 range (Bates et al. 1979; Rothbart and Derryberry 1981; Wilson and Matheny 1983).

Implications

Knowledge of the infant's or child's temperament enhances research in several ways. Explaining temperament to the mother can help her to better understand her child. It provides the clinician/researcher with an objective method of

interpreting the child's contribution to the mother-infant interaction. Temperament-environment interaction information may help clarify the developmental outcomes of these children. Many studies have linked temperamental patterns of the difficult child to behavior problems (Thomas et al. 1968; Graham et al. 1973; Mclnerny and Chamberlain 1978). If certain children can be identified at an early age as being at risk for behavior problems, it may be possible to intervene and teach mothers healthier ways to interact with their difficult children. It also may help to answer questions of future socialization in these children, because an important feature of temperament is its role in regulating social interaction.

Temperament research with perinatally drug-exposed infants and children may involve several unique considerations. Due to drug exposure, these infants tend to be more fussy and irritable at birth. It is difficult to know whether these infants' behaviors are a stable part of temperament or a result of drug exposure that will change as these children develop. It is also important that drug exposure is not diagnosed on the basis of temperament: Not all fussy/irritable infants are drug-exposed infants. Furthermore, it is not likely that all drug-exposed infants will have temperaments known as the "difficult child." Carey and coworkers (1979) examined MBD children and concluded that, although many MBD children have "difficult" temperaments, some fell into the other temperament types. Coll and colleagues (1982) emphasize that difficult temperament in infants with state organization difficulties may be an interaction between the infant's unique organization of state behavior and the mother's response to the infant. This may change as the child develops, making it difficult to demonstrate predictability and stability of temperament in these infants. Perinatally exposed infants have a compromised central nervous system that is reflected in their state organization. In the authors' research, these infants are less alert at 1-month observations. Crockenberg and Acredolo (1983) have observed that infants who are more irritable at birth are less alert at 1 month. Infants who have irritable temperaments and are less alert have less involved contact with their mothers, and interaction is strained. Bell and Ainsworth (1972) concluded that maternal behavior should be recognized as a determinant of infant irritability over the first year of life. Drug-dependent mothers have many expectations of the infant and have ineffectual coping mechanisms that may contribute to infant irritability.

Despite these confounds, questions asked in the right way will provide important data. However, researchers should use both parental reports and professional observations in evaluating infant and child temperament. Studies (Crockenberg and Smith 1982; Crockenberg and Acredolo 1983) also have demonstrated the need to evaluate not only infant temperament but also the mother's characteristics and mother-infant interaction. Antecedent mother and

infant characteristics contribute significantly to the prediction of mother behavior and mother-infant interaction.

CONCLUSIONS

Research into the factors that contribute to the optimal socioemotional, behavioral, and intellectual development of drug-exposed children is just beginning. The authors believe that this research must be multimethod and collect, at the least, detailed information on the child, the mother, interactions between the mother and child, interactions by mother and/or child with other family members, and the home environment.

Information on the child should include repeated medical, developmental, and behavioral evaluations from birth on to begin to differentiate those behaviors/characteristics of the child that are enduring over time and those that are affected by the environment. This information should be gathered from standardized tests assessing a range of capabilities, parental interviews, questionnaires assessing parental perceptions of the child's behavior and temperament, and observations by trained observers of the child's behavior over time in a variety of structured and unstructured situations.

Information about the mother and other significant adults in the child's life should include a detailed, lifelong drug-use history; information on the family of origin; evaluation of personal resources (intelligence, education, support systems, and psychological functioning before and after having the child, if possible); questionnaires or interviews assessing attitudes toward self and child; and direct observations of behavior by trained observers.

Assessments of mother-infant interactions (or interactions between the child and/or mother and any other person) should include discrete maternal and infant behaviors that are defined explicitly and occur regularly between mothers and infants. Interrater reliability either should be checked continuously with simultaneous observers or performed randomly on videotaped observation to maximize reliability. Repeated assessments should be done in a variety of situations to identify the continuous and discontinuous elements of interactions.

For maximum predictive validity of observational data from mother-infant interactions, a combination of scoring systems is recommended, including discrete infant and maternal behaviors, summative behavioral categories, and global ratings by trained observers of the quality of the interactions. Predictive validity will be enhanced further by analyzing the sequential patterns or coordination of maternal and infant behaviors.

Only by collecting information from many drug-using mothers and their infants from various socioeconomic backgrounds can factors be analyzed that are most likely to add to or detract from the optimal development of drug-exposed children.

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Discussion: Measurement Issues in the Study of Effects of Substance Abuse in Pregnancy

Claire D. Coles

INTRODUCTION

It has been fairly clear for many years that abusing substances during pregnancy leads to a higher risk for the mother, the pregnancy, and the offspring (Coles and Finnegan, unpublished manuscript). Increased use of cocaine by high-risk populations has strengthened concerns about its potential teratogenic effects because of the data generated by decades of research on heroin, methadone, alcohol, and other drugs. Consequently, greatly increased interest in the effects of cocaine use in pregnancy has generated more funds and research on the subject. There is considerable confusion about this issue due to emotional reactions by care providers, the media, and others in response to the genuine and perceived threats involved with substance abuse during gestation.

In attempting to investigate the issues of maternal addiction or drug use, the effects on pregnancy, and the short- and long-term outcomes for the child, both opportunities and problems arise. The chapters by Seiden, Bandstra, and Griffith and Freier (this volume) outline clearly the valuable knowledge to be gained by appropriate measurement of the areas of interest as well as the potential difficulties that must be circumvented. This chapter discusses sources of some hazards to accurate measurement and suggests some partial solutions.

ISSUES INVOLVING MEASUREMENT OF WOMEN USING DRUGS IN PREGNANCY

What Is the Construct Under Study?

At the present time, there is a good deal of confusion about cocaine's effects on pregnancy and the developmental outcomes for offspring. Several different

factors have become intermingled. In designing meaningful research, investigators have to decide what it is they want to measure. The first issue is whether they are going to measure only the teratogenic effects of cocaine or whether they are looking at the outcome of polydrug use. Polydrug use must be investigated since there is no population of any size to study that is using only cocaine. Nevertheless, studies continue to be proposed and reported as though the issue of exposure were simple and unambiguous. Unquestionably, it would be of great interest to isolate the effects of cocaine in the absence of confounding factors. However, this cannot be done adequately in human samples except through the use of sophisticated statistical procedures (see Ager, this volume).

A second issue is whether researchers are investigating the consequences of cocaine and other drug exposure or of associated variables such as the process of addiction or the effects of lifestyle. For example, would the same consequences occur if the drug under study were not illegal and, therefore, associated with a particularly deviant lifestyle? If cocaine could be purchased legally at the local convenience store it surely would continue to cause physical, emotional, and social damage as does its frequent associate, alcohol, but there might not be as many infants suffering the effects of sexually transmitted diseases, acquired immunodeficiency syndrome, and lack of prenatal care occasioned to some degree by their mothers' fear of being identified as substance abusers.

In deciding on the construct to be investigated it is also important to discriminate between "use" and "abuse." This distinction appears to be recognized conceptually in the investigation of alcohol. However, in dealing with illegal substances, particularly with cocaine, often there is no attempt to define what constitutes abuse, with the result that all use is assumed to be abuse, and people are lumped together into categories like "cocaine addicts" or "crack babies." Some proposals for intervention and treatment programs do not even attempt to measure impairment or addiction but assume that any baby with a urine positive for cocaine has been born to an addict who will require a protective service referral and drug treatment. Similar assumptions would not be made if the drug in question were alcohol, nicotine, or caffeine. Aside from the moral and ethical implications of this simplistic thinking, the problems in methodology and data interpretation that ensue are potentially serious with regard to social policy implications.

How Will Exposure Be Measured?

If researchers are not sure of the construct (e.g., the agent of exposure), deciding how to measure it is difficult at best. Still, it might be decided that

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interest centers on the teratogenic effects of cocaine and associated drugs, with lifestyle and addiction issues treated as confounders. But having made this decision, researchers are faced with a new set of measurement issues because there are certain rules about how to measure the effects of a teratogen (Vorhees 1986). Level of exposure (dose), timing during pregnancy, and duration are all important in determining how the offspring is affected. When dealing with legal drugs, these factors are difficult to measure even though the nature of the teratogen can be fairly well defined. That is, given that the pregnant woman will report what she was drinking or smoking, how much, and how frequently, the government can be relied on to have regulated the dose, and the exposure can be calculated. The problems that arise do so because self-report may not be reliable and because there are no biological tests that can be used to confirm self-report (Barrison et al. 1982).

However, these are only minor issues compared with those that arise when dealing with an unregulated commodity like cocaine. At the present time, there is no way, including self-report, to establish amounts used. Terms used to describe various quantities of cocaine in various forms (e.g., ball, rock, can, line) do not have specific referents in the same way that the term “ounce” does. Similarly, cocaine, like other illegal drugs, is cut to various degrees and with a variety of other substances so that the amount and kind of exposure may vary in this way also. These problems, added to the difficulties inherent in self-report, make establishing any kind of classic dose/response curve from nonlaboratory studies impossible.

Establishing Use: Some Other Problems in Measurement

There has been debate about how to identify women who are using cocaine and how to monitor use (Zuckerman et al. 1989). Advocates of urine screens and other biological measures point to the unreliability of self-report, and they may select samples based on outcome of screens of infants or postpartum women. These screens may be done on all women delivering in a particular hospital, on women in treatment programs, or on women who are considered “at risk” because they are minority women who did not receive prenatal care. The biases inherent in such approaches should be obvious (this volume, see Bracken et al.; Ostrea; Sokol et al.; Kidwell).

Advocates of self-report usually argue that the urine screen is inadequate as a measure of use since it is confined to a particular point in time and tells nothing about frequency or extent of use. They prefer to use repeated interviews of women, a process that allows evaluation of duration and extent of use over gestation (Day et al. 1985).

In a recently concluded study of the effects of cocaine and other drug exposure on neonates, Coles and colleagues (in press) used both methods of establishing use-repeated interviews of mothers and urine screens of mothers and infants. Although aware of the measurement problems discussed above, they at least hoped to establish that the infant was under the influence of the drug at the time of initial assessment and to relate that exposure to infant behavior. As table 1 indicates, even this modest hope sometimes was frustrated.

TABLE 1. *Consistency of measures of cocaine use among admitted drug users (n=79) and controls (n=39)**

Maternal Self-Report Postpartum: Use <7 days	Mother/Infant Urine Status (EMIT)†	Percent	Possible Interpretation
Negative	Both negative	56.76	• Correct
Positive	Both positive	20.34	• Correct
Negative	Both positive	12.71	• Maternal report incorrect?
Positive	Both negative	5.1	• Maternal report incorrect? • Sampling error?
Negative	Mother and infant inconsistent	2.5	• Maternal report incorrect? • Timing of sample?
Positive	Mother and infant inconsistent	2.5	• Correct? • Timing of sample?

*All control urines were negative. No false-positives noted in this group.

†EMIT=enzyme-multiplied immunoassy technique

Drug-using women and nonusing controls were interviewed postpartum and agreed to be tested using the EMIT screening test. Shown are the percentage of cases in which maternal report and outcome of urine screens were consistent or inconsistent. When the results were inconsistent there were several types of inconsistencies. In some cases both mother and infant urine outcomes were

the same, but these results did not agree with maternal report. This outcome suggests that maternal report was inaccurate. However, in other instances, maternal report agreed with one or the other of the urine outcome reports but not with the second urine screen. This outcome is harder to interpret, and it is easy to see how such an outcome might lead to inaccuracies when urine screens are used to establish maternal use or infant exposure.

Examination of table 1 suggests that although maternal report is frequently accurate, in some cases it is not. However, given the inconsistencies in outcome seen, it Is impossible to establish what factors are causing false-negative reports. In addition to inaccurate reporting, other problems may interfere with accurate results. Samples may be collected in a way that interferes with accurate analysis or may be collected at the wrong time. Finally, laboratory analysis may not be correct. In a Centers for Disease Control study conducted in a variety of laboratories, the accuracy of urine screen analyses ranged from 0 to 100 percent (Hansen et al. 1985).

Given such data, it is difficult to be confident that infants always can be classified correctly into the category “cocaine-positive,” particularly if only a single screening measure is used.

ISSUES IN THE MEASUREMENT OF THE EFFECTS OF COCAINE AND OTHER DRUG EXPOSURE ON INFANTS

In studying the effects of cocaine on infants, there are three layers of measurement issues: (1) The usual infant measurement issues are still in force, the most obvious of which is the discontinuity between neonatal outcomes and later development (McCall et al. 1972), which leads to the inability to measure constructs of interest in early infancy. This necessitates longitudinal followup and the need to measure the “system” rather than the individual. (2) Next are issues associated with measurement of teratogens and drugs of abuse in general. These include the difficulty of discriminating among the acute effects of prenatal exposures (and associated factors) and more permanent deficits and the relatively small effects of substances of abuse on infants when exposure is “moderate.” (3) Issues unique to the study of cocaine include any specific effects of the drug that can be measured and the problem of how to discriminate these effects from the “background” of other drugs and lifestyle factors. For instance, if the use of cigarettes, alcohol, and marijuana and the lack of prenatal care are all associated with low birth weight, how much of the lower birth weight usually seen in “cocaine babies” is associated with these other factors and how much with the drug under study? Will statistical means be adequate to parcel out these effects? Is enough presently known about the effects of these confounding factors to be able to establish the way in which they affect the outcome measure that will be used?

These are difficult issues and the most sensible approach at this early stage may be to arrive at a good description of what is being investigated. Of course, the ways this description will be carried out will be guided by previous observations as well as by theory. For instance, whereas it is possible to observe the cocaine-exposed infant in the neonatal period (always supposing that he or she has been identified correctly), it may be impossible at this time to discern the proportion of the child's behavior that results from acute effects of the drug vs. neurobehavioral alterations that will be associated with long-term outcomes. However, to assume permanent brain damage in these circumstances seems to be rash. Cocaine is a drug that has acute effects on the autonomic and central nervous systems. At least as a beginning hypothesis, therefore, should it not be assumed that behavioral alterations may be related to these acute effects rather than assuming long-term damage? Long-term effects only can be established by prospective followup, and such studies usually have found that neonatal tests overidentify children at risk.

Another way to exercise restraint is to avoid being misled by analogies (particularly verbal analogies). A common fallacy in this area results from the current fascination with "attention disorders." Most neonates show behavioral alterations in the newborn period as a result of exposure to any drug. Such alterations are usually apparent on the Neonatal Behavioral Assessment Scale (Brazelton 1984) and often involve orientation and motor behavior. Orientation often is described as the infant's ability to pay attention to animate and inanimate stimuli. From this observation, the assumption can be made that attention will be affected at a later time and that drug exposure underlies deficits in attention. However, there are at least two problems with this analogy. First, the infant may be reflecting the acute effects of the drug rather than long-term deficits; second, the neural systems that subsume orientation, a fairly primitive response, and the ability to sustain attention in later childhood are probably different. If the brain is sufficiently damaged, both systems may not work well, but this may be a correlation rather than a direct relationship.

Correlations are particularly seductive when experimental control is impossible. Correlation is not synonymous with causation. For instance, because a drug-using mother shows a particular response to a particular measure and the child shows another deficit on a different test does not mean one caused the other. In the absence of experimental control, there needs to be a good theoretical reason, as well as several replications of the effect, before such a relationship is interpreted as supporting evidence for causation. In addition, cross-validation is necessary. Finding a pattern of relationships in a single sample does not demonstrate that it is necessarily meaningful. The effect must be replicated in other samples.

Previous research on other substances of abuse (e.g., heroin and alcohol) has much to say to those currently working on the effects of cocaine. At least one finding has been identified consistently: Large environmental factors have major effects on postnatal development. Small factors produce few effects, which are often of short duration. Even factors like early intervention, which have clear and beneficial effects, are not persistent when the environmental changes are not maintained (Blumenthal 1989). Therefore, the investigator should find ways to take into account not only the child's status but also the nature of the significant factors in his or her environment. These include caretaking, social class, stability, social support, health, and family education, which have been shown repeatedly to have a much greater effect on the child's outcome than prenatal drug exposure (in the absence of certain very damaging circumstances) (Greene et al. 1991).

MOTHER/CHILD INTERACTION

Griffith and Freier's chapter (this volume) presents clearly the issues involved with the study of the interaction of substance-abusing mothers and their children. They discuss the constraints and the advantages of various methods of investigation of these phenomena. The authors also have identified an area that is probably of great importance in understanding the outcome of development in this group of children. Given the current status of research on cocaine, which appears to suggest that the primary problems threatening development in exposed children are preterm birth, polydrug exposure, and the postnatal environment, understanding how the process of substance abuse (in this culture and at this time) affects a woman's ability to rear her children is of great importance.

Because these issues have been so well outlined by Griffith and Freier, this chapter comments instead on some potential issues in the study of such relationships in a sample of addicted women and their children. First, it is important to avoid overinterpreting the effects of neonatal behavior on maternal response. Maternal feelings and behavior are influenced by several factors, and the maternal/infant relationship may have different dynamics in the special circumstances of addiction. Infant behavior has been shown to be a significant factor in the relationship between preterms and their mothers in middle-class samples and in disadvantaged samples. However, for the substance abuser, the infant's behavior, which may be temporary, may not be the most powerful determinant of her perceptions and attitudes. These may be much more influenced by her own feelings, her addiction process, her expectations (some of them supplied to her by the media and by health care professionals), and finally, by the nature and extent of her social support system. In research at the Human Genetics Laboratory in Atlanta, the author and colleagues have found

these factors to be much more powerful in influencing maternal perception at 30 days postpartum than the child's behavior, despite obviously aberrant infant behaviors probably related to alcohol exposure (Coles et al., unpublished manuscript).

Second, factors that influence children most are those that are consistent and continuous. Maternal behavior and specific interactions will powerfully affect the child only if the mother is the principal caretaker or an important presence for her child. If her behavior is unpredictable; if she is inconsistently present; or if she is emotionally unavailable due to her addiction process-these are all factors that must be taken into account.

Finally, in this sample of children and mothers who are under great stress, it may be necessary to adapt our thinking and the measures and methods that have proved useful with middle-class samples. Different ways of measuring or different ways of looking may have to be devised for the child growing up in a housing project who has seen gun fights, killings, and police raids, who is often unsure whether he or she will be fed, and who was born to a mother with a substance abuse problem.

CONCLUSION

It appears that researchers are at a relatively early stage In understanding the effects of cocaine on addiction; on the special treatment needs of women, in particular, pregnant women and those with children: and on infant outcome. Many questions remain to be asked, and there are several problems in forming these questions. Given this situation, it may be appropriate to consider the following:

1. Research should be directed at the appropriate level of investigation, Should investigators look at the social system, family, mother, child, organ system, or cell to find the effects of substance abuse? No single project can answer all questions, but each should develop specific questions and find measures to answer these. Researchers are still in the stage of needing good epidemiological research and adequate descriptions of and solutions to many methodological problems.

2. Given the great expense, effort, and potential risk involved with these studies, the cost and benefit of various methods to be used should be considered carefully. Should every cocaine-exposed child have a series of expensive procedures in the absence of any evidence that these produce meaningful effects? It could be argued that such procedures can wait until more descriptive studies are done and the empirical and theoretical basis is

laid. However, a counterargument also could be made that, because the cost to carry out such studies is so great, all available data should be collected.

3. Although the study of some of these issues is just beginning, a body of knowledge based on research findings already exists, and it seems appropriate to consult it in generating hypotheses and in planning methods for future work. This should be done with the rigor that is applied to any other scientific effort so that preliminary results will not be overinterpreted. For example, it was observed early in the process of clinical description that several children exposed to cocaine also had intraventricular hemorrhage (IVH). That these children were preterm and that such bleeds are common in preterm children was not emphasized. Rather, an analogy was drawn between infant bleeds and those of adults who had strokes as a result of cocaine use. Further research now suggests that the incidence of IVH does not appear to be higher in cocaine-exposed preterms than in nonexposed preterms (Karmel et al. 1990), making inappropriate the suggestion that all infants with cocaine exposure should have skull x-rays or ultrasound studies. However, as Bandstra (this volume) points out, a case can be made for investigation of some proportion of exposed infants with these procedures.

4. “Falling in love with the test” is a problem mentioned by Campbell and Stanley (1967). One also is reminded of the old saying, “To the man with a hammer, everything looks like a nail,” when, in the rush to investigate the horrible outcomes assumed to exist in children exposed to cocaine, investigators have suggested a variety of measures. However, choice of measures must depend on the problem to be studied. Just because a test or a piece of machinery exists, does not mean that this procedure will be important in the study of cocaine effects. Choice of measures should be dictated by previous research, theory, and common sense.

5. Negative effects may indeed mean something. in reference to prenatal cocaine effects on children it often is said that, “There must be something there; we just haven’t found the test that will measure it.” This may be so. However, it is important to continue to conduct investigations with the rigor that would be applied to the study of any other phenomenon and not make interpretations of outcome on faith but rather to use the methods of scientific inquiry.

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Studies of Prenatal Drug Exposure and Environmental Research Issues: The Benefits of Integrating Research Within a Treatment Program

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INTRODUCTION

During the past 20 years, a literature on the effects of prenatal drug exposure has developed. Concurrent with this growing database has been a recognition that such research is embodied within a methodological enigma. The focus of this chapter is on identifying environmental research issues that have an impact on studies investigating the effect of prenatal drug exposure. Within this context, two issues are discussed: (1) the need to ensure a scientific approach in what is a most difficult field of applied research and (2) the need to employ a model that addresses perinatal outcome within the framework of maternal disease.

SCIENTIFIC METHOD

A basic tenet of research is the necessity for it to be systematic and controlled if one is to have confidence in the data. That is to say, all variables that produce an effect must be systematically separated from the variable or variables under investigation. To separate confounding variables, an objective set of rules for gathering and evaluating information should be defined clearly. An objective set of rules demands that variables are operationalized, representative samples are obtained, extraneous variables are controlled, and the results can be replicated. Unfortunately, the most consistent feature of outcome studies investigating the effects of prenatal drug exposure is an absence of such control. The caveat that a number of confounding variables could account for the findings of a study is offered repeatedly, either as a qualification by investigators or as a criticism by reviewers. A list of potential confounding variables present in this research can be constructed easily by a review of the literature. Both between and within studies there may be variations in amount and quality of prenatal care, assessment of withdrawal

symptomotology, use of pharmacotherapy, dose and duration of drug exposure, and type of drug exposure. Often, this lack of systematic and controlled research is excused on the basis of the degree of difficulty obtaining samples within this population. Certainly, identifying and enrolling children born to drug-dependent women in a research study presents both a practical and a scientific challenge.

One of the most common approaches has been for investigators to identify potential subjects at birth through the use of routine neonatal urine toxicology screens, by urine toxicologies performed on "suspected infants," or by questioning "suspect mothers." However, the last two approaches may lead to biased samples. For example, if urine toxicologies are conducted only on infants in whom there is some indication of prenatal drug exposure, the sample may exclude infants who were exposed to drugs *in utero* but exhibited no symptomatology. Similarly, reliance on the accuracy of maternal report, especially when questions pertain to illicit drug use, may lead to a skewed sample. However, whatever procedure is used to identify subjects in a postpartum paradigm, documentation of prenatal drug use most often must rely exclusively on maternal self-report, precluding any objective measure of dose, duration, and type of drug use during pregnancy.

In the same manner, information pertaining to maternal health history obtained either by maternal report or from medical charts may be limited. Again, maternal self-report is often unreliable. And while one assumes that information from medical charts is reliable, it may not be inclusive; and, as such, necessary data may not be available. Another factor to be considered is that the amount of maternal data collected is often a function of the length of hospital stay. This constraint has several important implications. Minimum information may be obtained because there is not enough time to conduct a lengthy maternal interview; or, if extensive information is requested, maternal cooperation and consent may be jeopardized because of an inability of the interviewer to develop the necessary rapport. A lack of rapport also may affect the reliability of the data in that it may be particularly difficult to establish positive rapport among drug-dependent women within a short timeframe. A high incidence of physical and sexual abuse both as children and as adults, psychiatric comorbidity, involvement with child protective services, and involvement with the judicial system have been found among drug-dependent women. Any of these factors may impede the interviewer's ability to establish the rapport necessary for obtaining reliable information. Furthermore, if the woman has been "identified" or "labeled" as an addict, her experiences with providers within the health care system may have been negative. Pregnant drug-dependent women often receive condescending and prejudicial treatment and, thus, tend to have little trust in the system and less reason to cooperate with the system.

The punitive position reflected in the mandatory reporting regulations that exist in numerous States does little to assuage this lack of trust. Clearly, researchers who attempt to recruit a study population and obtain the wide array of information necessary to define precisely the characteristics of their sample, all within the timeframe of a 2- to 3-day postpartum hospital stay, have a most difficult task.

A number of these issues can be addressed by conducting prospective studies in which subjects are enrolled during pregnancy. Specifically, this approach provides for the opportunity to obtain data on several maternal, medical, and obstetrical variables that may be related to perinatal outcome and to obtain qualitative and quantitative data on prenatal drug exposure. However, this approach also can be limited and difficult. First, there is again the question of obtaining a sample. In this model, two criteria define the study population: pregnant and drug-dependent. If one uses the health care system and prenatal care as the vehicle to obtain a sample, the method used to identify substance abuse may affect the representativeness of the sample.

Second, if there is no integration of health care and substance abuse treatment, project attrition is likely to be high, as the amount of prenatal care received by drug-dependent women is often minimal. A lack of prenatal care is often a function of the discriminating attitude and lack of understanding of the special needs of this population present within the health care system. Furthermore, if one is investigating perinatal outcome as a function of drug exposure, a lack of prenatal care can be a significant confounding variable. An apparent solution would be to obtain study samples from drug treatment programs. However, although drug treatment programs would provide subjects that meet the drug-dependent criteria, they often do not provide for women who are pregnant. The availability of treatment programs for pregnant women is minimal. For example, Chavkin (1990), at the Columbia University School of Public Health, found that 54 percent of New York City's treatment programs excluded pregnant women.

The options available for pregnant drug-dependent women are limited because treatment programs rarely have the medical expertise necessary to provide the specialized care required by such high-risk pregnancies. Therefore, given the present litigious climate, treatment programs often choose to exclude pregnant women arbitrarily.

However, the high incidence of cocaine and crack use among pregnant women recently has precipitated a crisis among multiple service systems and has led to an increased recognition that it is essential to provide comprehensive services that address the complex needs of pregnant drug-dependent women.

Unfortunately, the increase of such comprehensive services is affected by regional and philosophical and political climates, and it is challenged by the exponential acceleration of criminal prosecution of women using illicit drugs while pregnant. While these issues may be interpreted as an esoteric discussion of a "catch-22" situation, the reality is that the research environment in which prenatal drug exposure must be conducted is indeed compromised and impeded by this circular dilemma.

THE DISEASE OF MATERNAL ADDICTION

Ambiguity also may exist in prenatal drug exposure research because outcome measures center on the infant. Most research investigating the effects of maternal substance abuse have been based on a linear teratogenic model. Variations in the patterns and timing of drug use throughout pregnancy, poor health and nutrition status, psychiatric comorbidity, high-risk behaviors, dysfunctional relationships, and physical and sexual abuse-all conditions common within the entity of maternal addiction-rarely are considered. One could argue that if addiction is defined as a chronic relapsing disease, then prenatal drug exposure research should be an attempt to determine the prognosis of the infant within the overall context of the maternal disease. For example, in a study designed to investigate the effect of maternal diabetes on pregnancy outcome, it would not be acceptable to simply identify the mother as a diabetic. All the factors pertaining to the disease, such as length of disease, ability to be controlled by diet, oral medication or insulin, medication dose, and compliance, would be just a few of the factors investigated in evaluating infant outcome. Yet, although the terminology of perinatal addiction studies is widely used, studies that evaluate the infant within the inclusive context of maternal addiction are rare.

Admittedly, employing a maternal disease model is a very difficult and complex task; and, as previously discussed, the existing research environment does not easily support such a model. The classification of addiction as a disease does not mean it has a singular biological etiology. Rather, the disease of addiction has been defined as a complex, progressive behavioral pattern having biological, psychological, medical, sociological, and behavioral components (Donovan and Marlatt 1988). As such, the effects of maternal addiction must be addressed within a multifactorial framework that takes into account all these factors.

Interestingly, within the past several years, perinatal addiction studies have been characterized by the acknowledgment (albeit usually as a disclaimer qualifying the data, as previously mentioned) that socioenvironmental factors related to maternal drug abuse may be significant factors affecting infant outcome.

It would appear that what these studies are actually identifying is the need to address perinatal outcome within the framework of the disease of maternal addiction and its concomitant effects. Clearly, it is a challenge to conduct research in this field. The issues addressed here have attempted to identify how prenatal drug exposure research is hampered by environmental constraints that only allow a narrow window through which to view the wide panorama of maternal addiction.

One of the ways to widen the window is to provide specialized comprehensive treatment programs for pregnant drug-dependent women in which research is an integral component.

THE FAMILY CENTER TREATMENT MODEL

Although several models of maternal addiction programs have been developed, differences among models usually reflect adaptations to local needs, institutional philosophies, and resources. The models contain basic components common across programs. As such, a model developed in Philadelphia at Family Center (Finnegan et al. 1991), while historically unique, includes denominators common to other programs and is presented here as an example of how research can benefit by being integrated within such a treatment program.

To promote effective addiction treatment and provide a framework for research and evaluation, Family Center has developed a treatment model that reflects a multivariable systems approach. Family Center is an outpatient voluntary program designed to provide intensive medical and psychosocial services to drug- and alcohol-dependent women who are pregnant. This multimodality treatment program endeavors to facilitate the best possible physical, psychological, and sociological outcomes for both mothers and infants.

Comprehensive medical services at Family Center include a prenatal clinic staffed by obstetricians specifically trained in the field of addiction and high-risk pregnancy. Infants exhibiting withdrawal are treated in the newborn nursery by specialists in newborn medicine.

A wide range of psychosocial services is offered. Those services comprise two components: education and treatment. The educational focus targets prenatal and parenting courses, as well as acquired immunodeficiency syndrome (AIDS) prevention counseling. Treatment aims are directed at developing personal resources, improving family and interpersonal relationships, reducing and eliminating socially destructive behavior, and facilitating the parent/child bond.

In addition to their substance abuse, women are often weakened by unemployment, illiteracy, homelessness, and legal issues. The Family Center treatment model is designed to respond to each of the medical and social variables that complicate addiction and recovery through the following components.

Outreach

Outreach services should be an integral part of any treatment approach. Utilizing workers who are indigenous to the neighborhoods and the culture of the women facilitates an overall understanding of the impact of diversity in treatment. Indigenous workers can serve as a conduit between addicted women and a treatment facility. This can be particularly helpful in facilitating appropriate medical care for pregnant substance abusers, who often do not seek prenatal care.

Because the women are poorly nourished, they are frequently deficient in vitamins, such as vitamin C (associated with nicotine smoking) and the B vitamins (associated with cocaine use). In addition, iron deficiency anemia and folic acid deficiency anemia occur during pregnancy. The frequent use of needles contributes to increased medical complications such as abscesses, ulcers, thrombophlebitis, bacterial endocarditis, hepatitis, and urinary tract infection. Sexually transmitted diseases such as gonorrhea, syphilis, herpes, and AIDS are common.

Due to the lack of prenatal care in women who are drug-dependent, fetal wastage is common, either secondary to early spontaneous abortion or later intrauterine death. The fetuses frequently are born prematurely and/or suffer from intrauterine growth retardation. The reasons for poor fetal growth are multifactorial and include intermittent intrauterine hypoxia, placental insufficiency, and intermittent drug withdrawal of the mother and the fetus leading to a need for more oxygen, The last problem is frequently complicated by the concomitant use of other drugs, such as nicotine and cocaine, which also decreases the oxygen supply.

The most common obstetrical complications in drug-dependent women who have no prenatal care are preterm birth and low birth weight. Therefore, infants may have all the complications of either intrauterine growth retardation or premature birth, which include respiratory distress syndrome, hypoglycemia, hypocalcemia, intracranial hemorrhage, hyperbilirubinemia, and infection. If the infants are born at term, they may have pneumonia or meconium aspiration syndrome.

If the maternal drug use includes opiates, neonatal withdrawal may occur. Significant withdrawal symptoms are seen in about 60 percent of the infants. These symptoms include central nervous system hyperirritability such as hypertonia, increased Moro reflex, tremors, increased deep tendon reflexes, and high-pitched cry. The infants have an exaggerated rooting reflex, yet their sucking and swallowing reflexes are ineffectual and uncoordinated. In addition, mottling, fever, rapid respiration, and sweating occur. Appropriate assessment and rapid treatment are essential so that the infants may recover without incident (Finnegan 1986).

Methadone maintenance has proven to be efficacious in the treatment of pregnant opiate-dependent women, Aside from the previously mentioned incidence of withdrawal symptoms in the neonate, other complications as a result of the medication usually do not occur. Methadone, used appropriately and coupled with comprehensive care, can decrease the complications of pregnancy, childbirth, and infant development (Connaughton et al. 1977; Silver et al. 1987).

Medical services for pregnant drug-dependent women must encompass the perinatal, pharmacological, medical education, and referral components. The perinatal services encompass care provided by a perinatalogist and a perinatal nurse clinician. Antenatal testing is performed. Counseling and testing for human immunodeficiency virus and nutritional counseling are provided. The mother should deliver in a hospital where emergency services are readily available in case complications occur in either the mother or the child. Since the infants are frequently small, many of them may need intensive care.

If the pregnant woman has any specific medical complications, such as hyperthyroidism or diabetes, appropriate medical consultation should be obtained. Additionally, due to the impoverished conditions in which many of the women live, many medical complications occur. By taking a good family history, one can frequently ascertain the background of the patient, which may lead to a clearer understanding of the addictive process in this woman. Therefore, the team also must deal with providing an appropriate environment so that the woman may stay in a healthy physical and psychological state.

Social/Demographic

Because of the many social problems associated with the women at Family Center, it is usually necessary to attend to these needs over several months before staff can focus on the psychological/behavioral/cognitive component. If housing, clothing, and food issues are unattended, the women rarely respond to drug treatment. When consistent provision for shelter, clothing, and food is made, dramatic increases in initial recovery occur.

Over the years, the Family Center staff has developed a network of agencies that assist in the area of housing. Even with existing liaisons, large amounts of staff time are necessary to obtain appropriate shelter for the women.

Family Center maintains a clothing bank for women and children. A more progressive plan is to have a small shop area and have members of the recovery group oversee the operation, as well as generate donations and sort, wash, and tag clothing.

The outpatient facility also has included a small food bank that consists of cereal, soups, crackers, peanut butter, infant formula, and regular milk. It is not unusual for pregnant addicts to appear at Family Center without having eaten for several days. In addition to food, bus and subway tokens are provided for transportation. The combination of a nourishing meal and a way to return to Family Center encourages attendance.

Cultural/Gender Sensitivity. Treatment approaches have been modified to account for gender-, race-, and culture-specific issues. In women-only groups, Medical Assistance recipients may feel threatened if the group is socioeconomically diverse. If the groups are sexually mixed, addicted women will not communicate with and tend to defer to the men in the group; the high incidence of sexual and physical abuse in drug-dependent women may contribute to difficulties in relating to men.

Therefore, Family Center presently operates women-only groups. The women express their fears and frustrations without fear of male retaliation. The participants make the rules of the group, and the staff members serve as facilitators only. These groups have been extremely successful in encouraging the members to work out individual and interpersonal issues in a supportive environment.

Treatment effectiveness is drastically reduced or impeded without a thorough understanding of the interaction between social, cultural, and demographic variables.

Psychological/Behavioral/Cognitive

Sobriety is only the initial step in the recovery, process. Behaviors related to drug intake are altered, but to remain in recovery, other behaviors must be modified.

Many times, the women remain developmentally at the age level of first drug use. This can interfere with traditional expectations of educational, cognitive,

psychological, and vocational levels. The Family Center model assesses and determines exactly at what level the woman is functioning. The woman is assigned developmentally appropriate tasks to expedite cognitive development delayed by long-term drug use.

Coping mechanisms are assessed and carefully monitored. Quite often, when drug-seeking behaviors are modified, there are no other coping mechanisms present. This requires intensive staff time to create and support tasks that promote the necessary mechanisms.

Education often is used by the staff to assist in the promotion of self-esteem. Classes for prenatal care, parenting, and child and adult development contribute to an understanding of the process of physical and mental growth.

When the women have negotiated the developmental tasks described above, they are ready for treatment regarding the issues of sexual abuse, physical abuse, intimacy, and introspection, as well as feelings and associations that trigger drug use. The Family Center model allows for differences in the woman's development and for variations in cognitive, psychological, and behavioral abilities.

Mother-Infant Interaction

Infants born to drug-dependent women often are subject to double jeopardy (i.e., biological risk and a mother with few parenting skills). It is imperative, therefore, that maternal addiction programs include strategies designed to facilitate positive mother-infant interactions. At the birth of an infant, the mother should be assisted in getting to know her infant and the infant's unique behavioral characteristics, Specific care-giving strategies for each dyad can be developed by educating the mother about the competencies and needs of her infant and by teaching comforting techniques and how to interact with her infant in a positive, responsive manner. This type of intervention is essential because infants exposed to drugs *in utero* tend to be difficult to feed; have a poor sucking reflex, a high-pitched cry, and a rigid muscle response; and are often irritable and difficult to console. They may have limited tolerance for sensory stimulation. Without intervention, mothers who have limited caregiving skills and resources are attempting to parent infants who are difficult to care for and who provide little positive reinforcement (Kaltenbach and Finnegan 1988).

Newborn care and feeding techniques should be taught upon discharge. Home visits also should be made to facilitate caregiving needs in relation to environmental realities,

Early Childhood Development

The Parent/Child Center provides an early education intervention program for both mothers and children. The primary focus of the center is on developing and enhancing positive, responsive parenting skills to promote optimal development of the children,

A children's program, directed by an early childhood specialist, provides a stimulating, responsive, and supportive environment for the children. Mothers and infants are expected to attend the Parent/Child Center biweekly. Videotaping is an important component in the development of responsive parenting during the first 3 months of the infant's life. The tapes can be used as therapeutic intervention by discussing the meaning of the infant behaviors, the maternal responsiveness to infant cues, and the effect of the mother's action on infant behaviors. After 3 months postpartum, the videotaping should focus on mother and infant interacting in play and caretaking behaviors. The meaning of certain infant behaviors, the mother's perception of the situation, and the effects of the mother's actions on the infant should be discussed (Fitzgerald et al. 1990).

Weekly parent education groups also should be conducted. These groups focus on the basic developmental milestones of growth and development. Drug-dependent women often have limited knowledge of the basic milestones of behavior and, therefore, unrealistic behavioral expectations of their children. This lack of knowledge, which may contribute to the incidence of child abuse among drug-dependent women, is a risk factor that can be reduced significantly with intervention.

Learning to set limits and practice appropriate discipline are also important components of parent education. Addicted women tend to have very low frustration tolerance; although this may foster abuse, conversely, it also may result in an inconsistent pattern of responses to children's behaviors in which no appropriate limits are set. Since they have difficulty perceiving themselves as capable of changing their own actions, the mothers often cannot see themselves as agents of change in the lives of their children, except by physical punishment. Thus, the behavioral problems often reported in preschool and school-age children of drug-dependent women may be a reflection of childrearing practices that are related to maternal addiction.

CONCLUSION

Environmental issues are key in accomplishing research in the perinatal patient when drug exposure is a complication. The benefit of integrating research

within a treatment program clearly can be justified and, in most cases, will enhance the quality of the research as well as satisfy ethical issues in this population.

Integration of this research within a treatment program will (1) permit the research to be more systematically accomplished and controlled; (2) permit more accurate evaluation of ongoing drug exposure by way of urine toxicologies and permit the establishment of rapport to obtain additional historical and, in some instances, extremely sensitive information; (3) permit identification and treatment of disease entities that may confound the outcome data; and (4) permit counseling regarding social and legal variables that prohibit compliance with research protocols.

Finally, the women and children in this study population are often disadvantaged from a medical, psychological, and social standpoint. It is the researchers' responsibility while seeking answers to research questions to provide the women with compassion, respect, and an environment that will enhance their recovery from addiction to drugs, as well as to assist them in ensuring the best possible intrauterine milieu for their unborn babies.

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How the Environment Affects Research on Prenatal Drug Exposure: The Laboratory and the Community

Claire D. Coles

INTRODUCTION

Study of the effects of substance abuse on women of childbearing age, pregnancy, pregnancy outcome, and child development must be carried out in clinical settings and in the community-in treatment centers, prenatal clinics, hospitals, well-baby clinics, social welfare agencies, child care and school settings, and the homes of the research participants. Undertaking work in these areas is enormously rewarding and provides ecologically valid data that cannot be gathered in any other way. However, these environments influence the way in which research must be carried out-the populations that can be studied, the questions that can be asked, and the methods that must be used. This chapter examines several aspects of these environments. In addition, some suggestions are made for dealing with challenges raised by working in these real world situations.

Although this chapter focuses on environments associated with collection of data on outcomes of substance abuse during pregnancy, it would be one-sided to suggest that only in the clinic, the housing project, or the crack house are there environmental and sociocultural factors that affect the planning and execution of research. The investigator's environment and the relationships between that environment and that of the substance abuser also affect the research process. The current scientific or research milieu will direct the investigator toward a particular question. Available resources will decide whether a particular project can be carried out. The latest test or a favorite methodology will direct the data to be collected. Experimenter preconceptions or unintentional biases (Rosenthal 1967) as well as scientific theories (Kuhn 1970) will affect all aspects of the research process from the formation of the problem to the interpretation and publication of the results (Koren et al. 1989).

Examination of the effects of substance use in pregnancy often is associated with emotional reactivity because it involves attitudes about race, social class, and women's rights as well as current concerns about drug abuse. Therefore, researchers have to be scrupulous in dealing with these issues to limit the extent to which studies will be biased by reactions to them.

The investigator touches the substance abuser's world at a few points only. Since the investigator's goal is to locate a population to study and/or to find subjects for longitudinal followup, these points of contact are, typically, medical settings, drug treatment agencies, and the homes of participants.

THE CLINICAL ENVIRONMENT: WORKING IN SOMEONE ELSE'S SYSTEM

The research protocol usually requires that many pregnant women be screened for substance abuse and other factors and that their infants be examined in the neonatal period to determine if they are affected by exposure. Therefore, the investigator must have access to sites where pregnant women can be recruited and where infants can be examined and medical records screened. The population must be sufficiently large and of such a character that the sample collected will be representative and will have a probability of exhibiting the effects, if these exist, of the putative teratogen.

Although in theory such a population could be collected at many sites, in practice such sites are limited and often related in systematic ways to social class and access to resources. Pregnant middle-class women use private physicians and health maintenance organizations. Although it would be desirable to conduct research in such settings, physicians or clinics may not have caseloads large enough or heterogenous enough to allow generalization, and due to concerns about legal and financial issues, they may not be willing to allow research to be conducted. They also may be concerned about the disruption of routine or loss of confidentiality that even well-conducted research may entail. It is probably not a coincidence that the majority of studies, therefore, are carried out among poor women who are accessible through teaching and charity hospitals and who are unlikely to object to research protocols. These factors can result in a biasing of studies toward poor and minority populations

Unless the investigators are part of the administrative hierarchy where research will be carried out, they will arrive as "outsiders." Hospitals, clinics, school systems, and other places where suitable populations of women and children can be found are often cooperative with research plans when they have had positive experiences in the past with such projects or are unfamiliar with the demands of research. They tend to be less cooperative when severely

stressed, when they have had negative experiences with past research, or when they are interested in conducting similar research of their own.

Situations confronting researchers in such settings have been well documented in the literature on program evaluation and community psychology (Anderson and Ball 1978; Datta 1978; Trickett 1984). This literature provides many suggestions for dealing with environmentally based problems that may arise. Many of these problems have a common source; that is, the considerations and constraints of the research process may come into conflict with, or be seen as coming into conflict with, other institutional functions (Lorion et al. 1988). Although most clinical staff members understand that research is important, particularly in areas such as the effects of cocaine in pregnancy, they often have difficulty dealing with the day-to-day activities associated with the process. Some of the systemic obstacles common in research on substance abuse and pregnancy are discussed below.

Systemic Obstacles

Stress Due to Clinical Considerations. Many settings where the effects of substance abuse in pregnancy are investigated are already stressful. For instance, a common setting is the neonatal intensive care unit of an inner-city hospital that often is understaffed and oversupplied with patients. Staff in such units deal with infants at high risk for mortality, multiple illness, and the prognosis of poor, long-term outcome. The additional risks associated with or perceived to be associated with maternal substance abuse may lead to emotional reactions (Good et al. 1990) that can affect cooperation with a research protocol.

Another common setting may be a publicly funded alcohol and other drug treatment program that has 10 treatment slots for pregnant women and a waiting list of several hundred. Staff may be struggling with reactions to legal pressures, medical emergencies, acquired immunodeficiency syndrome (AIDS), and child abuse as well as depressed and suicidal women. As a result, they may view the researcher, checklist in hand, as an annoyance at best or, at worst, as a frivolity that is draining away funds that could be used more effectively in extended clinical services (D. Carson, personal communication, 1990).

Competition for Resources. Competition has many sources. Pressure to publish and to attract funds is likely to produce competition even within a single institution, Even in the absence of such pressures, competition for available resources, including space, assistants, and computer time, may interfere with carrying out a particular research effort. When a topic of research is of interest

to many departments within a hospital (e.g., cocaine abuse), there may be competition for research subjects with particular characteristics (e.g., AIDS cases) (J.V. Brown, personal communication, 1989).

Participation in Goals. If the clinic staff is in concert with the goals of the research or see some benefit to themselves or their patients/clients, cooperation is more likely (Lorion et al. 1987). Coulter and colleagues (1985) reported gaining cooperation for a study of sexually abused children in the face of considerable skepticism by adapting research procedures to the perceived needs of the social agency and by providing services that the agency lacked. These services included psychological evaluation of children and expert witness testimony in custody proceedings even though both procedures added considerably to the time demands on the research staff.

If such cooperation is not possible or is constrained by the design of the experiment, protocols should be arranged, staff trained, and methods planned that cause as little disruption as possible and that are unobtrusive. Because people are more likely to be sympathetic to research they understand and support, other methods for improving cooperation include providing inservice and educational materials to staff, engaging staff in planning the goals of the research, and providing feedback about outcomes on a periodic basis (Lorion et al. 1987).

Increasing Staff Work Loads. In many settings, staff members already are stressed and overburdened from dealing with a difficult client population, making it unlikely that research procedures requiring extra work by the treatment staff will be successful. Similarly, it is unwise to rely on hospital or agency staff to carry out experimental procedures reliably or consistently unless research staff can provide supervision. If extensive work is to be done at a particular site, it is important to hire a staff person who works onsite and who has experience working in such settings.

System Change. Any social system will resist change (Kuhn 1974). However, systems that are under stress or in which personnel are dealing with emotionally difficult issues may become more rigid and resistant to change. Therefore, research procedures that are introduced should be as consistent as possible with the existing system and should involve as little inconvenience as can be arranged. Research personnel who are seen as outsiders and procedures that make extensive demands on an ongoing system are unlikely to be successful.

EFFECTS OF THE PHYSICAL ENVIRONMENT

Where you are affects what you can do. Many of the settings where low-income, substance-abusing women and their children are seen are publicly funded and are often old, inadequate, and overcrowded. As a result, the investigator often has to "make do" by accommodating research ideals to practical realities.

Although confidentiality considerations and common decency prevent interviewing a prospective research subject in the hall or in front of other patients, there may not be a room in a crowded prenatal clinic or postnatal ward that can be dedicated to research, where materials can be left, and privacy can be ensured. The ideal research protocol may have to be adjusted accordingly. This might mean collecting data during obstetrical rounds when residents are absent, leaving examination rooms available to conduct interviews, or negotiating with colleagues to use their offices on a part-time basis. It also may mean that lengthy interviews will have to be conducted during home or laboratory visits to ensure privacy and reliability.

Similarly, although it is desirable that all neonates be evaluated the same number of hours after birth, timing and hospital routine may interfere with scientific rigor. The confusion and disruption of morning pediatric rounds may prevent data collection, particularly if medical residents are not cooperative with the research protocols. Therefore, it may be necessary for infants to be tested only in the early afternoon when quiet spaces are available.

Even such seemingly irrelevant factors as the location of parking lots may affect the research protocol. For practical as well as experimental reasons, evening hours are most desirable for observation of sleep patterns in neonates. However, in a recent study of cocaine-exposed infants (Coles et al. 1991), research assistants, who were predominantly female, objected to evening hours because it was not safe to walk to unguarded parking lots near the hospital. Since morning hours were occupied with pediatric rounds and early afternoon hours with physical and behavioral examinations, arrangements had to be made to have hospital security guards accompany women to their cars. This problem became more acute after several assaults and shootings occurred within the hospital.

THE COMMUNITY: WORKING IN THE FIELD

Many factors related to the nature of development and the specific effects of substance abuse (Coles et al. 1987) make longitudinal followup necessary and an understanding of the social/cultural and physical environment important.

In the best of circumstances, longitudinal research is expensive and difficult. It has special methodological problems, like attrition and historical changes, that can threaten the validity of the data (Campbell and Stanley 1966), and it requires a large staff who are persistent in their dedication to the project. The socially disadvantaged women most often focused on in research on substance abuse are probably least compliant with the goals of longitudinal research. Also, such research has to be carried out in environments that are difficult for the researcher to work in for a variety of reasons. When problems associated with substance abuse are added, such research can be daunting to the well-informed investigator. The effects of some of these obstacles in practical terms are (1) the need to account for environmental effects on outcomes; (2) limitations on the types of procedures that can be carried out in such settings: (3) difficulty in locating and following subjects due to effects of social class, poverty, and substance abuse; (4) misunderstanding between research subjects and staff due to cultural and educational differences; and (5) personnel problems, including staff safety and staff burnout due to social and environmental conditions.

Effects of Special Physical and Social/Cultural Circumstances

The serious social problems associated with being poor, female, and of minority status in the United States in the 1990s have received great attention and do not need to be reexamined in detail here. However, it is in populations of this kind that the majority of the studies of the effects of prenatal drug exposure are being conducted. This situation has serious implications for the investigator. A few statistics will be provided to suggest the extent to which environmental effects must be taken into consideration.

In Atlanta, the population under investigation has many problems known to be related to developmental outcome among children (table 1). There is only one hospital that regularly provides prenatal and delivery services to the indigent. Although there is a range of income levels among patients, the majority of people served are black (89 percent), poor, and eligible for Medicaid (unpublished data, Parents/Infants Resource Center, 1990). Many women live in subsidized housing, which is the location of much of the drug-related activity in the city.

In Georgia in 1988 (the most recent year for which statistics were available), among black women, the infant mortality rate was 19.5 per 1,000, somewhat higher than in many Third World countries (Hughes et al. 1989) and approximately twice that of white women (L. Dismukes, personal communication, 1990). Low birth weight and prematurity are more common among the disadvantaged as well. Incidence of black infants weighing less

TABLE 1. *Average characteristics of prenatal drug exposure study sample(s) in Atlanta, 1980-1990**

Maternal Characteristics	Users of Alcohol/Other Drugs	Controls
Average age (years)	27	24
Race		
Black	93%	89 and 91%
White	7%	9 and 11%
Education (years)	10.3-12.1	11.5-12.5
Married	18%	40-50%
Parity (number of dependents)	2.5-3.6	1.9-2.5
Monthly income	$200-$600	$250-$800
Slosson IQ[†]	72	76

*These are averaged over several samples. Particular subsamples may vary.

[†]SOURCE: Coles et al. 1991

than 1,500 g (very low birth weight) was 2.7 percent for Georgia but was 5.5 percent for the city of Atlanta. This is in comparison with white infants for whom the equivalent figures were 1.0 and 1.9 percent, respectively (L. Dismukes, personal communication, 1990).

Table 1 indicates the average characteristics of prenatal drug study samples in Atlanta over the past decade by drug use status. In the samples studied, the mean educational level among alcohol and other drug users was reported to be around 11th grade, but reading tests in this population indicated a mastery of 5th grade skills only (unpublished data, Parent/Infant Resource Center, 1990). Intelligence testing of a subsample using standardized tests (which are probably biased against this group of people) indicated a mean intelligence quotient (IQ) of less than 80 (Coles et al. 1990).

In 1990, the Georgia Department of Family and Children's services reported that some kind of substance abuse was associated with 50 to 60 percent of all reports of abuse and neglect made to protective services (Neims 1990). Social services, including foster care, Project Head Start, medical and psychological services, alcohol and other drug treatment, and programs for children with developmental delays, are either overcrowded or unavailable (Hansen 1989).

In 1989, the Atlanta Police Department (Huguley 1989) reported that drug-related crimes had increased significantly over the past 5 years (table 2) and

TABLE 2. *Increase in illegal drug activity in Atlanta, 1982-1988*

Drug-Related Crimes	1982 N	1985 N	1987 N	1988 N
Drug-related arrests (% change)	3,295	3,077 (-7)	4,721 (+53)	6,898 (+46)
Arrests for cocaine possession (% change)	276	395 (+43)	1,268 (+221)	3,450 (+172)
Value of drug seizures by narcotics unit (% change)	$518,243	$408,006 (-21)	$1,117,426 (+17)	$2,057,548 (+84)

SOURCE: Huguley 1969

that 12 percent of all homicides were drug-related, with most of them occurring in low-income areas, frequently in the same housing projects where the women in the study samples live. Given these factors, it is incumbent on the investigators who work with such a population to take into account the consequences of crime, poverty, and racism.

Several strategies can be attempted to deal with the experimental consequences of these problems, including matching subjects or samples as well as using statistical controls. However, it is unlikely that all such factors can be "controlled" adequately or that the effect of all these negative elements can be completely eliminated. Investigators should be constantly aware of these issues and must remember that it will be difficult to overestimate the effects on outcome. The safest procedure will be to document as fully as possible the environmental factors that may be related to outcomes of interest and to examine their interactions with the perceived effects of drug exposure.

Some Effects of Poverty and Limitations on Services. Limitations on resources experienced by the population under study affect the research outcome. Women may not have had adequate prenatal care and may have been unable to find treatment for their substance abuse. These factors may have affected the outcome of pregnancy through a higher incidence of preterm birth, low birth weight, and other factors.

Postnatal services for children with special needs are limited and hard to access. Even when investigators identify problems and make treatment referrals, children may not be served (Neims 1990). In many cases,

researchers are in the position of observers who note problems, are aware of potential solutions, but are unable to effect any changes in the situation even though they may be mandated to report such things as child abuse. This situation leads to secondary effects on the research staff who are often upset and discouraged with their lack of ability to help people with whom they have become involved. An argument could be made that the investigators, as observers, should not attempt to intervene in this fashion. However, this attitude is difficult to maintain in the face of extreme need.

Limitations on Procedures

Although the scrupulous researcher will want to assess environmental factors carefully to ensure that there are no differences between contrast and experimental groups and to provide information about the extent and power of what differences do exist, the realities may limit the kinds of questions that may be asked. Experimental procedures that are useful in middle-class samples may lose their significance in samples that are overwhelmed by negative social factors. In addition, the particular constraints resulting from environmental factors may vary from location to location or among different ethnic and social groups.

It is obvious that the limited reading and educational levels of many research participants require that all questionnaires be read to participants and that interview methods include ascertaining the women's ability to understand the questions asked. All research instruments and procedures have to be selected and pretested with these limitations in mind. Questionnaires cannot be sent out to be completed independently; they must be read to participants. Mothers cannot be asked to keep logs of infant behavior or to use many currently available materials on child development or parenting.

Another difficulty occurs due to mothers' limited financial resources. Most study participants do not have access to cars and must travel by bus. Therefore, women cannot be asked to travel by themselves to the laboratory to keep appointments. They either must be transported or the investigators must go to them. Because child care is hard to arrange, siblings often must accompany mother and infant anywhere they go. During data collection, some provision must be made for these other children.

Even if a home visit is made, certain kinds of procedures are inappropriate or impossible where space is limited or the area is dangerous. For instance, although it is sometimes possible to conduct confidential interviews in the home, in other cases no private place is available to the mother who may not want to discuss her substance abuse history or current use in front of children or other

family members. When children are being tested it may be impossible to do tests in a standardized way if there is no place available that is not subject to interruptions by siblings or television noise. The experimenters who are not cognizant of these issues will find their data invalid or unreliable.

Another problem arises when the investigator would like to perform procedures that involve equipment. For instance, if a higher incidence of sudden infant death syndrome is suspected, it might be interesting to monitor infants' physiological processes over the first few months of life. However, provision of apnea monitors or similar expensive equipment in homes of substance abusers where educational level is low and need for money high is likely to be unsuccessful. Similarly, it is probably unwise, in the current climate, to take expensive and easily resalable video equipment into drug abusers' homes. Therefore, although it would be interesting and probably informative to videotape patterns of mother-child interaction (for example) in the home environment, it would probably also be dangerous. More examples could be given, but the basic point is obvious. The social and physical circumstances of the research participants directly affect the choice of procedures and instruments, and such decisions determine what data can be collected.

Finally, when research is undertaken in an area where there are strongly held and perhaps unexamined beliefs, the potential for experimenter bias is particularly great. Goldberg (1979) discusses how this tendency plays out in longitudinal research on human development. Repeated assessment of infants in a nonlaboratory environment where neither blindness nor strict protocols may be maintained is an invitation to unconscious bias on the part of data collectors as well as for research participants to be "helpful" in providing the most desirable data (Orne 1962).

Subject Recruitment and Retention

Subject recruitment and retention is a matter of great concern in longitudinal research. Unfortunately, motivation to enter into and participate in research probably is limited among minority women of low socioeconomic status who are abusing illegal substances. In addition to providing financial incentives (Capaldi and Patterson 1967) and social and medical services (Thomas and Chess 1987) to the research participants, among the most effective ways of maintaining the sample are frequent contacts by telephone, letter, and home visits (Goldberg 1979). However, many poor women do not have telephones, and others live primarily with relatives and may move frequently. This problem is even more acute among women who are abusing illegal substances. Such women may be involved with illegal activities or involved with men who are. They may live in crack houses. Also, they may be homeless due to

disagreements with family and friends about their behavior. In such circumstances, interest in participating in a research study may be low, and there may be considerable suspicion regarding the motives of the research team who can be seen as agents of social service agencies, This last problem has become acute lately due to the increased threat of arrest of women who are identified as using cocaine in pregnancy (R. Moeti, personal communication, 1990).

Given these conditions, it is amazing that most women who are approached do agree to participate and will sign an informed consent (Smith et al. 1987). Among the populations studied in this research, however, recruitment does not guarantee retention, and noncompliance with followup is common. Either women cannot be located or do not respond to appeals to return for followup. In addition, on some occasions when they can be found and do agree to be retested, they will fail to comply, usually by not keeping the appointment or not answering the door if a home visit is made. This behavior is frustrating to the research staff who have a strong investment in maintaining the sample and resent "wasting" their time. Sometimes staff have difficulty understanding why a woman agreed to followup if she did not mean to cooperate. However, it is common in Georgia, at least, for minority women to act in a compliant manner when talking to people who seem to represent authority. They usually will not say no to a direct request but often will indicate their lack of willingness to participate by missing appointments, refusing to return calls, and so on (M. Foster, personal communication, 1990).

This "misunderstanding" is a good example of the conflict in customs and values that can occur between research staff and subjects. The majority of the subjects in such research probably have a limited understanding of the researchers' purposes as well as many more urgent concerns of their own. Therefore, since they do not place the same value on research as do the investigators, they are most likely to continue in the project if they see some value in this for themselves or for their children, Otherwise, they have little reason to comply with the generally intrusive, boring, or annoying procedures.

There are several ways to handle these problems including treating research participants with respect, providing monetary and other incentives, establishing an ongoing relationship, and ensuring adequate funding to be able to carry out these procedures, Finally, it is important for investigators and staff to be aware of factors that interfere with followup.

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Cultural and Other Possible Sources of Misunderstanding

Characteristics of the Investigators. Unlike the populations described above, the majority of people who conduct research are middle class, well educated, and do very well on standardized tests. When they begin research on substance abuse or child development among the poor, many researchers have little experience with or understanding of the population they will be studying. Although usually sympathetic, they often have life experiences and values different from those of research participants. These factors make it important that investigators are sensitive to the effects of these different cultural, social, and physical environmental factors.

There are many potential sources of misunderstanding between these two groups of people. Like most laypersons, the research participants may misinterpret the meaning of the sometimes esoteric experimental procedures to which they or their children are exposed. They may believe that test outcomes are more significant than they actually are. For instance, if they are anxious that the child has been harmed by their prenatal substance abuse, mothers may interpret the examiner's comforting or concerned remarks as more meaningful or predictive than they actually are.

On the other hand, investigative staff may not understand some aspects of the behavior of research participants or may find aspects of their lifestyles upsetting. Local dialects or idioms may be hard to interpret or may prevent subjects from understanding questions. Research staff members who are asked to sit on a tattered couch in a room in which cockroaches are visible scurrying up walls may exhibit distaste that will affect subsequent cooperation by their hostess.

Personnel and Safety Considerations

It may be dangerous for research staff to go to the homes of drug abusers, and many people feel concerned when asked to do so. However, the majority of home visits will be carried out without any problems. In several longitudinal research projects carried out in Atlanta in the past 10 years, participants, including alcoholics, drug abusers, persons with schizophrenia, depressed women, and contrast group members have been almost universally pleasant in welcoming a variety of research staff, questionnaires, tape recorders, and other paraphernalia into their homes.

Nevertheless, the circumstances place certain restraints on procedures that can be conducted. For instance, as discussed later in this chapter, safety concerns affect staffing patterns and training, which, in turn, affect research costs.

Consideration of the potential dangers in the environment also affect the kinds of procedures that will be possible. If followup is planned, home visits of some kind are inevitable with this population. Researchers have devised a variety of methods to deal with the potential problems of visiting drug users' homes, including sending a cab or university car with driver to the woman's home to pick her up, sending staff out in pairs in cars with State emblems on the side, hiring off-duty policemen to accompany research workers to homes, and hiring recovering drug users from the same neighborhoods to make contacts. Although these are all reasonable solutions, each has particular potential consequences for the data collection procedure and the possibility of future contacts with the family, and these should be taken into consideration.

COPING WITH THE EFFECTS OF THE ENVIRONMENT ON RESEARCH

This brief overview of some of the effects of environment on the study of the consequences of prenatal substance abuse may sound somewhat daunting. However, despite these problems, there are many ways in which the investigator can cope. Although there are real limitations on research methods, collection of valid and reliable data and understanding of outcomes can be facilitated by understanding the situation and planning ahead, selecting and training staff, taking safety precautions, monitoring the research process, and responding in a flexible way when necessary.

Understanding the Problems

The study of a new issue or area, particularly when it involves several real world problems, must be undertaken with respect. Even for the person experienced in the field, new situations arise. For instance, with the recent increase in cocaine use, there were significant changes in the working environments with which many investigators thought themselves familiar. Home visiting, which had always been dangerous, became more dangerous. Followup over time, which had been difficult, became impossible in some instances. Addicts exhibited behavior changes consistent with alterations in drug use, and these changes were potentially related to effects on infant development.

For these reasons, it is important for those undertaking work in this area to have a thorough knowledge of the issues at both intellectual and practical levels. Since the issues of substance abuse and child development encompass several areas of specialization in medicine as well as the biological, behavioral, and social sciences, the careful researcher will recruit appropriate colleagues to contribute to the effort. For the obstetrician or developmental specialist, this probably will involve working with professionals experienced in treating substance abusers. For the alcohol or other drug treatment specialist, this will

involve finding an expert in high-risk infancy and/or a sociologist to avoid the error of attributing all developmental problems to the teratogenic effects of the drug.

Investigators also can avoid many errors in planning and execution by examining the experience of previous workers in the same or similar areas. Although this sounds simple (equivalent to researching the literature), it is apparent that many people who are presently undertaking the study of the effects of cocaine in pregnancy have omitted the obvious step of reading the work of those who carried out very similar studies on infants of women who abused other substances such as heroin and alcohol, thus putting themselves in the position of "trying to reinvent the wheel."

Staff Selection and Training and Safety Considerations

Staff should be selected and trained with consideration of the work that will have to be done, the sites where it will be conducted, and the population involved. It is probably not wise to plan to employ only white, middle-class college students to interview low-income minority women because this discrepancy could raise many cultural issues that might interfere with adequate data collection. The extent to which the protocol requires rapport to be established to gain confidential information should suggest the kinds of experience needed by staff in a particular position. Similarly, if home visiting is required, persons who will do this should be comfortable in this role not only for their own sakes but also to put the research subject at ease.

However, although it is necessary to be attentive to cultural and ethnic issues, it is important that this be done in a sensitive way. It is not appropriate, for instance, to assume that because an individual is black that he or she will necessarily be knowledgeable about the behavior and experience of low-income black women who are abusing drugs. Nor should it be assumed that an educated white male will necessarily be insensitive, inept, or out of place in such a role. More important than people's social and ethnic backgrounds are their attitudes, their social and professional skills, and their experience.

Staff should be trained thoroughly in the administration of all materials, in methods for making research participants feel comfortable and respected, and also in methods for maintaining their own physical and emotional safety. In Atlanta, the author and colleagues at the Human Genetics Laboratory first informally and then formally established several safety rules (appendix) that are discussed with all staff persons before they are allowed to go into the field.

For instance, the research directors do not allow anyone to make a home visit alone; information about staff travel plans as well as information adequate for tracing them is left with office personnel before each trip. Staff are required to report back to the office before leaving for the day so that their whereabouts are known, and the office is not closed until all staff have returned.

In the field, staff are instructed not to enter areas where they have reason to believe that they may be in danger. They are encouraged to dress modestly and not to carry large sums of money. Following a particularly unsettling incident, it was decided that home visitors should never decide in the field to go to another site where they could not be located.

Emotional well-being is also a concern because dealing with high-risk populations, even when only collecting data, can be stressful. Not only can it lead to emotional distress and burnout, but it can be associated with inaccurate data collection. After some experience, the author and colleagues began screening staff applicants carefully to ensure that they would be comfortable in the sometimes difficult environments they would encounter. The difficulties and potential dangers are carefully explained and applicants with some experience in similar situations are preferred.

Despite these precautions, there have been some problems specifically related to the issue of environment and the reaction of staff to environmental and social factors. Staff may burn out and quit; if they stay, they may become less efficient or less concerned with maintaining adequate data collection standards. In less extreme situations, staff may allow their own feelings to bias their interactions with research subjects. In one case, an interviewer systematically, although unintentionally, biased a question about mothers' feelings. Finding the idea that mothers might have negative feelings about 30-day-old infants to be personally unacceptable, the interviewer unconsciously worded the question in a way that ensured that the mothers would answer positively. (That is, "You really like the baby now, don't you?")

In another case, an interviewer did not reveal to the investigators that her father's alcoholism had influenced her to take the research position. As a result, it was some time before her reluctance to talk with women about alcohol abuse was uncovered, and valuable information about mothers' drinking behavior was not obtained.

Process Monitoring and Flexible Response

In the real world, things do not always work out as planned. The research protocol is set up in advance based on theory and the best possible

assessment of methodological issues. Custom dictates that it should then be carried out as planned. Unfortunately, this does not always work. Problems arise as the project proceeds. Some might have been anticipated; others occur as a result of environmental changes and could not have been foreseen.

Such a change occurred in a recent protocol that investigated neonatal effects of cocaine in a hospital environment very familiar to the investigators. Infants were to be tested on the third day of life because this would allow them to recover from the birth process and because this period was consistent with previous research. However, several months into the study, the hospital implemented an early release policy (at 48 hours postpartum) for all full-term infants. This change was due to financial constraints and was not subject to negotiation to meet the needs of the research protocol nor to anticipate the potential problems that might be associated with prenatal drug exposure. Therefore, the assessment time had to be changed to the second day even though new infants' data could not be compared with that from previous studies. In addition, infant testers had to adopt an "on-call" schedule since identification and assessment of infants had to be done in such a short period.

A less obvious problem involved the collection of urines that were used to confirm recency of cocaine and other drug exposure. Urines were ordered on all consenting mothers and their infants. However, nurses who had to obtain the samples sometimes let the urine, especially of female infants, be contaminated and often did not obtain a second specimen. This bias tended to be systematic rather than random in-two ways. First, this was a more significant problem for female infants due to anatomical constraints. Second, nurses were more reliable about collecting samples from babies known or suspected to be drug exposed because they saw a purpose in the procedure in such cases but not in the case of control infants. This problem was discovered through monitoring of the outcome of data collection procedures on a monthly basis and by sending the project nurse to question the neonatal nurses when the bias was suspected. Following the discovery of this problem, changes were instituted to correct it. Although it was difficult to deal with the female infant bias, it was possible to have the research staff nurse collect samples from all infants at the end of her routine examination.

Similarly, problems in questionnaire presentation can be found fairly quickly if data are consistently examined and staff supervised on a routine basis. Such rigor can be maintained only when there are adequate resources (i.e., supervisor time and money), and provision should be made for such processes when research is planned and costs estimated.

Other changes in protocol and errors in collection are more difficult to anticipate, and one can only adjust to them. In some cases, changes in drug use habits or characteristics of the population, which are annoying because they interfere with established protocols, are data. An example of this process occurred during 3 years of data collection on neonatal cocaine effects. From 1987 to 1990 the drug-using patterns of cocaine users in Atlanta underwent some changes. For example, use of powdered cocaine (sniffing) and intravenous cocaine use decreased, while crack use increased. Concurrent with this change were several changes in vocabulary describing usage, drug type, and amount that had to be incorporated into the research instruments.

Outside forces also affect clinical research protocol. As mentioned above, economic constraints affect access to service as well as hospital policy. Legal issues, particularly the prosecution of women using cocaine in pregnancy, have affected the number of women willing to admit to cocaine use and to participate in research. These factors cannot be anticipated or controlled. The only possible response is to record what is going on and see how outcome is affected.

SUMMARY

This has been a brief overview of some of the many ways in which the environment in which prenatal drug research is carried out affects the process of research and its outcome. In many ways, this chapter is a review of factors that many people know about but rarely discuss in public. Most scholarly articles present research in this area as though it is a smooth and orderly process not much troubled by environmental constraints. The extent to which research flaws are criticized, even those that are inevitable to the process, discourages frank discussion of these problems that are familiar to most investigators who attempt to conduct clinical research in difficult areas. The purpose of this chapter is to make some of these issues more explicit so that they can be planned for in future work and taken into account when current work is reviewed.

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APPENDIX

Policy and Safety Guidelines for Field Workers

The following information is provided as a guideline for all individuals involved in making home visits for the purpose of research or intervention. We would like you to take every precaution to ensure your safety. Please follow these guidelines carefully. Remember, your own intuition is often the most reliable source of information. If you encounter a situation that “feels” dangerous, leave.

General Safety

1. In the field, wear your State ID or hospital badge so that people will know why you are there.

2. Always go out in pairs and never separate. No exceptions. Both workers should go to the client's home when making a home visit, and no one is to stay in the car. If one partner does not feel comfortable proceeding into any area, neither one should go.

3. Always leave name, study number, address, telephone number, and approximate time of visit of each client home visit with secretary before leaving. When returning, inform secretary that you are back safely. Someone must stay in the office until you return.

4. Go only to designated home address (see above). If you have to go to another location for any reason, call into office and give notice so that someone will know your whereabouts at all times.

5. If you are doubtful about the safety of a given area, telephone or write client and ask if she would meet you in a central location to conduct the interview.

6. Do not carry valuables when going on home visits (e.g., jewelry, cash) and do not leave personal items in the car.

7. Be alert to the people in the neighborhood, the position and location of the building, exits and entrances, where public telephones are located, and whether they are functioning. Do not enter a building whose entrance is blocked by a group of people or objects.

8. Know where the entrances and exits in a client's house are. Do not allow client to lock an inside door and remove the key.

9. In case of an emergency, dial 911 immediately to get assistance and then call project office.

10. Develop a code or signal with your partner that will alert him or her to a dangerous situation and practice this beforehand. Have a word whose use will indicate that it is time to discontinue the interview and leave.

Automobile Rules

1. In making home visits, use project or State cars that are clearly identified with university and State logos. All drivers must be covered under State or university insurance coverage.

2. Before deciding to use your personal car, be sure that your insurance carrier provides adequate coverage.

3. If you receive a State car and it seems unreliable (e.g., does not start well), do not drive it. Similarly, do not leave the office without adequate gasoline. If something happens to a car in the field, call the office immediately and someone will come to you.

4. Although you should always use seat belts and keep doors locked while traveling, always keep vehicle doors unlocked when you are not inside so that you will have an easy access if you have to leave quickly. Always check inside car after completing home visit before entering the car.

5. Never transport clients in your own car under any circumstances.

6. Infants and children must be transported using approved safety equipment and seats.

7. In the field, park only where there is easy access to the car or the street. If this is not possible, use good judgment as to whether you should proceed with the visit.

Relationship With Clients and Community

1. Make every possible attempt to get permission from client to schedule a home visit rather than arriving unexpectedly. This is not only courteous but will avoid unpleasant surprises.

2. Always treat clients with courtesy and respect. Respect their homes, family, and property. Always act appropriately and with good manners.

3. Speak to residents in the neighborhood when passing, and if anyone informs you not to proceed into a given area or apartment, do not proceed.

4. Act like you know where you are going, as if you belong, and as if you should be in the neighborhood.

5. Do not run errands for clients. This is discouraged because it creates a dual relationship.

6. To avoid violating confidentiality, do not leave any identifying patient information in the car. Take only the information necessary for the current visit(s) and keep it with you.

7. Do not discuss client's history or business with family or neighbors Do not identify yourselves as associated with substance abuse or with mental health. If you have to give any information mention the university or the hospital.

SOURCE: Adapted from safety guidelines developed by the staff of the Georgia Addiction Pregnancy and Parenting Project and the Clinical and Developmental Research Project, Human Genetics Laboratory, Georgia Mental Health Institute, Atlanta, GA.

Discussion: Research Environment and Use of Multicenter Studies in Perinatal Substance Abuse Research

Kenneth C. Rich

INTRODUCTION

In the field of perinatal substance abuse, the research environment is a major factor in determining the type and content of studies that can be performed and the likelihood of their success. The challenges presented by the research environment are greater in perinatal substance abuse research than in many other research fields because of the complex interrelationship between political, social, environmental, and medical factors and the outcome that the study is seeking to assess. As a consequence, the investigator is forced to contend with a variety of factors that superficially appear to be peripheral to the research agenda but require careful attention. These include the local clinical environment in which the study is conducted and the broader philosophical and political environment that determines the priorities for this type of research and, consequently, the funding for it.

MACROENVIRONMENT AND PERINATAL SUBSTANCE ABUSE STUDIES

The macroenvironment in which studies are conducted influences whether a study in a specific field of interest can be performed. Researchers prefer to believe that good science will be recognized and supported regardless of national or local political priorities and local institutional goals. The researcher who is planning a study will find it useful to examine the different levels of the macroenvironment to make the best fit to the national and local environment under which the study will be conducted.

National Environment

The national environment is based on priorities developed through the political and scientific policymaking process. The budgeted monies available for research in a given discipline vary in response to both these forces as, for

example, in the priority given to acquired immunodeficiency syndrome (AIDS) in the recent past and to cancer research in the distant past. This translates into changing funding availability and, consequently, changing the concentration of research in a given field. There can be practical problems in the execution of scientific initiatives that are stimulated by the political process resulting from the different agendas and frames of reference of scientists and politicians (Bell 1990; Negrete 1990). However, the initiatives can provide good opportunities for funding for investigators.

In areas that have not received intense pressure from the public and Congress, fields of concentration are established on the basis of scientific and clinical priorities identified by the agency or institute. The institute's interest often is specified by announcement of a specific initiative and the issuance of a Request for Applications (RFA). An RFA may be backed with a specific budget allocation, although the review process is generally a standard grant review mechanism. RFAs from the Alcohol, Drug Abuse, and Mental Health Administration or the National Institutes of Health (NIH) are published in the weekly "NIH Guide for Grants and Contracts"' and in the *Federal Register.* Several agencies have an interest in perinatal drug abuse and publish RFAs in the *Federal Register.*

Institutional Environment

In a time of decreasing public funding for health care for the indigent, many institutions are becoming increasingly reluctant to participate in any initiative that may increase their indigent population. Furthermore, some (particularly private) institutions, may refuse to allow publicity for programs that seem to cater to patients who might be perceived as undesirable by more affluent patients. This may hamper recruitment efforts for a study and make obtaining an institutional commitment more than a mere formality. However, the indirect cost recovery of Federal grants and contracts may partially offset this problem.

MICROENVIRONMENT AND PERINATAL SUBSTANCE ABUSE STUDIES

Coles (this volume) and Kaltenbach and Finnegan (this volume) pointedly raise many of the problems associated with designing a study to fit into and to make use of study populations and resources. They also suggest several creative solutions that may be useful to those embarking on similar studies.

Local Environment

The local environment consists of several components, including the clinical, psychosocial, and cultural environments.

Clinical. The clinical environment comprises the patient population and facilities for their care. In some cases, the study population is a predetermined group of patients who are participants in a multifaceted, multidisciplinary program. Kaltenbach and Finnegan describe the Family Center "multivariable system" approach in which comprehensive care is offered from prenatal care through long-term postnatal care. The approach incorporates substance abuse treatment, case management to deal with basic living needs, parenting education, infant enrichment programs, and psychological care when a woman is ready for it. Note that the basic needs, such as food, lodging, and medical care, are handled first. Psychological care and helping the patient have insight into her problems come considerably later and only after she has the psychological resources to look at them. The approach is ideal for integrating clinical care and research. It allows the ready incorporation of research studies into the clinical milieu with a minimum of disruption of clinical procedures. It also abrogates some of the methodological problems, such as bias of patient selection, that are encountered in other studies that use convenience samples. However, integration of the clinical and research programs in a single staff does have the problem of the conflicting roles of the participant and the observer (see below).

As Coles discusses, in many cases the investigator must use study subjects who are not under the investigator's direct control. Many groups will not embrace the possibility of doing research, viewing it as a disruption of their primary role of serving patients and as a potential cause of additional work. These objections must be dealt with sensitively and the study procedures altered as much as possible to take these problems into account. An approach to similar problems has been discussed by Young and Dombrowski (1989). Staff education and making the clinical staff feel a part of the process by soliciting suggestions for improvement and listening to complaints are important.

Psychosocial. The psychosocial environment in which one encounters the study participants helps determine their willingness and ability to participate in perinatal substance abuse studies. The participants have different views of how the medical system can meet their needs and different priorities in their lives than the investigators. The success of the study may hinge on its ability to deal with these needs, including details of patient care. With a high scientific agenda in mind, such problems as transportation or child care arrangements may seem minor but may determine the study's success. It is important to incorporate adequate personnel into the study plan to deal with these problems, It is also incumbent on review groups to recognize the importance of these persons to the success of the study and to allow for them in considering proposed budgets.

Cultural. Another part of the local environment is culture. Many of the potential study subjects are from minority groups or from quite different social backgrounds than the investigators. Coles gives an example of a potential participant who cannot say no directly to an authority figure about participation but indicates her lack of desire to participate by not showing up for appointments, The author's group has experienced similar behavior, usually associated with very creative explanations about a busy schedule or what was wrong with the car. This can have an adverse effect on staff morale unless staff members are made aware of the different significance of the behavior in the potential subjects' culture and environment. It also follows that even staff members who are from minority groups may have little firsthand knowledge and understanding of those groups' cultural issues if they have upper middle class backgrounds and have no experience with the culture of the target population. Thus, the investigators need to identify sources of information and guidance about the culture of the study population.

Staff Stress

Staff stress may have many sources and take many forms. The identified irritant often is markedly displaced from the source. The frustration expressed about a noncompliant patient may be a reaction to the stress generated by a dangerous environment, It is important to recognize the manifestations of stress and deal with the root instead of the overt manifestation. Stress management may include providing formal staff education and incorporating staff members into selected parts of the decisionmaking process. Finally, a means of generating psychological support from within the study staff should be developed. In the author's group, this is incorporated into the weekly team meetings that plan and review clinical and study care of individual patients. This helps reduce the tendency to burn out in the high-stress environment of the study.

Role of Observer vs. Participant

Coles points out that the researcher has conflicting roles as both a scientific observer and a participant in the life of the study participants for whom the researcher is a care provider and an advocate. These roles easily can become blurred, resulting in unsatisfactory research, difficult ethical dilemmas, and staff burnout.

From the researcher's viewpoint, the social supports developed by the team as a part of patient care and participant retention efforts can influence the outcome. For example, the outcome measure of many studies is infant development. Efforts that are dictated by sound clinical care, such as

enrichment of the social environment, improve the developmental outcome. Treatment of chronic medical problems can lead to an apparent reduction in the medical consequences of substance abuse. These results (desirable from a patient viewpoint) bias the outcome measures by mitigating the adverse effects of drug exposure and can cause these effects to be underestimated. Social support efforts must be applied as uniformly as possible to the study and control groups, and data must be collected to document that uniformity. One assumes that both groups would experience enhanced infant development and that differences between the groups could be attributed to drug effects.

From the social and ethical viewpoint, information may be collected by the study that can affect the participants. For example, the observer may have documented continuing drug use in the mother of a newborn. This information might never have become available except as a part of a study in which a sense of trust has developed between the mother and the study team. The ethical dilemma is whether this information should be supplied to the State child protection agency. An even more demanding situation occurs when an infant's urine tests positive for illicit drugs. In many States, one is required to report this, The author's group has attempted to deal with this by establishing ground rules with the mother early in the interaction with the study. She is told that staff members will report abuse and neglect but that they will take every step possible to prevent the need for reporting. The group also has a Federal Certificate of Confidentiality* that protects study data from subpoena but does allow staff members to take action if there is evidence of abuse and neglect that needs to be reported. Other chapters in this monograph (Weber; Besharov) discuss these problems more fully.

Finally, a corollary to the social and ethical conflict for the researcher and clinician is the conflict between the researcher collecting data for the study and the researcher and others collecting data for clinical purposes. At the author's institution, the neonatologists care for the infant after delivery. They may order tests and perform procedures that influence the outcome or, in the case of prenatal substance abuse, determine whether the case is reported to the State. The fine line between collection of data for study and for clinical purposes and the difference in how the data may be handled with its long-term social consequences is not readily comprehended by study participants. Thus, researchers must be careful about promising confidentiality that cannot be delivered because part of the care is under the direction of nonstudy personnel. As both Coles and Kaltenbach and Finnegan point out, a study in the area of perinatal substance abuse is dynamic, changing in response to the changing environment and the needs of patients. It is not possible to set the process in motion and then collect data. The challenge is in the ability of the study team to meet many needs of participants while keeping the overall direction of the study

on course. No study in perinatal substance abuse can be as "clean" as one might wish, but by keeping in mind the factors that influence the outcome measures, quality research can be performed.

MULTICENTER COLLABORATIVE STUDIES

Some of the compelling questions of perinatal substance abuse cannot be answered given the patient resources available at a single center. Enrollment can be increased by a multicenter collaborative effort, which increases the spectrum of questions that can be answered. However, the investigator must consider carefully all the ramifications of developing a multicenter study.

Multicenter collaborative studies provide enormous advantages for some types of studies but also are filled with potential pitfalls. These studies are often complex, expensive, and cumbersome. The Federal medical and scientific research program has several examples of multicenter collaborative studies that have a well-developed scientific agenda but only a marginal managerial structure for handling the added complexity of multicenter studies. For those contemplating setting up a multicenter collaborative study, the following are points to consider.

Reasons for Using Muiticenter Collaborative Studies

The most obvious reason for using multicenter studies is that they quickly allow enrollment of many subjects with an uncommon trait. Many of the compelling questions that face researchers in perinatal substance abuse are about traits that are sufficiently uncommon that a single site cannot hope to enroll enough subjects to draw reliable statistical inferences.

The essential first step in determining the need for multisite studies is making power calculations to determine sample size needs. The basis for these calculations can be a literature review, preliminary data, or an educated guess. Unfortunately, many applications ignore these calculations and propose examining questions that have no hope of being answered given the limits of the accessible sample. The estimates of the number of subjects that can be enrolled and retained and the frequency of the trait of interest often are made based on ideal circumstances that do not occur in most clinical studies. However, with realistic estimates, the investigators can make a decision about the need for additional sites and can justify the additional complexity and cost to the funding agency.

Multicenter studies have other advantages. Chief among these is the development of a critical mass of expertise and creativity among the

investigators. Truly involved collaborators add immeasurably to the richness of the fabric of the study. One of the most exciting aspects of multicenter studies is the flow of creativity that can be generated from a diverse spectrum of colleagues. However, the investigators should guard against the inclusion of a "name" investigator whose only role may be to lend a patina of respectability to the application. The review group usually will see through the ploy, and it is demoralizing to the harder working members of the team.

Another potential strength is forcing a more organized and focused approach to the study. In view of the need to ensure comparability between sites (see below), multicenter studies often put additional efforts into formalizing the study questions and methods. This has the added benefit of eventually producing a better designed study that is more likely to answer the proposed questions.

Special Problems of Multicenter Studies

Multicenter studies bring a host of problems that are unique to these studies and accentuate some of the routine problems encountered in any study of a difficult patient population, such as determining a management style, ensuring comparability between sites, ensuring that young investigators receive adequate academic credit and a chance to show creativity, and imposing special design considerations.

Management. Management of scientific endeavors has been described as "organized anarchy." Scientific activities do not fit easily into a strict reporting system, and any system that attempts to force a good fit runs the risk of stifling creativity and attracting investigators who lack imagination. However, a critical need of multicenter studies is sufficient central direction to keep an eye on strategic issues while allowing creativity. Physicians and nonphysician scientists usually are untrained in management; therefore, some form of central management is a critical need for multisite studies. The amount of time management takes and the distraction from scientific issues it involves should not be underestimated.

Different styles have been used for the management of multicenter studies. The best one for a given study depends on the size of the study and the cast of investigators. One style is a hierarchical management system. In this system, the principal investigator (PI) assumes responsibility for many of the overall management decisions and scientific direction of the study. This has the advantage of providing a coherent, directed approach to the study. A scientifically sound PI can "just say no" to side issues and data collection of marginal importance and keep the focus on the central questions.

Another management style is a matrix in which investigators use a networking technique in which leadership is decentralized and based on working groups with different areas of expertise. Numerous informal connections are made, and decisions are reached by consensus. This takes advantage of creativity and initiative but can result in an incoherent, unfocused study. Central coordination and accountability become essential to take advantage of the matrix style's strengths and not be derailed by its problems. Examples of such a management style are some of the large, federally financed experimental treatment trials that took years of trial and error to create all the informal connections and to meld them into an effective, efficient study. The ideal format at any site depends on the resources and size of the project and on the participants.

Coordination Between Sites. Coordination between sites is a necessity. This requires the clear spelling out of specifications for all parameters of subject characterization and procedures. It requires an agreement on procedures, definitions, and techniques that is codified in a comprehensive procedure manual. Formal training for the onsite personnel who collect data will be necessary, and periodic reevaluation at each site will be necessary to ensure that small changes in procedure are not inadvertently being incorporated, which could cause a divergence of the long-term direction of the study at the different sites.

Other more basic issues need to be resolved. If the referral patterns and participant pool at different sites are dissimilar, results could be biased by the number of subjects enrolled at each site. For example, long-term neurodevelopmental outcome in drug-exposed infants may be altered by environmental factors that are the result of socioeconomic status, To prevent these biases, enrollment criteria need to be carefully spelled out and data collected to define the sample population at each site.

Consideration also should be given to having a single site conduct nonroutine laboratory studies to reduce site-to-site variability. If samples cannot be saved or shipped, then an agreement will need to be made on the specific technique, and some form of a quality assurance program will need to be developed. An example of this need for comparability is urine testing for substances of abuse that can be done by several techniques that vary by an order of magnitude in sensitivity and also vary in specificity.

Data Management. Data management is more complex in multicenter studies than in a single center study. The initial decision is whether a centralized or distributed system or a hybrid of the two will best meet the needs of the study. In a centralized system, the local data are collected and sent to the central data

manager for checking, computer entry, and analysis. In a distributed system, data are collected, checked, and entered into the computer locally and transmitted to the central system.

The advantages of the central system are the ease of ensuring the quality and integrity of the database after the data entry stage, the need for fewer data management personnel, and the comparability of procedures between sites. However, the central system has some disadvantages. Among these is the slow and cumbersome query process if problems are found with filling out forms. For example, if an item is left blank on a form, it may be due to lack of information, or it may be an inadvertent omission. Rapid feedback can allow many of these queries to be resolved easily, whereas a long delay and a lack of a sense of involvement in the data management process may lead to a greater number of data points that cannot be resolved. Furthermore, in a centralized system, data are not readily available for onsite quality assurance or examination, and there may be delays in obtaining requested minianalyses due to a backlog at the central data management center, especially at times when abstract deadlines are approaching.

Academic and Scientific Credit. A major motivation for coinvestigators to join a study is to obtain academic credit for promotion and tenure. In multicenter studies, a degree of individual autonomy is lost, and considerable effort is required on the part of all the participants. The opportunity for academic payoff is delayed and, unless credit is fairly attributed to individuals, may be entirely abrogated. Therefore, a system is required that preserves the ability of coinvestigators to have their name as first author on some of the publications and for them to have the opportunity to do important side studies.

At the same time, the integrity of the overall project must be preserved. Possible conflicts between the individual study and the overall study include competition for blood samples (especially in the newborn) and adding procedures that make the study group subjects feel so overstudied that it jeopardizes the central study. There is also the risk of individual investigators using data from the central study that should be preserved for presentation as part of the central study.

To keep coinvestigators vested in the study, a means of encouraging initiative and creativity needs to be developed. A set of ground rules to which all participants agree to adhere should address the issues of primacy of authorship, restriction of certain topics to the main study, and quality of publications. The latter issue is important to enhance the good name of the study but needs to be done without appearing to promote censorship.

Periodic Review and Advisory Group. In a complex organization, a periodic review of the overall emphasis and progress of the study has considerable merit. An outside review can either confirm the impression that the agenda is correct or point out areas of needed change. Independent outside reviewers who periodically evaluate the study also defuse future criticism about the scientific merit and priorities of the studies.

An advisory group from the community that is being served also has value by ensuring responsiveness to the community and constituency being studied. Active members on the advisory group may help with recruitment and fundraising. An advisory group also can help forestall criticism of exploitation of study subjects by individuals or groups who have a political agenda.

Funding Mechanisms

Multicenter studies are expensive. They require duplication of some of the costs at each site, such as the infrastructure for patient recruitment and retention and for execution of the study. The issues of establishing comparability between sites and developing a complex data management system also add to the cost. However, many questions cannot be answered without resorting to multicenter studies. Once a multicenter system is set up and running efficiently, data and new knowledge stream from it.

Different funding mechanisms usually are used for multicenter studies rather than for individual studies. Not all funding mechanisms are the same, and some thought and discussion with a program officer should go into deciding the type of application to make. The traditional and most flexible mechanism of funding is the investigator-initiated grant (R01), which allows the investigator to propose and execute a project with little input from the funding agency staff. However, it should be remembered that the funds available usually are not sufficient for a costly multicenter application unless an RFA has been published,

Another mechanism is the program project that covers a group of individual but related studies and shares a core of facilities and expertise. Greater funding is usually available for program projects than for individual grant applications. The PI has flexibility in the execution of the project and can, within reason, alter the direction of the project in response to changing knowledge. There is also more flexibility in expenditure of funds.

A cooperative agreement is a mechanism in which the awarding agency anticipates substantial programmatic involvement during the performance of the award. It is used for some of the large, multicenter projects, such as the AIDS Clinical Treatment Group sponsored by the National Institute of Allergy and

Infectious Diseases (NIAID). In the treatment trials, the PI at an individual site has general discretion in determining participation in specific subprojects and in expenditure of local funds. However, progress of the group goals is closely monitored.

Another mechanism is the contract. It is extensively used by components of NIH but not by the National Institute on Drug Abuse (NIDA). A specific area of research need is identified, the work scope is defined by the agency, and a list of "products" is drawn up. The awardee is expected to deliver the product that has been defined by the agency, whether it is a specific set of data or a laboratory technique. As a consequence, the program staff has major input into the study, although they may elect to work in a collegial relationship with the investigators in defining the specifics of the study. Contracts have the advantage from a programmatic viewpoint of allowing a focused approach to a well-defined question, and this mechanism might be especially valuable when development of an important watershed of new knowledge is being hampered by an identifiable missing piece of research infrastructure, information, or technique or if there are few investigators working in the area. The major disadvantage is the cumbersome process that must be observed to alter the direction of the study in light of new knowledge and changing conditions. Changes that are more than minor must be accompanied by an amendment of the contract. From an investigator's viewpoint, the contract mechanism reduces investigator initiative and flexibility as the investigator must concentrate on the products.

CONCLUSION

The environment influences the ability to perform studies of perinatal substance abuse on many levels. At the macroenvironment level, national priorities and national scientific agenda and priorities determine the funding availability. The institutional environment determines the reception and support given to the study. On the microenvironment level, the ability to conduct research depends on the availability of a patient population. A multidisciplinary clinical environment enhances the ability to retain and study patients but also poses some scientific and ethical dilemmas as the investigators are often a part of the clinical care team. Finally, since some scientific questions cannot be answered unless many patients are available, multicenter studies should be considered as a means of increasing the patient pool. However, they present several challenges such as ensuring comparability between centers, more complex data management, and the need to ensure academic and scientific credit to all the investigators.

NOTES

1. A subscription to the Guide can be obtained free of charge from NIH Guide, Printing and Reproduction Branch, National Institutes of Health, Building 31, Room B4BN08, Bethesda, MD 20892.

2. A Federal Certificate of Confidentiality can be obtained from NIDA.

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Program and Staff Characteristics in Successful Treatment

Elizabeth R. Brown

INTRODUCTION

Women are a minority population in the majority of drug treatment programs. Many outcome studies of addiction treatment omit women from their patient populations. Therefore, a significant gap exists in understanding the characteristics and successful strategies that will result in good treatment outcomes for women. Moreover, the data gathered on male populations have shaped the approaches to treatment used in most programs, and this male-oriented treatment model may not be appropriately applied to drug-dependent women.

Until the 1970s few studies addressed the need for specialized drug treatment programs for women. At that time new Federal legislation was enacted (Public Law 94-371) that mandated the development of specialized drug treatment programs for women. As a result, the National Institute on Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse (NIDA) funded research efforts to define the characteristics of drug-using women and to develop treatment programs designed to meet the special needs of female addicts.

One of the first studies contrasting male and female narcotics addicts was reported by Eldred and Washington (1975), who interviewed 79 male and 79 female narcotics addicts as they presented for treatment in a methadone maintenance program in Washington, DC. Both men and women presented at a mean age of 25 years, had a mean of about 5 years of heroin use, began using drugs at a mean age *of* 20, and had been admitted previously (63 percent of 158 adults) to the program for treatment. However, there were significant differences in the life situations and social contexts of drug use in the female vs. the male addicts.

Male addicts most often were “turned on” to drug use by another man, whereas female addicts were most often turned on by males. Female addicts were more likely to report that their drug or money for drugs was given to them by someone

else, usually their spouse/partner. In addition, female addicts were more likely to be separated, divorced, or widowed and living alone and also were more likely to report that they had children. More women than men were unemployed, and the majority of all patients were not receiving financial aid on program entry.

Women are not a homogeneous group and differ in both patterns of drug use and psychosocial dysfunction. Harrison and Belille (1987) analyzed 1,776 women entering inpatient chemical dependency treatment facilities affiliated with the Chemical Abuse-Addiction Treatment Outcome Registry during 1982 and 1983. This was largely a white, Midwestern population base. There were significant differences noted between women ages 30 and younger and women older than 30 who entered treatment. Younger women were more likely to have minority status, to be unemployed, to be single, to have dropped out of high school, and to list their families or welfare benefits as their primary means of support. Alcohol and tranquilizers were more commonly used by older women compared with the use of marijuana, cocaine, other stimulants, and hallucinogens by younger women. Polydrug abuse also was more common in younger women. Younger women were more likely to report psychological distress, such as depression, and were more likely to report legal offenses during the previous year. A much higher proportion of the younger women reported familial drug use and a higher prevalence of alcohol abuse and violence in their family of origin and current family. Thus, approaches to treatment not only need to be gender based but also need to recognize the impact of the increased psychosocial adversity faced by younger women.

Although white women remain the largest group of female addicts, there have been major shifts in the past decade toward increased drug use in minority women, with Hispanic women showing the largest percentage increase. Tyler and Thompson (1980) analyzed drug use patterns by race, age at first use, and education for a group of 14,428 female patients who were admitted to 1,400 federally funded drug treatment centers during the third quarter of 1976 and for whom data were compiled as part of the Client-Oriented Data Acquisition Process. White women used heroin to a lesser degree than either African-American or Hispanic women. Although marijuana was the second most commonly used drug across all racial groups, it was used to a greater degree by white women than by those of other races. Women who were 26 years of age or older at first drug use were more likely to use sedatives, whereas women who first used drugs at age 19 or 20 were more likely to be using heroin.

Another study of white vs. African-American women entering drug treatment in either a therapeutic community or a methadone maintenance program was reported by Moise and colleagues (1982). The subjects were 582 women who

were participating in research studies carried out as part of the Women's Drug Treatment Collaborative Project. Women of both races were socially isolated, lacked education and job experience, and were having difficulty with custody disputes with respect to their children. White women more often had a history of being married, and there was a greater tendency for the spouse or partner of a white woman to be using drugs. Black women were more likely to have ongoing responsibility for childrearing and to be living alone. White women as a group used drugs earlier, had a greater incidence of drug use by their family members, had more suicide attempts, and had more involvement in illegal activities. More black women than white women grew up in broken homes and economic disadvantage, but white women were more likely to access professional services (private physicians, outpatient mental health facilities, psychiatrists, and lawyers).

Although a majority of all women seek treatment primarily in outpatient settings, white women are significantly more likely to enter residential treatment. This may reflect the ability of white women to access more expensive residential services as well as the increased number of black women with current childrearing responsibility, because there are few programs that provide accommodations for residential drug treatment of women with children. Often, the only option available to a woman with children who is seeking residential drug treatment is to place her children in foster care during the period of her residential treatment. This is a major reason for failure to seek treatment for many women, because they fear that once their children enter the foster care system they will be unable to regain custody.

There has been concern in recent years that as the use of drugs by women, particularly pregnant women, is increasingly criminalized, minority women will be identified and prosecuted more often than white women. Chasnoff and colleagues (1990) reported that the incidence of drug use in pregnant women in Pinellas County, FL, as measured by anonymous urine toxicology studies done at the first prenatal visit, was 16.3 percent in a public clinic vs. 13.1 percent in patients receiving care in a private practice setting. The pattern of drug use also was different. Respectively, public and private patients had 12.4-percent vs. 11.3-percent positive urine toxicology for marijuana and 5.0-percent vs. 1.5-percent positive samples for cocaine. White patients were more likely to use marijuana, whereas black patients were more likely to use cocaine. Of the total births (5,083) in Pinellas County during the time interval of this anonymous sampling, 793 infants were black and 4,290 were white. Of infants reported to the department of social services because their mother used drugs, 10.7 percent were black and 1.1 percent were white, despite a nonsignificant difference in actual drug use rates.

It is clear that women entering treatment programs in the 1990s present with complex problems. Table 1 shows characteristics of a sample of women who participated in a pilot project to assess the treatment needs of drug-dependent pregnant women at Boston City Hospital in April-May 1990.

The impact of treatment for maternal drug use on the outcome of pregnancy will be lessened considerably if the treatment is not comprehensive in nature because many of the maternal health habits associated with drug use adversely affect the pregnancy and, therefore, need to be addressed at the same time as the drug habit. The confounding variables present in drug-using pregnant women that contribute to low-birth-weight infants were described in an elegant study of 1,226 women reported by Zuckerman and colleagues (1989). Of the 1,226 women, 216 (18 percent) used cocaine during their pregnancy. The mean birth weight of infants of cocaine-using women was 2,847 g compared with 3,254 g in drug-free women, and the mean head circumference of the infants was 33.0 cm vs. 34.3 cm, respectively. This large difference was highly significant but confounded by many other differences between the cocaine-using and drug-free groups. Multiple regression analysis showed that 93 g of the 407 g difference in birth weight was due to cocaine use as measured

TABLE 1. *Characteristics of drug-dependent pregnant women in a pilot project*

Characteristic	Mean
Age	29 years
Gestational age	28 weeks
Gravida	4.25
Parity	2.13
	Percentage
Race=black	75
Medical problem	83
Current physical abuse	50
Felony conviction	38
High school dropout	50
No driver's license	75
Lost custody of child	75
Not registered for WIC*	63

*Special supplemental food program for Women, Infants, and Children

by positive urine toxicology during pregnancy. Women who reported cocaine use but had negative urine toxicology with multiple urine samples (correlating with infrequent use) did not show any significant decrease in infant birth weight due to cocaine use. Women who used cocaine were more likely to smoke cigarettes, to smoke marijuana, to use other drugs, to have a lower prepregnancy weight, to have a lower weight gain during pregnancy, and to have a greater number of sexually transmitted diseases than women who did not use cocaine. Thus, any treatment program that aims to improve the outcome of pregnancy in drug-using pregnant women will be unsuccessful if the focus is on abstinence alone. Such programs need to be comprehensive and to address the prenatal, medical, social (including food and housing), and psychiatric (including issues of family violence) needs of women in treatment.

In Massachusetts, only 4 of 47 non-hospital-based treatment programs accept pregnant women. Boston has only 15 residential beds for drug treatment of pregnant women. Even if women are accepted, most treatment programs operate on a male-oriented model, most patients and treatment providers are men, and there is a lack of orientation to women's help-seeking patterns, a lack of provision for child care, and a lack of provision for attention to women's particular medical needs (general medical, prenatal, and postnatal care). Many programs accentuate women's social isolation and do not address economic barriers for women by providing appropriate job counseling, vocational training, or housing. As a result, women continue to underutilize substance abuse treatment programs.

A comprehensive approach to drug treatment should include drug treatment along with medical, social, and vocational services for women and child care, preferably including medical and early intervention services for their children. Studies of alcohol treatment facilities in California, reported by Beckman and Amaro (1986), clearly showed that the availability of children's services attracted more women into treatment. Finnegan (1979) has demonstrated that a family-oriented comprehensive treatment program for pregnant drug-using women can result in pregnancy outcomes that approach those seen with comparable non-drug-using pregnant women from the same socioeconomic strata. Chasnoff and colleagues (1989) reported that if cocaine-using pregnant women entered treatment in the first trimester and were able to stop their drug use for the remainder of the pregnancy while remaining in prenatal care, then the birth weight of the infants would closely approximate that of drug-free women. Thus, a comprehensive approach to drug treatment in pregnant women can substantially improve the outcome of pregnancy.

The multiple needs of drug-using women in Boston are further defined in a recent presentation by Amaro (1990), who described the demographic profile of

the first 157 women recruited into the National AIDS Demonstration Research Project, funded by NIDA. The Boston project, called the MOM's Project, is designed to conduct human immunodeficiency virus (HIV) prevention with pregnant women at high risk for this infection. Women receive a structured interview on recruitment to the project, and a followup interview is done 6 months after entry. Services include counseling, HIV testing, group education and discussion sessions, case management, and advocacy.

Women at high risk for HIV recruited into the MOM's Project were mainly young (ages 20 to 29, 66.7 percent), black (81.4 percent), and high school dropouts (58 percent). One-fifth of the women were homeless and another fifth were living with friends or relatives in an unstable living arrangement. One-third had children living with them, but only half of these women were receiving public assistance. Eighty-five percent of the women were actively using drugs when recruited, and 30 percent were abusing two or more drugs; however, only 54 percent had ever been in any kind of treatment program. "Crack" was by far the most commonly used drug of abuse (74 percent). Nearly half of the women were engaging in sexual activity one or more times per day without using a condom. The health history of these women was also significant: 57 percent had a history of sexually transmitted diseases; 2.6 percent were diagnosed with acquired immunodeficiency syndrome (AIDS) or AIDS-related complex; and 40 percent rated their own health status as fair or poor.

This description of a large group of pregnant drug-using women makes it clear that the success of drug treatment will depend on the ability to provide comprehensive services. Substance abuse treatment cannot occur successfully unless other needs of women-social, medical, economic, and emotional-are addressed at the same time. Currently, there are many barriers within the drug treatment system that prevent such a comprehensive approach. There are limited treatment slots available to pregnant and postpartum women who wish to keep their children with them while in treatment. Few programs provide treatment services that are culturally sensitive to the treatment population. There is little prolonged aftercare provided after "graduation" from a drug treatment program. Service agencies focus on separate pieces of a problem (housing, battered women's shelters, WIC, health services, mental health services, child care, and job training) and are not able to coordinate activities. Moreover, women must apply separately for each of these services and are assigned a separate case worker in each agency. Often, women have as many as 5 to 10 separate case managers coordinating services, none of whom is aware of the work done by the others. Reimbursement mechanisms do not recognize the need to provide "family care"; thus, residential treatment programs cannot be reimbursed for child care activities.

The Family Life Center at Harvard Street Neighborhood Health Center and Boston City Hospital is moving to provide a "one-stop shopping" approach with a focus on drug treatment in the context of improved parenting. One of the greatest fears of drug-using women is that they will have their newborn infant taken away from them. The Family Life Program, developed at the Boston City Hospital and implemented in a neighborhood setting within a local health center in the inner city, provides day treatment for substance abuse, prenatal care and classes, postpartum obstetric care, pediatric primary care, parenting education (including child development, nutrition, and parenting skills development), early intervention programs for young children, onsite child care, and advocacy services to help with the myriad social ills affecting women in treatment. The services in this latter area range from a food bank and instructions for cooking nutritious meals on a hotplate, to an onsite laundry with washers and dryers to use while at the center, to a literacy training program leading to high school equivalency certification.

An important aspect of advocacy is dealing with personal and sexual violence. More than 50 percent of patients in treatment currently are abused; as abstinence is achieved, women may become increasingly depressed, anxious, and fearful of increased violence in their lives. The need for drug therapists to be well versed in the treatment of abused women is discussed by Root (1989), who suggests that drug treatment may be unsuccessful for many women unless the issues of past and current physical and sexual abuse are concurrently addressed. She suggests that many so-called treatment failures represent the inability of some women to cope with ongoing abuse without the numbing effect of drugs.

SUMMARY

Women come to drug treatment with lower self-esteem (Regan et al. 1984), more social isolation, and more difficult life situations than men. Women are more likely to present with mental health comorbidity such as depression (Regan et al. 1982). Treatment programs modeled on outcome research on male patients may not yield strategies that are successful with women. Only in the past decade has research been undertaken into the specific population characteristics of women in drug treatment. Programs must be designed with a clear understanding of women's psychological makeup and particular life stress, including the need to care for their children and the reality of physical and sexual abuse. Drug treatment often unmasks a variety of psychosocial problems that, if not adequately addressed by the drug treatment program, may result in relapse into drug use. Many women live in poverty and are inadequately educated, two factors that can interfere with reintegration of the recovered addict into the community. Thus, the drug treatment program, to

provide successful long-term outcomes with respect to drug use, must provide long-term aftercare that includes attention to the variety of social, medical, and emotional problems faced by women who use drugs.

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Process Measures in Interventions for Drug-Abusing Women: From Coping to Competence

Elaine A. Blechman, Thomas A. Wills, and Vera Adler

INTRODUCTION

The purpose of this chapter is to recommend process measures to evaluate interventions with drug-abusing women. The first part of the chapter answers the question "What process?," and the second part recommends process (and related outcome) measures.

FUNDAMENTAL COPING PROCESSES

One kind of process that might be targeted is the psychological process (or processes) crucial to a specific intervention. Taking this specific-process approach, elements of a specific intervention, such as a residential treatment program, would be described, and the crucial processes thought to be set in motion by those program elements would be enumerated. Measure then would be selected to assess whether program elements are faithfully implemented and whether specific changes are reliably followed by improvement on key outcome measures such as dirty urines. Thus, a residential treatment program might encourage clients through daily encounter groups to engage in higher levels of self-disclosure; in turn, increments in self-disclosure might be expected to predict fewer dirty urines.

A second kind of process that might be targeted is a process (or processes) involved with the abuse of drugs of all kinds that must be altered by any type of treatment program to achieve a successful outcome. Taking this fundamental-process approach, psychological processes are specified that are presumed to distinguish drug-abusing from non-drug-abusing women and that, when changed, are presumed to predict significantly reduced drug abuse.

This chapter does not take the specific-process approach. A variety of specific interventions now are being tested in the field. Each specific intervention requires measures tied to its own elements. A compendium of measures tied to

several specific interventions would be long and unlikely to advance knowledge about shared processes of change resulting from diverse yet successful methods of treating drug abuse in women.

Instead, this chapter takes the fundamental-process approach, focusing on processes presumed fundamental to drug abuse and its successful treatment (Bowers and Clum 1988; Garfield and Bergin 1986; Miller and Heather 1986; Wills 1982). More specifically, this chapter focuses on adaptive and maladaptive coping processes reflected in reinforcer management, challenge management, and affect management. This approach leads to a consideration of how women faced with objective challenges (such as poverty and abuse) shift from maladaptive to adaptive coping because of a specific intervention or spontaneous, fortuitous life experiences.

A focus on fundamental coping processes offers two benefits to the field. The first benefit is the development of a theoretical model specifying how drug-abusing women cope maladaptively and how women who have ceased to abuse drugs, or who never abused drugs, cope adaptively. This theoretical model must be comprehensive enough to accommodate the mechanisms underlying diverse specific interventions for women's drug abuse. Such a comprehensive theoretical model of the healing process would permit interventions to be designed and evaluated on a rational basis. Researchers could address questions about psychological and biological mechanisms underlying all successful interventions, in addition to the usual questions about whether a specific intervention works.

Proceeding from previous work on behavioral interventions with women (Blechman 1984; Blechman and Brownell 1988), on substance abuse in general (Blane and Leonard 1987; Kaplan 1980; Meyer 1986; Wills and Shiffman 1985), and on opiate addiction in particular (Alexander and Hadaway 1982; Khantzian 1980, 1985; Tucker 1985), we develop a model that seems appropriate to substance-abusing women and argue that:

1. Maladaptive coping is a central feature of women's drug abuse.

2. Adaptive coping is characteristic of fully recovered drug-abusing women.

3. Maladaptive coping characterizes poorly recovered drug-abusing women at high risk for relapse.

4. Spontaneous recovery involves a shift toward adaptive coping.

5. Interventions for drug-abusing women are most likely to succeed when they impart adaptive coping.

This model pays particular attention to the plight of women in poverty since they are faced with a disproportionate number of objective challenges, few opportunities to learn adaptive coping, and many opportunities to learn maladaptive coping.

The second benefit of studying fundamental coping processes is the potential for development of measures that can chart the course of recovery. These measures must be suitable for administration to drug-abusing women of all socioeconomic classes and racial and ethnic backgrounds, including women who are illiterate, physically ill, and psychologically distressed. They must be suitable for administration in the settings where drug-abusing women are most often found: Public hospitals that are crowded and noisy and in which space and time for administration of research-focused measures are a luxury. At the same time, measures must be chosen that are capable of capturing the strengths of women who have ceased to abuse drugs or who, despite the difficulties of their lives, have never abused drugs. These measures also must be sensitive to methods of maladaptive coping (e.g., risky sexual behavior, binge eating) other than drug use that are relied on by drug users and by women who do not abuse drugs. Establishment of a theoretically informed set of measures sensitive to the full range of coping strategies of adult women would offer a great practical advantage to the evaluation of interventions and to theory-driven basic research.

This chapter proposes measures to assess the fundamental coping processes of *reinforcer management, challenge management,* and *affect management.* Assessment of these processes is required for complete documentation and understanding of the course of recovery. Since this chapter's purpose is to recommend process measures the scientific evidence for the proposed theoretical model is only briefly noted. These questions now are being addressed in our laboratories.

Coping via Reinforcer Management

The most basic coping process involves the continuous management of reinforcers required for the individual's physical, social, and psychological survival. Individuals differ in the number and types of reinforcers they prefer and in their capacity to delay pursuit and consumption of reinforcers. Despite these individual differences, continuous management of reinforcers is a basic requirement of human life.

In adaptive coping, the individual has a relatively large pool of preferred reinforcers, which confer both short- and long-term gratification and benefits. The individual knows how to obtain and consume these reinforcers and pursues

and consumes them only when pressing life problems have been adequately addressed. In maladaptive coping, the individual's pool of reinforcers is restricted to those with short-term gratification and long-term costs. The individual is ignorant about how to obtain and consume some prized reinforcers and often pursues short-term reinforcers instead of taking care of urgent problems.

Sources of Survival and Gratification: Reinforcers. A commodity, activity, or event can be said to have hedonic reinforcement value for an individual if the individual makes a concerted effort to come in contact with the potential reinforcer (the Premack principle). With the exception of extremely depressed individuals, all people spend some time trying to contact reinforcers, particularly reinforcers that have universal survival value (e.g., food, water, shelter) (Blechman 1981).

Reinforcer Preference. People vary greatly in their attraction to reinforcers (judged by their efforts to contact those reinforcers). In no particular order, potential reinforcers include food, shelter, sleep, work, company of friends and family, physical exercise, sexual gratification, money, status, love, shopping, gambling, and of course, tobacco, alcohol, and other drugs of abuse. Origins of reinforcer preference may be rooted in biology, learning history, and culture.

People vary greatly in the range of reinforcers to which they are attracted and in the intensity of their pursuit of one or more reinforcers. Reinforcers are also likely to be affected by multiple causes, including biology, learning history, and culture (Leavitt 1982; Levison et al. 1983). Individuals whose lives are organized around the pursuit of a limited range of reinforcers are popularly considered addicts even when the reinforcer pursued has short- and long-term benefits (e.g., exercise). The behavioral evidence of addiction (even to activities like shopping that do not directly induce changes in brain function) is apparent when the individual spends a large amount of time trying to get in contact with the reinforcer. What is interesting about the addictive pursuit of reinforcers is that the behavior involved in chasing them is similar across classes of reinforcers (e.g., shopping/using cocaine, going to the store/getting cocaine, thinking and dreaming about shopping/cocaine, talking about shopping/cocaine to others). Daily plans are made to have contact with the reinforcer (e.g., finding ways to get money to shop/buy cocaine). The individual looks forward with pleasure to the next contact with the reinforcer and is willing to forego other pleasures and endure punishment (e.g., bankruptcy, family arguments, sexual victimization, arrest) to hasten and increase opportunities for contact with the reinforcer. The individual strongly believes that contact with the reinforcer will induce a good mood and chase away a bad mood.

Individuals who act as if they are addicted to a reinforcer generally report that (and act as if) the reinforcer has mood-altering effects-abolishing bad moods, promoting good moods, or both. A biological basis for these effects has been established for drugs of abuse (Levenson et al. 1987; Pickens and Svikis 1988; Schuckit 1987; Searles 1988) and for physical exercise. Some people report (and display) mood-altering effects from activities (e.g., shopping) whose biological basis is less clear.

Experimentation with reinforcers is inherent in human development from the beginning of life. In adolescence, teens experiment with chemical substances, sex, sports, school, and work. Some (with the help of learning history and temperament) find healthy reinforcers with short-term mood-elevating an mind-distracting benefits and long-term benefits as well. Some select unhealthy reinforcers, such as drugs, that have short-term mood-elevating and mind-distracting benefits and substantial long-term costs. Some find no reinforcers. They become prone to depression and anxiety. Consistent with this perspective, Shedler and Block (1990) have reported about a longitudinal study of three groups of 18-year-olds. Those who experimented in moderation with drugs and alcohol during adolescence were psychologically healthy; heavy users and total abstainers were significantly less healthy.

Adaptive and Maladaptive Reinforcer Management. The list of reinforcers provided above includes some with positive long-term consequences (e.g., exercise) and some with negative long-term consequences (e.g., drugs). Coping is adaptive so long as preferred reinforcers have short- and long-term benefits and do not replace management of life challenges. Coping is maladaptive when there are evident short- and long-term risks and when reinforcers are pursued instead of coping with challenges. Coping is also maladaptive when nothing has hedonic value for the individual and when the individual never veers from a focus on problems to pursue pleasure.

Coping via Challenge Management

The most obvious mode of coping involves the individual's way of dealing with life challenges. When coping is maladaptive, the individual employs a strategy that is poorly matched to the nature of the challenge (e.g., denying the existence of a real threat). When coping is adaptive, the individual employs a strategy that is well matched to the nature of the challenge.

Objective Challenges. An objective challenge is evoked by any acute or chronic event or condition with statistically probable negative consequences for the individual (Lazarus and Folkman 1984). (Challenges also could be called stressors or problems.) These may be challenges to affective, social, or

achievement competence or challenges to physical hardiness. Pregnancy, poverty, minority ethnic/racial status, sexual victimization, human immunodeficiency virus (HIV) infection, and diabetes all constitute such challenges. Objective challenges include stressors operationally defined as major life events (e.g., job loss), daily hassles (e.g., an argument with a boyfriend), and problems created by the individual's own actions (e.g., the drug cravings of an addict in withdrawal). Thus, objective challenges are an antecedent to and a result of coping. Maladaptive coping to objective challenges threatens the individual's survival by eroding physical hardiness and affective, social, and achievement competence (Blechman 1981, 1984).

Subjective challenges are events without probable negative consequences but are followed by increased distress and maladaptive coping on the part of an individual. The discussion that follows focuses for the most part on coping with objective challenges. It is presumed, however, that individuals who generally cope adaptively (or maladaptively) with objective challenges do the same with subjective challenges.

Objective challenges differ in respect to potential for avoidance, escape, resolution, and accommodation. Some can be avoided (e.g., using condoms to avoid pregnancy and HIV infection). Some can be escaped (e.g., getting an education and a job to escape poverty). Some can be resolved (e.g., reaching an agreement with a boyfriend to have sex as often as he wants but always with condom protection). Those that cannot be avoided, escaped, or resolved are at least amenable to accommodation (e.g., adopting a drug-free lifestyle and getting prenatal care to ensure that a high-risk pregnancy results in a relatively healthy mother and baby).

Many challenges in modern, urban society are chronic and recurring (e.g., possibility of rape) and require accommodation in which the individual exercises self-control to make the best of a bad situation (e.g., marshalling resources to recover from a brutal rape). Poor women are faced with a multitude of chronic, recurring challenges yet are bereft of resources useful in coping with these challenges (e.g., having no money to gain access to rehabilitative care after a rape) (Blechman 1990a).

Challenge-Management Strategies. As noted above, some objective challenges are amenable to avoidance or escape, others to resolution, and others only to accommodation. Each of these approaches represents a challenge-management strategy. (Since some of these strategies do not resolve the problem at hand, they cannot be called problemsolving strategies.) Each challenge-management strategy can be adaptive if it is wisely matched to the challenge at hand. Imminently dangerous, uncontrollable challenges

require avoidance or escape. Challenges that will unleash a cascade of new challenges if avoided or escaped require resolution or accommodation.

For an adaptive match between challenge and strategy, the individual must sense threat or potential harm associated with the problem, acknowledge that a problem exists, and recognize the nature of the problem. Thus, in adaptive coping, the individual must be in affective and cognitive contact with an objective challenge, experiencing short-term distress, "facing facts," and selecting and implementing a strategy that will minimize long-term risk and maximize long-term benefit for self and others.

Maladaptive Challenge Management. Escape and avoidance are the most readily available challenge-management strategies, perhaps genetically programed, certainly available to all people from an early age, and sometimes effective because they minimize short-term distress (Suls and Fletcher 1985). Yet, escape and avoidance when mismatched to challenges are maladaptive. Escape and avoidance when secured through the use of mind- and mood-altering substances (such as drugs and alcohol) are doubly maladaptive because the substances incur a cascade of new objective challenges. Each time the distress precedes a successful escape from a challenge, future distress (and future escape attempts) are strengthened by negative reinforcement. At the same time, mounting unresolved challenges promote more real reasons for future distress (Alexander and Hadaway 1982).

Adaptive Challenge Management. In adaptive coping, the individual uses resolution and accommodation when a challenge calls for these strategies (Lazarus and Folkman 1984; Moos and Billings 1982). In turn, resolution and accommodation require the use of subordinate skills of information exchange, behavior management, and problemsolving with others and with self (Blechman and Tryon, in press; Wills 1990a). Therefore, resolution and accommodation are more arduous and less appealing than either escape or avoidance. Whereas escape and avoidance minimize short-term distress, resolution and accommodation require the individual to tolerate distress while grappling with a challenge. The ability to successfully gain social support from significant others has been shown to be effective for helping smokers (Mermelstein et al. 1986; Wills and Vaughan 1989) and opiate users (Rhoads 1983; Tucker 1985) avoid use of dangerous substances. Social integration also has been shown to be a protective factor for drug abuse (McMahon and Kouzekanani 1991; Timmer et al. 1985; Pakier and Wills 1990) and acquired immunodeficiency syndrome (AIDS) risk behavior (Zielony and Wills 1990).

Coping via Affect Management

The feelings tolerated while an individual grapples with a challenge, pursues a reinforcer, or succeeds or fails at managing challenges and reinforcers require coping via affect management (Blechman 1990b). Tronick has observed this process in infants and calls it affect regulation. Lazarus studies this process in adults and calls it emotion-focused coping. Wills studies this process in adolescents and reports that adolescents with chronically high levels of negative affect and low levels of positive affect, presumably resulting from inadequate affect management, are at high risk for substance abuse (Wills 1990b; Vaccaro 1991).

We use the term "affect management" (rather than affect regulation or emotion-focused coping), recognizing that the process of dealing with affect is continuous, often involves awareness and acceptance of affect rather than its change, and is associated with reinforcer pursuit as well as with confrontation of challenges. Affect management is defined here to subsume (1) monitoring of feelings, (2) regulation of feelings, and (3) mood recovery.

Adaptive Affect Management. When coping is adaptive, the individual manages feelings in ways that optimize the pursuit of reinforcers and the confrontation of challenges. More specifically, when coping is adaptive, there is:

1. Continuous awareness and tolerance of the full range of feelings associated with reinforcers and challenges. Continuous access to feelings provides the individual with information that maximizes the management of reinforcers and challenges.

2. Skillful regulation of feelings (e.g., from negative to neutral) and control of impulses (e.g., delaying inappropriate action) so that neither feelings nor impulsive behavior interferes with management of challenges and reinforcers.

3. Rapid recovery of stable good mood, despite the outcome of struggles with challenges and reinforcers. In adaptive coping the individual can bounce back relatively quickly after failure confronting a challenge or loss of a highly valued reinforcer.

Maladaptive Affect Management. When coping is maladaptive, the individual manages feelings in ways that obstruct the pursuit of reinforcers and the confrontation of challenges. More specifically, when coping is maladaptive, there is:

1. Continuous denial and avoidance of many of the feelings associated with reinforcers and challenges. Limited access to feelings reduces information about how to manage reinforcers and challenges.

2. Inept regulation of feelings (e.g., negative feelings cannot be moderated) and control of impulses (e.g., action cannot be delayed) so that both feelings and impulsive behavior interfere with management of challenges and reinforcers. In addition, inept expression of feelings involves the interpersonal domain of coping; responding to negative emotion through inappropriate expression (e.g., blaming, yelling, or taking it out on others) would have several negative consequences, including the erosion of social support.

3. Difficulty returning to a good or neutral mood once struggles with challenges and reinforcers are over. In maladaptive coping, the individual does not bounce back after a failure in confronting a challenge or the loss of a highly valued reinforcer.

Drug Abuse, Poverty, and Maladaptive Coping

When women abuse drugs, three maladaptive coping processes contribute to, sustain, and are sustained by drug abuse. Maladaptive reinforcer management, challenge management, and affect management trap women into drug use and make escape from drug use and acquisition of adaptive coping increasingly impossible (Billings and Moos 1983; Marlatt and Gordon 1985; Tucker 1985). Most important, because of their short-term payoffs, these maladaptive coping strategies become central features of drug-abusing women's lives.

Processes of positive and negative reinforcement conspire to train women to use drugs for reinforcer management (as the primary means of obtaining pleasure), for challenge management (as the primary means of avoiding or escaping from challenges), and for affect management (as a means of regulating affect and impulses and recovering a good mood). Positive reinforcement of drug use (presentation of a pleasurable event contingent on the operant drug-using behavior) derives from the drug's physiological impact (when the user's mood is elevated and sexual impulses are heightened), from the drug user's social milieu (when the user maintains social support and status via drug use), and from the user's economic plight (when the user turns a profit by selling drugs). Negative reinforcement (removal or reduction of an aversive event contingent on an operant behavior) of drug use derives from the drug's physiological impact on the drug user, particularly its capacity to distract attention away from challenges, to diminish a bad mood, and to dull hard-to-control violent and sexual impulses.

Poverty and Maladaptive Coping. Given these multiple opportunities for learning maladaptive coping, it is understandable why drug use is so prevalent, particularly among people facing numerous chronic and unmanageable challenges (e.g., inner-city women) with few opportunities to learn adaptive modes of coping and with many opportunities to observe maladaptive coping. In addition to subcultural pressures for drug abuse, there are individual social learning pressures from observing parents or friends use drugs (Biglan et al. 1985; Kandel et al. 1978) and biological pressure from an irritable temperament that increases the hedonic value of drugs such as cocaine (Lerner and Vicary 1984).

Maladaptive Coping Among Poor Women. Among poor women, biology, learning history, and the culture of poverty may conspire to promote a drug-centered way of life characterized by maladaptive coping. The culture of poverty limits women's access to reinforcers with long-term benefits (e.g., nutritious food, uninterrupted sleep) and overexposes them to reinforcers with long-term costs (e.g., risky sex). Quite often, poor women's survival seems to require them to seek reinforcers with long-term costs. This is particularly the case for risky sex, which many poor women barter for food, shelter, and drugs.

MEASUREMENT OF FUNDAMENTAL COPING PROCESSES

In the preceding section of this chapter, we argued in favor of measuring fundamental coping processes central to drug abuse and to successful treatments for drug abuse and specified three fundamental coping processes: management of reinforcers, management of challenges, and management of affect. Finally, we proposed that maladaptive coping reinforces and is reinforced by drug abuse.

This section suggests methods for measuring these coping processes and associated constructs (e.g., challenges). These same methods can be used to measure outcomes likely to result when a woman shifts from maladaptive to adaptive coping and begins to profit from drug abuse treatment. Recommended process and outcome measures are listed below. Because the methodology of coping assessment is still developing, several approaches to coping assessment are suggested and the strengths of particular approaches are noted. We make recommendations for specific measures when clear evidence is available linking them to drug use and the measures are appropriate for administration with a young, uneducated population.

Measures of Reinforcers

1. Addiction Severity Index (ASI) (as revised by Blechman and Adler) (material reinforcers)

2. Perceived social support-Interpersonal Support Evaluation List (ISEL)

3. Social network structure-Social Network Index (SNI)

Measures of Reinforcer Management

4. ASI (as revised by Blechman and Adler)

5. Urine and breathalyzer tests

6. Expectancy for drug effects-Alcohol Expectancies Questionnaire (AEQ)

7. Self-reinforcement-Frequency of Self-Reinforcement Questionnaire (FSR)

Measures of Challenges

8. Major life events-Life Events Schedule (LES); weekly events-Recent Events Scales (RES); subjective stress-Perceived Stress Scale (PSS)

9. Mincy-Sawhill-Wolf measure of residential environment stress

Measures of Challenge Management

10. Intention-Based Coping Inventory (IBCI) (adoptation of Wills' RBCI)

11. Coping with temptation-Situational Competency Test (SCT)

12. Interpersonal communication (INTERACT/BLISS)

13. Substance-related assertion-Multidimensional Assertiveness Inventory (MAI)

Measures of Affect Management

14. Bipolar mood adjectives (Zevon and Tellegen factors)

15. Depression-Beck Depression Inventory (BDI)

16. Vagal tone

17. Self-control-Self-Control Schedule (SCS)

18. Impulsiveness (Eysenck scales)

General Strategies for Selecting Process Measures

The following five principles guided the selection of the specific measures enumerated above.

1. Choose measures that tap fundamental, universal processes associated with recovery from dysfunction. The decision to measure coping processes was guided by this principle.

2. Sample key processes repeatedly over time. This approach allows for documentation of the course of recovery.

3. Sample key processes under varying environmental circumstances. Measure the environment as carefully as the person. Documentation of the timing of daily hassles, major life events, and changes in the general quality of the environment (e.g., associated with a move from one neighborhood to another) allows for inferences about the way in which key processes shape and are shaped by the environment.

4. Assume that every important outcome was once a process. Having chosen measures of fundamental processes, transform these into outcome measures. This is most easily done by administering the same measure (of challenge management, for example) repeatedly during participation in treatment (to reflect process) and repeatedly at the end of treatment and during followup (to reflect outcome).

5. Measure key process and outcome variables with diverse methods, including self-report, direct observation, and physiological measurement. Expect discrepancies among these measures.

Measures of Reinforcers

Reinforcer management is a fundamental coping process. The following sections describe methods of measuring reinforcer management. However, it is a mistake to measure how the individual manages reinforcers while ignoring the

range of available reinforcers. When a limited range of reinforcers is available, as is the case for indigent women, management of reinforcers is (for good reason) likely to appear deficient.

Two classes of reinforcers deserve consideration and careful measurement: material reinforcers (e.g., money, property) and social reinforcers (e.g., social support).

Material Reinforcers (ASI). Availability of material reinforcers can be assessed by gathering information about all sources of income available to the respondent. The ASI, which has been revised by Blechman and Adler (1991) for use with indigent substance abusers and described below as revised, includes questions that can be used for this purpose.

Social Reinforcers (Assorted Measures). The perceived availability of social reinforcers has an important impact on drug use initiation and relapse (Billings and Moos 1983; Wills 1990c). Perceived social support depends on the size and structure of the social network and the availability of particular supportive functions (Cohen and Wills 1985; Wills 1991). The ISEL (Cohen and Hoberman 1983) is a psychometrically derived measure that taps dimensions of emotional support, instrumental support, informational support, and social companionship. The ISEL and related measures have been shown to predict drug use and relapse (Billings and Moos 1983; Fondacaro and Heller 1983; Mermelstein et al. 1986; Wills et al., submitted for publication; Wills and Vaughan 1989). Standard measures of social network structure, such as the SNI (Cohen 1985), independently predict drug abuse (McMahon and Kouzekanani 1991; Pakier and Wills 1990; Tucker 1985) and AIDS risk behavior (Zielony and Wills 1990).

Recommended Measures of Reinforcers. We recommend the ASI (as revised by Blechman and Adler 1991) to measure availability of material reinforcers, the ISEL to measure perceived social support, and the SNI to measure social network structure. These measures have demonstrated correlations with drug use and have been administered successfully with similar populations.

Measures of Reinforcer Management

Reinforcer management can be operationalized and measured in several ways (for general discussions see Alanko 1984; Donovan and Marlatt 1988; Rouse et al. 1985). This section lists a variety of approaches to measuring reinforcer management, beginning with the most widely used self-report and biochemical measures and ending with more experimental measures.

Self-Report Measure of Addictive Substance Use (ASI). The ASI (McLellan et al. 1980a, 1980b) provides a self-report measure of the individual's reliance on drugs. The instrument includes scales for severity of drug abuse, psychiatric symptomatology, and social relationships. The ASI scores for psychiatric impairment and severity of addiction to alcohol and other drugs have been shown to predict treatment outcome for drug abuse patients (McLellan et al. 1983; Rounsaville et al. 1986) and AIDS-related risk behavior (Zielony and Wills 1990). The ASI has been used widely with drug-abusing populations and, when resources are limited, is the best choice of a measure of reinforcer management. Blechman and Adler (1991) have revised the ASI for use with populations of indigent, pregnant substance abusers (Blechman and Adler 1991). They have simplified and adapted the language used in the ASI to reflect the needs, abilities, and culture of this inner-city population of pregnant substance abusers. In addition, they have included additional questions dealing with pregnancy issues (e.g., the subject's discovery of her pregnancy, the degree and extent of the subject's drug use before and after discovery of pregnancy). Wills' RBCI, described below, also includes scales to index use of drugs as a coping mechanism.

Biochemical Measures of Addictive Substance Use (Assorted). Urine drug screens and breathalyzer tests provide objective measures of the individual's reliance on drugs as a source of pleasure and relief from pain (Callahan and Pecsok 1988). Although urinalysis aggregates drug use over considerable periods, it has been shown to be sensitive for demonstrating the effect of life challenges on drug abuse among methadone patients (Pakier and Wills 1990).

Measures of Expectancies About Addictive Substances (AEQ). Self-report measures of expectancies about drug effects index the extent to which the individual believes drugs will improve mood, reduce stress, and improve performance. Generic measures tapping the expectancy that pleasure will be enhanced and pain reduced by various drugs (alcohol, cocaine, marijuana) have been shown to predict serious drug abuse in several populations (Annis and Davis 1988; Kandel et al. 1978; McKirnan and Peterson 1988; Newcomb et al. 1988). Measures of expectancies for alcohol consumption also have shown predictive value for adolescent and adult drinking (Brown et al. 1985; Christiansen et al. 1989; Cooper et al. 1988). The AEQ (Brown et al. 1980, 1985) has been used widely and seems well suited for use with drug-abuser populations.

Cognitive Reinforcer Management (FSR)

It is important to assess cognitive mechanisms of reinforcement as well as biological ones. The FSR (Heiby 1983) is a 30-item self-report scale that elicits

information about positive self-reinforcement. Items include thinking positive thoughts about the self, praising oneself for good performance, maintaining appropriate standards for performance, and not blaming oneself for failure. Although this scale has not been extensively used in drug abuse research, it taps a construct that is important for treatment outcome.

Recommended Measures of Reinforcer Management. The following measures of reinforcer management are recommended: the revised ASI for self-report of addictive substance use, urine and breathalyzer tests for biochemical indices of substance use, the AEQ for expectancies about drug effects, and the FSR questionnaire for cognitive reinforcer management,

Measures of Challenges

Challenges (problems or stressors) refer to aspects of the environment with which a woman must cope to survive. All too often the woman's style of challenge management is assessed while the challenges facing her are ignored. Challenges can be assessed subjectively via self-report or objectively through checklists. In the assessment of interventions for drug-using women, the substantial environmental challenges these women face cannot be ignored. A successful intervention necessarily will affect the real and perceived challenges that threaten women's competence.

Subjectlve Challenges (Assorted Measures). Challenges usually are measured via self-report checklists that index the occurrence of major life events and/or everyday negative events ("hassles"). Although there are some unresolved methodological issues (Baum et al. 1982; Cohen 1988), there is general consensus for measuring challenges in this way. For measures of major life events in general populations, the LES (Sarason et al. 1978) is a 57-item checklist that indexes the occurrence and severity of major events during the previous year. Adaptations of life events checklists also have been developed for young adults (Newcomb et al. 1981; Johnson and McCutcheon 1980). Everyday negative events can be measured with the Hassles and Uplifts Scales, which contain 117 and 135 items, respectively (DeLongis et al. 1982; Lazarus and Folkman 1988). A shorter version is the RES (Wills 1985), a 24-item weekly events checklist based on the Unpleasant Events Schedule (Lewinsohn and Amenson 1978) used with adolescents. In addition, measures of subjective stress such as the PSS (Cohen et al. 1983) assess some challenges not represented in stressful events checklists. The measures noted above have been shown to predict substance use in samples of adolescents and adults (Cohen and Williamson 1988; Newcomb and Harlow 1986; Wills 1986, 1990b). Because measures of major events, daily events, and subjective stress may be differentially related to drug use, we recommend assessing challenge at ail three levels whenever this is feasible.

Environmental Challenges. Challenges from the residential environment can be measured by a residential index of underclassness (Mincy et al. 1990). This index uses ZIP Codes of residence combined with census tract data to determine the extensiveness of social marginality and behavioral deviance (e.g., teen pregnancy, unemployment, homicide) in the immediately surrounding neighborhood. The presumption is that neighborhoods in which social marginality and behavioral deviance are high represent an extremely stressful environment.

Recommended Measures of Challenges. For measures of psychological challenges we recommend the LES for major life events, the RES for weekly events, and the PSS for subjective stress, because these scales all have demonstrated relationships with drug abuse. For a measure of environmental challenge we recommend the Mincy and colleagues (1990) residential measure.

Measures of Challenge Management

Challenge management can be operationalized and measured in terms of coping, communication, assertiveness, or self-esteem.

Coping (Assorted Measures). There are three fundamental coping processes directed at reinforcer management, challenge management, and affect management. However, in common usage, coping is equated with challenge management. This section describes measures of coping with challenges (problems or stressors).

The measurement of coping with challenges is the subject of active discussion about methodology (Carver et al. 1989; Moos and Billings 1982; Stone et al. 1988, in press: Wills and Shiffman 1985). Investigators with a cognitive bent favor the intention-based approach in which respondents set priorities for goals in dealing with challenges (problems, stressors) (e.g., Stone and Neale 1984). Investigators with a behavioral bent favor the response-based approach in which respondents either report how they deal with a specific challenge (problem, stressor) or demonstrate how they deal with challenges,

Self-report, response-based measures of coping include the Health and Daily Living Form (Moos et al. 1984), the Ways of Coping Checklist (Folkman et al. 1986; Folkman and Lazarus 1988), and subsequent adaptations (Vitaliano et al. 1985, 1990; Carver et al. 1989). An adaptation tested by Rohde and colleagues (1990) with a sample of older adults produced a 17-item factor termed Ineffective Escapism, which includes items on drug use. Items contributing to this factor can be used as a measure of escapist, avoidant coping.

The RBCI, a 54-item self-report, response-based inventory used with adolescents (Wills 1985), measures 11 coping dimensions, including behavioral coping, cognitive coping, social support, drug use, avoidance, aggression, and entertainment. Wills (1985, 1986) has administered his response-based coping measure and an eight-dimensional, intention-based inventory based on work by Stone and Neale (1984) (in research with adolescents). He found that response- and intention-based measures yielded equivalent, significant relationships between coping and adolescent substance use. In Wills' adaptation the intention-based measure is relatively brief and can be used to assess coping with different types of problems and/or over different occasions. There is some suggestion that the repeated measures approach produces more reliable assessment (Wills 1986).

Role-play tests provide an opportunity to observe how respondents cope with simulated temptations to substance use (Abrams et al. 1987; Chaney and Roszell 1985; Shiffman 1985). Although more expensive than self-report measures of coping, role-play tests are more suitable for young and poorly educated adult populations because they present clients with specific situations in which behavior can be elicited. Measures such as the SCT have been shown to predict relapse to drug use (Chaney et al. 1978; Chaney and Roszell 1985).

Communication (INTERACT/BLISS)

During real-life, face-to-face communication (with peers, family members, therapists) respondents demonstrate how they manage interpersonal challenges (how they exchange information, influence behavior, solve problems) (Blechman 1990a). The INTERACT/BLISS (Dumas and Blechman 1990) provides a direct observational measure of these three dimensions of communication. The INTERACT/BLISS can be applied to live or videotaped interactions with significant others or strangers in unstructured or structured situations. Moreover, the INTERACT/BLISS can be applied to a verbal administration of the ASI as revised by Blechman and Adler. The INTERACT/BLISS is an interactive computer coding system that yields scores believed indicative of the effectiveness of small-group communication (Blechman and Tryon, in press).

Assertiveness (MAI). Measures of assertiveness presumably index success at the behavior management dimension of communication. Assertiveness can be measured via observation of response to specific temptations (as in the Chaney and Roszell measure described above) or via self-report to a range of assertion situations (Botvin and Wills 1985). Wills and coworkers have adapted a self-report assertiveness inventory originally developed by Gambrill and Richey

(1975). Several applications with the MAI (Wills 1985; Wills et al. 1989) have shown that nonassertive responses predict drug use among adolescents (Wills et al. 1989) and AIDS risk behavior among adult drug addicts (Zielony and Wills 1990).

Self-Esteem and Self-Efficacy (Assorted Measures). Measures of self-esteem or self-efficacy index the individual's subjective appraisal of success at challenge management. Increased self-efficacy and self-esteem are demonstrated outcomes of successful psychotherapy (Wills 1982) and a predictable ingredient in effective social support systems (Thoits 1986; Wills 1987; Wills, In press). The use of multidimensional measures of esteem and efficacy seems advisable because different dimensions correlate in opposite directions with drug use. For example, feelings of generalized efficacy and self-regard are associated with low drug use, while social esteem and efficacy are associated with high drug use (Wills and Vaughan, submitted for publication). Psychometric studies with the Multidimensional Esteem Scales (MES) (Fleming and Watts 1980) and the Spheres of Control (SOC) measures (Paulhus 1983) have provided excellent subscales of self-esteem and self-efficacy that may be adapted for specific populations.

Recommended Measures of Challenge Management

For measurement of challenge management, we favor the Wills IBCI with scales to measure both productive coping and avoidant coping. When use in a repeated-measures version, this inventory can be used to determine how clients cope with different types of problems, and aggregate scores for coping over different problems can be constructed. For assessing how clients cope with specific temptations for drug use or other risky behavior, we favor the Situational Competency Test. For measuring interpersonal behavior, we recommend the INTERACT/BLISS for communication patterns and the MA for assertiveness.

Measures of Affect Management

Affect management can be viewed and measured from four vantage points: the communication of affect (Buck 1984), the subjective experience of affect, the physiological expression of affect, and the self-control of affect-related behavior. The INTERACT/BLISS, recommended above as a measure of interpersonal challenge management, provides a measure of the communication of affect. This section describes measures corresponding to the other three vantage points on affect management.

Subjective Experience of Positive and Negative Affect (Assorted Measures). Mood adjective checklists administered daily (e.g., Stone and Neale 1984) or weekly (e.g., Wills 1986) yield information about respondents' specific mood states and general sense of well-being (Diener 1984). Wills and coworkers have found that adolescents prone to drug use report frequent negative and infrequent positive mood states (Wills 1986; Wills and Vaccaro 1991). Tellegen and colleagues (Watson and Tellegen 1985; Zevon and Tellegen 1982) have conducted factor-analytic research to determine mood adjectives that are pure markers of independent dimensions of positive and negative affects. Other measures of mood states have been derived from this work (e.g., Diener and Emmons 1984; Watson et al. 1986).

The measures just described assess positive and negative affects. Other measures focus specifically on negative affect (Watson and Clark 1984) and on the occurrence and severity of depressive symptomatology. The BDI (Beck 1967) is used extensively to assess clinical levels of depression. For assessing milder levels of depressive symptomatology in groups that are more like the general population, the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977) has been used and validated with a variety of adult and adolescent populations. Depression has been linked with drug abuse in retrospective and prospective studies of adults (Christie et al. 1988) and adolescents (Deykin et al. 1987; Kandel et al. 1978).

Physiological Expression of Affect (Vagal Tone). A measure of vagal tone (more precisely, the respiratory component of heart rate variability) gathered before, during, and after a challenge (e.g., a distressing conversation with a boyfriend) provides an interesting, albeit experimental, measure of the individual's capacity to manage affect and remain calmly attentive in the face of a challenge. What is known about vagal tone comes mostly from children, who exhibit curious, sociable behavior and high vagal tone and have many chances for learning during exposure to challenges (Kagan et al. 1984). Vagal tone was chosen by Fox (1989) as a measure of reactivity based "on a well-documented association between it and reaction to sensory stimulation," Fox (1989) collected longitudinal data from 88 healthy infants with high and low vagal tone. Infants with high vagal tone were more reactive to positive and negative events at 5 months and more sociable at 14 months. Thus, vagal tone seems a promising physiological index of affect management and of preparedness for learning and performance.

Self-Control of Affect-Related Behavior (Assorted Measures). In the midst of reinforcer or challenge management, affect management is always an issue. Effective reinforcer and challenge management requires self-control over affect and affect-related behavior so that impulsiveness is limited and thoughtfulness

predominates. Several self-control inventories are available to measure this process,

Eysenck and Eysenck (1977) developed three 134-item scales as independent measures of impulsiveness, risk-taking, and nonplanning. These three behavioral tendencies predict drug use in young adult populations (Labouvie and McGee 1986; Newcomb et al. 1986; Wills et al. 1991).

The Rosenbaum SCS (Rosenbaum 1980) is a 36-item scale tapping a range of problemsolving and emotion-control strategies, It has been used successfully with a variety of clinical populations but not with addicts (Rosenbaum 1990), as has a similar measure developed by Heppner (1989). Kendall and Wilcox's scale for children and adolescents (Kendall and Wilcox 1979; Kendall and Williams 1980) contains simple items appropriate for school or institutional administration with self-report or staff ratings, The Kendall-Wilcox scale has been used in several clinical settings (Kendall and Williams 1980). A 22-item adaptation of this scale is a strong predictor of drug use in adolescent samples (Wills et al. 1991).

Recommended Measures of Affective Management. For measurement of recent affective experience we recommend the mood adjectives developed by Zevon and Tellegen (1982). For assessing depression we recommend the BDI for clinical populations. Measures for vagal tone are described above. For measuring self-control we recommend the Kendall and Wilcox scale and the Eysenck scales for impulsiveness and risk-taking because these measures have empirical support for predictive substance abuse. We suggest that investigators carefully examine all the measures discussed above.

SUMMARY

As a guide to the selection of process and outcome measurement in interventions with drug-abusing women, we have offered a model of fundamental coping processes. Three coping processes-reinforcer management, challenge management, and affect management-appear critical to women's competence and physical hardiness. When these processes go awry, substance abuse is a likely result. For successful recovery from substance abuse, good fortune or purposeful intervention must promote these coping processes, To measure the impact of any intervention with drug-abusing women, methods of assessing fundamental coping processes during intervention (process measures) and repeatedly after intervention (outcome measures) are needed.

We have described multiple methods of measuring fundamental coping processes from diverse vantage points: self-report, behavioral observation, biochemistry, and physiology. We have discussed how these measures relate to the theoretical model. Finally, we have indicated measures favored and used in our longitudinal and intervention research on adolescent and perinatal substance abuse.

The final set of measures, as summarized in the list of recommended process and outcome measures on pages 324-325, is somewhat lengthy because the process of intervention is complex. Given the financial and structural limitations of research in drug treatment settings, it may not be possible for a single investigator to employ all the recommended measures. An adequate research design would employ two measures from each of the domains outlined. If resources allow, more extensive measurement procedures would be possible.

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Discussion: Dilemmas in Research in Perinatal Addiction-Intervention Issues

Loretta P. Finnegan

In their chapters, Brown and Blechman and colleagues present much useful information about several aspects of intervention. Both encouraging and distressing comments were heard at the technical review. Of concern are such statements as the following: "We do not know what treatment is" and "We do not know what works and what does not." Researchers *do know* what works. They need to utilize sound principles of patient management (e.g., a good medical, social, and family history; physical examination; and psychiatric evaluation) and then make a diagnosis or diagnoses. Subsequent to this, a treatment plan can be developed, and intervention into the multitude of physical, psychological, and sociological issues that pregnant drug-dependent women experience can begin. It is not easy, but it is feasible. Many basic problems will complicate interventions. For example, in Philadelphia, Kaltenbach and Finnegan (1989) found that 80 percent of the women enrolling in treatment had one or two parents who were addicted to alcohol or other drugs. Moreover, 70 percent of the women had been sexually abused by age 16.

Extensive information is available in the literature so that individuals interested in research in the area of perinatal addiction can develop a sound knowledge base. The first responsibility of any individual interested in pursuing the treatment or intervention aspects of perinatal substance abuse is to understand the accumulated knowledge in this and related fields. Knowledge of the following areas is essential: perinatal medicine, neonatology, genetics, pharmacology, drug abuse treatment, child development assessment, psychiatry, sociology, and human immunodeficiency virus and other infectious diseases. These are the foundations of the knowledge base.

In her chapter, Brown comments that social interactions between men and women are extremely important to treatment outcome. The research team also needs to recognize the heterogeneity of women in general and the important impact of ethnicity. The team must realize that women encounter tremendous

barriers when seeking treatment. Equivalent professional services should be provided for white and black women. When looking at the mean age of the women enrolled in treatment research programs, it is clear that they have been addicted for a long time. What happened when they were adolescents, frequently pregnant, taking drugs, and involved with delinquent activities? Where were the pediatricians, nurses, and social workers?

As indicated earlier, the researcher interested in this area must be familiar with many disciplines and carefully review what he or she reads. Reading the abstracts of articles is not enough. One must analyze and assess the literature to ascertain any bias that may have been presented in an article. A good example of bias is described by Koren and colleagues (1989) in a report titled "Bias Against the Null Hypothesis: The Reproductive Hazards of Cocaine" that examined whether studies showing no adverse effects of cocaine in pregnancy have a different likelihood of being accepted for presentation by the Society for Pediatric Research. The abstracts reviewed were those submitted between 1985 and 1989. There were 58 abstracts on fetal outcome after gestational exposure to cocaine. Of the 9 abstracts showing no adverse effect, only 1 (11 percent) was accepted, whereas 28 of the 49 positive ones were accepted (57 percent), a significant difference. Moreover, one could argue that the studies with negative outcomes were stronger than those with positive outcomes. The negative studies tended to verify cocaine use more often and to have more cocaine and control cases. Of the 8 rejected negative studies and the 21 rejected positive studies, significantly more negative studies verified cocaine use and predominantly reported cocaine use rather than use of other drugs. The investigators concluded that this bias against the null hypothesis may lead to distorted estimation of the teratogenic risk of cocaine and that it may cause women who have used cocaine to terminate their pregnancies unjustifiably.

Another dilemma with regard to clinical research studies is illustrated in a paper authored by Doering and colleagues (1989) titled "Effects of Cocaine on the Human Fetus: A Review of Clinical Studies." This paper reviews the published studies of pregnancy outcome in cocaine-abusing mothers with a special focus on structural malformations and other neonatal risks. In their review of 14 clinical studies, the researchers contrasted the differences in the literature with regard to congenital malformations, neurological outcome, and sudden infant death syndrome (SIDS). They concluded that, given the limitations of studying any drug in pregnant women, the absolute risk of maternal cocaine intake may never be known; however, they did make some meaningful conclusions about the fetal risk associated with maternal cocaine use from these clinical studies. It was clear that placental dysfunction due to vascular compromise probably increases the fetal risk for growth retardation or prematurity. Fetal loss due to *abruptio placentae* also may occur. Cocaine-induced neuroexcitation can

cause neonatal behavioral abnormalities (e.g., increased startle response, abnormal sleep patterns, and jitteriness), but it is not clear if these behavioral effects are lastlng. Although there may be an increased risk for fetal structural abnormalities due to disruption of *in utero* events possibly related to the vasoactive properties of cocaine, this result is not consistent across studies. Several other articles look at the differences in studies regarding SIDS (Bauchner et al. 1988; Chavez et al. 1979; Kandall et al. 1991). Because of the differences in results, one must think critically in terms of risk. A review of fetal and maternal risk factors and neurological outcome studies (Jones and Lopez 1990) indicates much is still unclear. In addition, epidemiological studies are needed before the risk for structural fetal abnormalities is defined more precisely.

One of the few epidemiological studies reporting on congenital malformations from maternal use of cocaine during pregnancy is published by Chavez and colleagues (1989) at the Centers for Disease Control. They were able to observe urogenital anomalies at a statistically significant level. In the 1970s and 1980s many researchers were concerned about the potential hazards of methadone on child development. Using then-current methodology, no significant effects of methadone on infant development were found using the Bayley Scales of Infant Development.

A recent study by Rodning and colleagues (1989) on a few children has demonstrated that those age 1 1/2 to 2 years who are exposed to a polydrug environment *in utero* do not function as well as those who have not been exposed. The investigators postulate that this may indicate an early sign of future problems. Clearly, longitudinal followup in these and other children is essential to confirm this hypothesis.

In studying human populations, there is another vital consideration. Although researchers may be interested in evaluating the symptomatology of an infant who is undergoing narcotic abstinence or the neurobehavioral effects on the child exposed to cocaine, they must be cognizant of what is going on with the mother of this child and consider interventions with the mother. She needs help from a medical and psychological standpoint, and research goals will not be accomplished without her.

There are many who say, “Can addiction truly be cured?” It is clear that it cannot in every case, but have researchers tried hard enough? Has a nourishing environment been established for the baby and for the baby’s mother? Many researchers did not plan to become involved with the treatment of drug-addicted mothers; however, in the process of researching the issues around perinatal substance abuse, concerned clinicians saw that the small, very

ill neonates arriving in intensive care nurseries did not exist in a vacuum. It was clear that, to help these babies and to learn more about the effects of drugs *in utero,* in the neonatal period, and in infancy, efforts had to be initiated when they were in the uterus, and the mother also had to be considered. The problems seen in the current literature, the controversies and the dilemmas, are inherent in research in humans. Because researchers are not dealing with an animal population that can be well controlled, the rules surrounding research must be complex and varied.

The best advice for those interested in perinatal addiction research is not to be a "research litterbug." Each researcher must critically assess the work of others and his or her own work and not rush to publish after studying just a few subjects but consider collaborating with other centers that have similar patients. The National Institute on Child Health and Human Development has developed an effective mechanism called the Neonatal Network. Under cooperative agreements, multiple centers are looking at the same research questions, This provides a large subject pool and offsets the many confounding variables found in human populations.

In summary, from reading the chapters in this monograph, it is clear that researchers in the field of perinatal substance abuse must surround themselves with knowledgeable people. No one knows or ever will know everything about the multitude of areas that assist with the development of the appropriate methodology for the research as well as the appropriate treatment aspects for the maternal-infant dyad. The Nation is faced with a tragedy, and the impact of perinatal addiction must be thoroughly studied. Turf issues must be forgotten. This country's needs and the individual needs of drug-dependent pregnant women must be placed above personal gain. If all the superb information presented in this monograph is utilized, many fewer children would suffer from the effects of perinatal substance abuse.

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Alcohol- and Drug-Dependent Pregnant Women: Laws and Public Policies That Promote and Inhibit Research and the Delivery of Services

Ellen Marie Weber

INTRODUCTION

Significant public attention has focused on the urgent need to deal with maternal alcohol and other drug dependence. Alcohol and other drug dependence clearly leads to physical, mental, and developmental problems in women and children, including the increased risk of human immunodeficiency virus disease and the destabilization of families.

Yet, in the face of this crisis, appropriate drug and alcohol prevention and treatment services for all women, particularly pregnant women, have been grossly inadequate. In addition, essential social and health services needed to support poor families who are affected by substance abuse have been inadequate. Public response to this crisis has ranged from efforts to increase prevention, treatment, and health services for drug- and alcohol-dependent pregnant women, to mandating treatment for pregnant women, to removing children from families, to criminally prosecuting pregnant women.

Although there is disagreement about the appropriate response to this thorny issue, no one disputes that women must be encouraged to enter treatment early-before alcohol and other drug use affects their children-and that effective treatment services must be expanded dramatically to care for the women who seek rehabilitation. Early entrance of women into treatment programs is also crucial for conducting research that is needed to develop and study effective treatment models for pregnant women.

This chapter examines the laws and recent public policies that encourage women to enter treatment or deter them from doing so. It first examines the Federal statutes and regulations that provide for confidentiality of alcohol and other drug information about individuals who seek or enter treatment. Second,

it examines recent trends to use criminal law to prosecute women who use alcohol and other drugs during pregnancy and to amend State child abuse and neglect reporting laws to mandate reporting of infants who are exposed prenatally to or born dependent on drugs and alcohol. Finally, it examines how the trend toward punitive measures and expanded reporting requirements may affect treatment programs and the mission of researchers who work with those programs.

CONFIDENTIALITY OF DRUG AND ALCOHOL PATIENT RECORDS

Several Federal laws and two sets of Federal regulations provide for confidentiality of information about individuals who are in alcohol and other drug treatment programs and who are the subjects of research. The most comprehensive protections are found in the two Federal statutes and the set of implementing regulations known as the Confidentiality of Alcohol and Drug Abuse Patient Records regulations (hereinafter referred to as confidentiality regulations).[1] The other Federal law and set of regulations, which overlap the confidentiality regulations in some respects, permit researchers who obtain a Confidentiality Certificate to withhold information about research subjects[2]

Confidentiality Regulations

The Federal confidentiality laws and regulations guarantee strict confidentiality for persons who have sought or received treatment or diagnosis for alcohol and other drug-related problems. Congress enacted extremely strict confidentiality protections to protect clients' privacy rights because it recognized that alcoholism and other drug dependence are stigmatizing illnesses and that the disclosure of such conditions can lead to harsh results such as loss of employment or children. Thus, Congress feared that individuals would not enter treatment or benefit from it fully unless their identities as alcohol and/or other drug users and information about their treatment were protected by strict confidentiality.

Accordingly, the confidentiality regulations protect virtually all information about a woman if she has applied for or received any alcohol-or-other-drug-related services, including diagnosis, treatment, or referral for treatment, from a covered program. The restrictions on disclosure apply to virtually all information, recorded or not, that would identify the woman as an alcohol and/or other drug user, either directly or by implication. Thus, for example, a treatment program that is subject to the regulations cannot disclose the identity of a patient or even confirm that an individual is receiving alcohol or other drug treatment unless the request for information falls within one of the limited exceptions recognized by the regulations.

Virtually all treatment programs are covered by the confidentiality regulations. The regulations govern any federally assisted individual or program that specializes, in whole or in part, in providing treatment, counseling, and/or assessment and referral services for women with alcohol and other drug problems. The regulations define Federal assistance broadly, so as to include direct Federal funding, State and local funding that originates with the Federal Government, and indirect Federal funding such as having a tax-exempt status. Programs that are not technically covered under the regulations may choose nonetheless to comply with the standards.

The regulations prohibit a covered program from disclosing patient-identifying information[3] to a third party unless certain conditions have been met. The regulations also prohibit *redisclosure* by the recipient of information without compliance with the same conditions. The most common way that a program may permissibly disclose information is with the client's consent,[4] but there are several circumstances in which patient-identifying information can be released without the client's consent. Two exceptions to the nondisclosure rule that are particularly relevant to research on drug- and alcohol-dependent women are those relating to research and child abuse reporting.

Scientific Research. The exception to the nondisclosure rule most relevant to the National Institute on Drug Abuse's (NIDA) research mission is the research exception. Under these regulations, a program may, but is not required to, disclose patient-identifying information to researchers without patient consent, provided certain safeguards are met.[5]

The program may release information only to researchers who the program director determines are qualified. This decision depends on the appropriateness of the particular researcher for the research to be conducted. Researchers also must have a protocol ensuring that information will be stored securely and will not be redisclosed except as allowed by the regulations. The researcher must provide a written statement that the protocol has been reviewed by an independent group of three or more individuals who have determined that the rights of patients would be adequately protected and that the potential benefits of the research outweigh any potential risks to patient confidentiality posed by the disclosure of records.

With the sole exception mentioned in the next paragraph, researchers who receive patient-identifying information are strictly prohibited from redisclosing any patient information to anyone outside the treatment program. Research reports may not identify a patient either directly or indirectly.[6] Finally, no patient-identifying information obtained by a researcher may be used to conduct any criminal investigation of a patient, even in response to a Federal or State court order.[7]

Thus, for example, a scientist who wishes to conduct research on effective treatment modalities or detoxification procedures for pregnant women can obtain patient-identifying information if the treatment program authorizes such research upon determining that the researcher is qualified to conduct the research and will protect the confidentiality of the patients. However, the researcher cannot disclose any patient-identifying information in any report or to anyone not involved with the research project other than the program. The sole exception to this rule is that the researcher may make an initial report of child abuse or neglect if State or local law requires it.[8,9] However, the researcher cannot be compelled to disclose information about a woman's criminal activity or abuse or neglect of her children to prosecutors.[10]

Special precautions also must be taken if the researcher seeks to conduct long-term or followup studies of former patients. A researcher may attempt to contact a woman only if it can be done without disclosing to a third party her relationship to the treatment program. Accordingly, no inquiries-whether to relatives, friends, employers, or others-designed to locate a former patient may be conducted unless they can be carried out in a way that will not reveal the individual's status as a former drug or alcohol abuse patient or unless the patient has signed a proper consent form under the regulations.

Child Abuse and Neglect Reporting. The Federal law and regulations specifically provide that the regulation's "restrictions on disclosure and use [of patient-identifying information] do not apply to the reporting under State law of incidents of suspected child abuse and neglect to the appropriate State or local authorities."[11] Thus, all covered alcohol and other drug treatment programs and scientific researchers who work in such programs must, to the extent mandated by the State's child abuse statute, comply with the provisions of the mandatory reporting laws.

However, this exemption for child abuse reporting applies only to the *initial* reports of child abuse or neglect. The exemption does not apply to followup requests or subpoenas for additional information or records, even if the records are sought for use in civil or criminal proceedings resulting from the program's or researcher's initial child abuse report. Thus, patient files and information about patients must be withheld from child protection agencies absent an appropriate court order[12] or patient consent. And, as noted above, the information obtained by researchers never can be disclosed for purposes of a criminal investigation or prosecution for child abuse or neglect even if a court orders such disclosure.

The legislative history of the provision permitting reporting of child abuse makes clear that reporting is permitted only when there is danger or harm to the child

and is not permitted merely because a parent has abused alcohol or other drugs. According to one of the authors of the provision:

> The amendment should be applied so it does not dissuade persons from coming forward for drug or alcohol abuse treatment, especially since the children of untreated substance abusers are among the most common victims of child abuse. *The amendment is not intended to suggest that substance abuse by itself is a condition that must be reported as child abuse or neglect.* As under current practice, there must be some reason to suspect actual or imminent harm to the child (Edwards 1986). (emphasis added)

This guiding principle is extremely important to women who need treatment and to treatment programs because a requirement that all substance-abusing parents be reported would deter individuals from entering treatment for fear of a child abuse investigation and ultimately would result in the closing of many treatment programs. The sponsors of the amendment permitting child abuse reporting emphasized that confidentiality is extremely important even in the face of suspected child abuse. “The amendment is not intended to relieve treatment providers of the continued responsibility of insuring that the interests of patient confidentiality are protected to the fullest” (Edwards 1986).

Confidentiality Certificates

A second source of confidentiality specifically protects individuals who are the subject of research. This law permits researchers engaged in biomedical, behavioral, clinical, or other research, including research on the use and effect of alcohol and other psychoactive drugs, to obtain authorization from the Secretary of the Department of Health and Human Services[13] to withhold the names or other identifying characteristics of research subjects from all persons not connected with the research. If a researcher is issued a Confidentiality Certificate, he or she may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals.[14]

This law is both broader and narrower than the Federal confidentiality regulations. It has a more expansive reach because all researchers may seek authorization to protect the privacy of research subjects.[15] Since the confidentiality regulations only apply to programs that receive Federal assistance, a researcher may not be bound by the confidentiality regulations if the program in which he or she conducts research is not federally assisted. On the other hand, the confidentiality regulations restrict voluntary and compelled

disclosures, while a Confidentiality Certificate only protects a researcher from being compelled to disclose identifying information, Theoretically, a researcher who had such a certificate could, if not bound by the confidentiality regulations, voluntarily release information about research subjects.[16]

Thus, with regard to child abuse and neglect reporting, researchers who work with drug and alcohol programs that are bound by the Federal regulations must comply with those regulations to obtain patient information and conduct their work. All other researchers may wish to obtain a Confidentiality Certificate to assure women who are the subjects of the research that their confidentiality will be protected to the greatest extent possible. Such assurances probably will be necessary to encourage alcohol- and drug-dependent women to participate in such projects.

PUNITIVE MEASURES AGAINST ALCOHOL- AND DRUG-DEPENDENT PREGNANT AND POSTPARTUM WOMEN

One alarming response to the crisis of maternal drug and alcohol dependence has been the criminal prosecution and incarceration of women for alleged drug use during pregnancy. A second response has been for States to amend their child abuse and neglect reporting laws to require reporting of infants who have been exposed prenatally to and/or are dependent on drugs and, in some cases, alcohol. These legal measures have had and continue to have an impact on the willingness of women to obtain prenatal care and drug treatment. They also will affect the scientific community's ability to conduct research in this area.

Criminal Prosecutions

Seventeen States have arrested and criminally prosecuted at least 45 women for drug use during pregnancy. These States generally have relied on four criminal charges. The first and most commonly used charge is distribution of drugs to a newborn.[17] Prosecutors have brought charges based on the theory that the woman has distributed drugs to the newborn through the umbilical cord during the brief period—60 to 90 seconds-after birth and before the cord was clamped or severed.[18]

A second charge is that of child abuse and endangerment, which usually is based on a newborn's positive toxicology test at birth.[19] In many cases, these charges have been dismissed because the State's child abuse statute was not intended to cover fetal abuse.[20] However, in at least one case, a judge in South Carolina sentenced a 21-year-old woman to 3 1/2 years in prison, suspended to 5 years probation, on child neglect charges because of her cocaine use during pregnancy (Plazza 1989).

Criminal charges for use or possession of drugs also are being brought against women based on a newborn's positive toxicology test. In South Dakota, a woman who was charged with ingestion of drugs on the basis of the infant's toxicology test was arrested 7 months after the birth of her child. The woman pled guilty and was given the maximum possible sentence even though she had participated successfully in a treatment program after the birth of her child.[21] In Indiana, a woman was charged with possession of cocaine based on findings that her child was born addicted to cocaine. The charge grew out of the hospital's child abuse report made pursuant to Indiana's statute that requires a report of newborns who exhibit signs of drug or alcohol addiction.[22]

Finally, some courts, in an effort to prevent drug use for the duration of the pregnancy, have sent pregnant women convicted of non-drug-related criminal charges to jail. In most cases, these women would have been sentenced to probation were it not for their status as pregnant drug users. In one highly publicized case, *United States v. Vaughn,*[23] the judge sentenced a woman convicted of second-degree theft to a prison term rather than to the usual sentence of probation when he determined that she was 7 months pregnant and used cocaine. In imposing the sentence, the judge noted that other judges of the Superior Court of the District of Columbia had similarly incarcerated pregnant drug abusers. It is relevant to note that the defendant in this case received no drug treatment or prenatal care while she was incarcerated.

These cases represent an alarming trend for several reasons. First, and most important, many experts are warning that punitive measures are counterproductive and result in deterring women from seeking prenatal care and treatment (American Society of Addiction Medicine 1990; Chavkin 1990a, 1990b).

Second, in many cases, evidence of drug use and possession is being gathered from the results of drug tests that are conducted on newborns and women—often without notice, informed consent, or probable cause to believe the woman has used or possessed drugs. These practices violate women's constitutional rights to due process and to be free from unreasonable searches and seizures. Many commentators have pointed out that tests conducted without notice and consent are performed more often by public hospitals on poor and minority women.

Finally, these cases also raise privacy issues. The U.S. Supreme Court has held that women are entitled to protections from government intrusions during pregnancy, although those protections may vary depending *on* the trimester involved (Roe *v. Wade).*[24] Criminal prosecutions against drug-dependent pregnant women penalize a woman solely for her decision to continue a

pregnancy. Therefore, they may send the unfortunate message that if you are drug-dependent and choose to continue your pregnancy you can be prosecuted, but if you abort you will not be.[25]

Often, criminal cases have been brought with the goal of deterring other pregnant women from using drugs during pregnancy, but such prosecutions will have little deterrent effect. The criminal law appears to have little effect on drug abuse in general. The proposition that it somehow will have a greater effect with pregnant women is unsupported by any evidence. Alcohol and other drug dependence are diseases that must be treated to halt the behavior.[26] The sad fact is that pregnant women seeking treatment are often unable to obtain it (Chavkin 1990b). The real danger is that criminal prosecutions will deter women from seeking help for fear they will be punished for exposing their addiction.

Child Abuse Reporting Statutes

States also have begun to amend their child abuse and neglect statutes to expand the definition of abuse and neglect to encompass a newborn's dependence on or exposure to alcohol and/or other drugs. These statutes raise significant concerns for drug and alcohol treatment programs and researchers because treatment providers may be required in some cases to make abuse and neglect reports solely on the basis of a woman's prenatal drug or alcohol use. As noted above, this requirement conflicts with the principle guiding child abuse reporting under the Federal confidentiality regulations (see section above).

Nine States have amended their statutes to deal specifically with prenatal drug and/or alcohol use. Florida, Indiana, Massachusetts, Nevada, Oklahoma, and Utah mandate reports if a child is born dependent on or addicted to a controlled substance or addictive drug.[27] In addition, Indiana, Nevada, and Utah also require reporting of children born with fetal alcohol syndrome (FAS).[28] Three other States—Illinois, Minnesota, and Wisconsin-require reports of infants who have been exposed to drugs.[29] In addition, Minnesota requires a physician to report the nonmedical use of a controlled substance by a woman during pregnancy and, when there are medical indications of possible use of a controlled substance, to administer toxicology tests and report positive results that are found.

Although each State law varies as to which individuals are required to report suspected child abuse and neglect, some of the above laws may require treatment programs and researchers to do so.[30] In such States, reporting most likely will be required when the program or researcher works with a child who

demonstrates signs of alcohol or other drug dependence or gathers sufficient information from parents to form a suspicion that a child was born drug- or alcohol-dependent.

For example, in Florida, any person with knowledge or reasonable suspicion that a child was born dependent on drugs must make a report. Thus, a treatment program or a researcher working directly with a drug-dependent infant in a residential program may be obligated to make a report. Similarly, in Indiana, any individual, including health care providers, who have reason to believe that a child was born with FAS or drug addiction must report. The statutes in Nevada and Minnesota are also sufficiently broad to trigger the obligation to report if the treatment program or researcher has reason to believe that a child is suffering from alcohol or other drug dependence.

These laws represent a new trend in child abuse reporting. In addition, States that have not specifically amended their child abuse statutes may impose an obligation to report under their case law when evidence of maternal drug use and infant exposure to drugs exists.[31] Because State law interpretations vary dramatically and change constantly, treatment programs and researchers should seek legal advice on the scope of their obligations.

IMPACT OF MANDATORY REPORTING LAWS AND CRIMINAL PROSECUTIONS ON TREATMENT PROGRAMS AND RESEARCHERS

To further the goal of curtailing maternal drug and alcohol dependence, it must be determined what impact punitive actions will have on the wiilingness of women to come forward for treatment and, consequently, the ability of researchers to conduct their work. Clearly, without research, it will not be possible to develop and implement effective intervention and treatment programs for women and their children.

Many experts have warned that punitive measures may deter women from seeking prenatal care and treatment (for example, see American Society of Addiction Medicine 1990; Chavkin 1990a, 1990b), and anecdotal information supports this prediction. Moreover, interviews of 22 recipients of demonstration grants from the Office for Substance Abuse Prevention for Model Projects for Pregnant and Post-Partum Women and Their Children revealed that 15 programs believed that these measures were indeed deterring women from coming forward for treatment, 3 programs did not see a deterrent effect, and 4 did not have sufficient information to respond.[32]

Efforts to criminalize addiction during pregnancy also threaten to change the role of treatment providers and researchers in that treatment professionals may

be transformed from health care providers and advocates for patients to what one commentator coined, “pregnancy police” (McNulty 1987-88). It seems clear that this is a dangerous trend that will not result in either healthier mothers or babies.

CONCLUSION

The Federal confidentiality regulations establish a logical scheme that carefully balances the privacy rights of women and men in treatment against the public’s need to protect children against harm. These protections are necessary to ensure that women and men will enter alcohol and other drug treatment, recover, and provide a stable life for their children. These protections also ensure that scientists will be able to develop the most effective intervention and treatment programs for women and children.

This careful balance is being threatened by efforts to criminally prosecute women and report them for child abuse based on their conduct during pregnancy. Such “quick-fix” solutions raise serious legal questions and are not likely to achieve what is most needed for women and children: services to recover and create stable families.

NOTES

1. The statutory protections are set forth in the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970, 42 U.S.C. 290dd-3, and the Drug Abuse Prevention, Treatment, and Rehabilitation Act, 42 U.S.C. 290ee-3. The Federal regulations are found at 42 C.F.R. Part 2.

2. The statute is found at 42 U.S.C. § 241 (d), and the regulations on Protection of Identity-Research Subjects are found at 42 C.F.R. Part 2a.

3. 42 C.F.R. Section 2.11 of the regulations defines “patient-identifying information” as the name, address, social security number, photograph, or similar information by which the identity of a patient-one who has sought or received alcohol or other drug services-can be determined with reasonable accuracy and speed either directly or by reference to other publicly available information.

4. 42 C.F.R. Section 2.31 of the regulations sets forth a specific format for the client’s consent and provides that the consent form is not valid unless it contains all the required information. The consent form must be in writing and contain the following nine elements the name of the program

making the disclosure; the name of the individual or organization that will receive the disclosed information; the name of the patient; the purpose for the disclosure; how much and what kind of information will be disclosed; a statement that the patient may revoke the consent at any time, except to the extent that the program already has acted in reliance on it; the date or condition on which the consent expires if not previously revoked; the client's signature; and the date the consent was signed.

All information provided via a client's consent must be accompanied by a written prohibition on redisclosure stating that the information disclosed is protected by Federal law and that the recipient cannot make any further disclosure of it unless permitted by the regulations.

5. See 42 C.F.R. Section 2.52. This exception to the nondisclosure rule was created to ensure that research to advance drug and alcohol treatment could be conducted effectively. At the same time, the regulations sought to balance the researcher's need for information against the patient's right to privacy by imposing strict protections against the subsequent disclosure and use of all patient-identifying information.

6. Research reports can discuss a client's case as long as the report does not contain any information that could be used to accurately and quickly identify the client. Reports also can describe aggregate data about the research subjects since that type of information is not patient identifying.

7. See 42 C.F.R. Section 2.62.

8. See 42 C.F.R. Section 2.62.

9. See 42 C.F.R. Section 2.12(c)(6). The Federal laws were amended in 1986 to remove any restrictions on compliance with State laws mandating the reporting of child abuse and neglect.

10. See 42 C.F.R. Section 2.62.

11. See 42 C.F.R. Section 2.12(c)(6). The Federal laws were amended in 1986 to remove any restrictions on compliance with State laws mandating the reporting of child abuse and neglect.

12. Subpart E of the regulations allows a court to issue an order permitting the program to make a disclosure of information and records that otherwise would be prohibited. The regulations require the court to follow special procedures before it issues an order. In contrast to most

situations in which records are sought, a subpoena or search warrant, even when signed by a judge, is *not* sufficient, standing alone, to require or even permit a program to make a disclosure. See 42 C.F.R. Section 2.61 (b).

In short, if additional records are sought to conduct a civil investigation or proceeding against a patient for child abuse or neglect, a motion must be made for a hearing on the issue, and the program and the patient (or his or her representative) must be notified that a hearing will be held and must be given an opportunity to appear in person or file a responsive statement. See 42 C.F.R. Section 2.64(b).

To issue an authorizing court order, at the required hearing the court must find that "good cause" exists to issue the order (Section 2.64(d)). The regulations provide that

> [t]o make this [good cause] determination the court must find that:
>
> 1. Other ways of obtaining the information are not available or would not be effective; and
>
> 2. The public interest and need for the disclosure outweigh the potential injury to the patient, the physician-patient relationship and the treatment services.

The Federal regulations also limit the type of material that a court may order a program to release. Section 2.63 provides that a court may not order any disclosure of confidential communications made by a patient unless (1) the disclosure is necessary to protect against an existing threat to life or of serious bodily injury (including circumstances that constitute suspected child abuse and neglect); (2) the disclosure is necessary in connection with the investigation or prosecution of a serious crime such as homicide or rape; or (3) the patient already has offered evidence about confidential communications. In addition, Section 2.64(e) provides that an order must "limit disclosure to those parts of the patient's record which are essential to fulfill the objective of the order" and that only those persons having a need for the information may receive patient records.

To criminally investigate a patient for child abuse or to bring criminal charges, the court must also find that (1) the crime involved is extremely

serious, such as an act causing or threatening to cause death or serious injury (including child abuse); (2) the records sought are likely to contain information of significance to the investigation or prosecution; (3) there is no other practical way to obtain the information; (4) the public interest in disclosure outweighs any actual or potential harm to the patient, the doctor-patient relationship, and the ability of the program to provide services to other patients; and (5) when law enforcement personnel seek the order, the program has an opportunity to be represented by independent counsel.

A complete description of the court order procedure is contained in the Legal Action Center's publication Confidentiality: *A Guide to the New Federal Regulations.*

13. Under the regulations, the Directors of NIDA, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Mental Health issue confidentiality certificates upon application by the researcher. See 42 C.F.R. § 2a.3.

14. See 42 U.S.C. *§* 241 (d).

15. See 42 C.F.R. § 2a.1.

16. See 42 C.F.R. § 2a.4(j)(4) and § 2a.7(c).

17. Florida, Illinois, Georgia, Massachusetts, Michigan, and North Carolina have charged and prosecuted women on this basis.

18. Women have been convicted in at least two cases. In *State of Florida v. Black,* No. 89-5325 (Cir. Ct. Escambia County, Jan 3, 1989), a woman who admitted to using cocaine twice during pregnancy to induce labor was sentenced to 18 months in prison and 3 years probation for passing cocaine to her baby through the umbilical cord. In *State of Florida v. Johnson,* No. E89-890-CFA (Fla. Cir. Ct. Jul 13, 1989), *appeal docketed,* No. 89-1765 (Fla. Dist. Ct. App. Aug 31, 1989), a woman was found guilty on two counts of delivery and sentenced to 15 years probation during which she is prohibited from using drugs or alcohol, going to bars, or associating with people who use drugs or alcohol.

19. Florida, Michigan, Nevada, Ohio, South Carolina, South Dakota, Texas, and Wyoming have sought prosecutions on this basis.

20. See, for example, *Reyes* v. *Superior Court,* 75 Cal.App.3d 214 (Ct. App. 1977); *State of California v. Stewart,* No. M508197 (Municipal Ct. County of San Diego, Feb 26,1987) (A woman was arrested under a child support statute and charged with "falling to follow her doctor's advice to stay off her feet, refrain from sexual intercourse, refrain from taking street drugs, and seek immediate medical attention if she experienced difficulties with her pregnancy." The court dismissed the charges finding that the statute did not apply to the actions of a pregnant woman and did not create a legal duty of care owed by a pregnant woman to her fetus.); *State of Florida v. Gethers,* No. 89-4454 CF10A (Cir. Ct. for Broward County, *Nov 6,* 1989); State *of Ohio v. Andrews, No.* JU 68459 (Ct. C.P. of Stark County, Jun 19, 1989); *State of Ohio v. Gray,* No. (CR88-7406 (Ct. of C.P. of Lucas County, Jul 13, 1989); and State *of Wyoming v. Osmus,* 276 P.2d 469 (Wyo. 1954) (State child abuse statute not intended to apply to an unborn child).

21. See *State of* South *Dakota* v. *Christenson,* No. CRI. 90 (S.D. Cir. Ct. Mar 12,1990).

22. *State of Indiana v. Yurchak, No. 64* D01-8901-CF-181B (Porter County Super. Ct. filed Oct 2, 1989).

23. No. F-2172-88B (Super. Ct. of D.C., Aug 23, 1988).

24. 410 U.S. 959 (1973).

25. In addition, many criminal prosecutions have involved an expansion of a criminal statute to encompass conduct that was never intended to be proscribed by the statute invoked. For example, some women have been charged with delivery of a drug to a minor for ingesting a drug during pregnancy and passing it to their fetuses through the umbilical cord.

26. Indeed, the U.S. Supreme Court held in 1962 that criminal conviction for being addicted to the use of narcotics violated the Eighth and Fourteenth Amendments because addiction is a disease. The Court in Robinson emphasized that drug addiction is a disease:

> It is unlikely that any state at this moment in history would attempt to make it a criminal offense for a person to be mentally ill, or a leper, or to be afflicted with a venereal disease... [I]n light of contemporary human knowledge, a law which made a criminal offense of such a disease would doubtless be universally thought to be an infliction of cruel

> and unusual punishment in violation of the Eighth and Fourteenth Amendments...[T]he prosecution is aimed at penalizing an illness, rather than at providing medical care for it. We would forget the teachings of the Eighth Amendment if we allowed sickness to be made a crime and permitted sick people to be punished for being sick . . . . *(Robinson v. California,* 370 U.S. 660, 1962).

27. Fla. S. § 415.503(9)(a)(2) (1989) (abuse or neglect includes "physical dependency of a newborn infant upon any drug controlled [under state law]" with the exception of those used for detoxification or medically approved treatment); Ind. Ann. Code § 31-6-4-3.1 (Burns 1987) (child in need of services includes "child...born with fetal alcohol syndrome or an addiction to a controlled substance"); Mass. Gen. Law Ann. § 51A (West Supp. 1990) (mandatory report of child "who is determined to be physically dependent upon an addictive drug at birth"); Nev. Rev. Stat. § 432B.330 (child in need of protection if "he is suffering from congenital drug addiction or the fetal alcohol syndrome, because of the faults or habits of a person responsible for his welfare"); Okla. Stat. Ann. Q 646 (West Supp. 1990) ("child born in a condition of dependence on a controlled substance" must be reported); Utah Code Ann. Q 78-36-3.5 (Cum. Supp. 1989) ("child born with fetal alcohol syndrome or dependent on a controlled substance" must be reported).

26. Depending on the State's definition of "addictive drug," the Massachusetts statute (see endnote 27) also could encompass dependence on alcohol.

29. Ill. Rev. Stat. ch. 23, § 2053 (Smith-Hurd 1990) (neglected or abused minor includes "any newborn infant whose blood or urine contains any amount of a controlled substance as defined [in state law] or a metabolite of a controlled substance" with the exception of controlled substances whose presence results from medical treatment to the mother or newborn); Minn. Stat. § 626.556 ("neglect includes prenatal exposure to a controlled substance, as defined [under state law], used by the mother for a nonmedical purpose, as evidenced by withdrawal symptoms in the child at birth, results of a toxicology test performed on the mother at delivery or the child at birth, or medical effects or developmental delays during the child's first year of life that medically indicate prenatal exposure to a controlled substance."); Wisc. Sess. Laws § 146.0255 (West 1989-90) (infant who has a controlled substance in bodily fluids must be reported).

30. Several reporting statutes are structured so that treatment programs or the researchers working with them would not be required to make a report. For example, in Illinois and Wisconsin, a report is triggered by a finding of controlled substances in the newborn's body fluids. Treatment programs probably would not be responsible for conducting such tests; and indeed, in Wisconsin that responsibility is given to physicians who must obtain parental consent prior to testing. In Utah, the obligation to report rests with medical personnel who attend the birth or care for a child who is born with fetal alcohol syndrome or dependent on drugs. Only hospital-based drug and alcohol professionals and researchers who serve these functions and are deemed to be medical personnel would be obligated under this statute to make a report. Finally, in Oklahoma, the duty to report is on those who attend the birth of the child.

31. See, for example, *In the Matter of Stefanel Tyesha C.,* 157 A.D. 2d 322,556 N.Y.S.2d 280, 1990 W.L. 69335 (N.Y.A.D. 1st Dept., May 29, 1990).

32. The interviews were conducted by the Treatment Committee of the Coalition on Alcohol and Drug Dependent Women and Their Children between February and June 1990. Copies of the interviews are on file at the National Council on Alcoholism and Drug Dependence, 1511 K Street, N.W., Washington, DC 20005.

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Mandatory Reporting of Child Abuse and Research on the Effects of Prenatal Drug Exposure*

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INTRODUCTION

Research on the effects of prenatal drug exposure raises several serious legal issues. Many of these issues, such as informed consent and human subjects protection, have been explored extensively elsewhere and are not discussed here.[1] Instead, this chapter examines one important question that arises in this specific context, namely: Does prenatal drug exposure fall under mandatory child abuse reporting laws? Or to put it more directly, must researchers report the prenatal drug abuse revealed in their studies? A review of the applicable laws and court decisions indicates that, in most States, the answer is a qualified yes.

MANDATORY REPORTING LAWS

All States have laws that require an array of professionals to report suspected child abuse and neglect. Most *professionals who serve children are required to report.* In every State, those required to report include physicians, nurses, emergency room personnel, coroners, medical examiners, dentists, mental health professionals (sometimes specified as "psychologists" or "therapists"), social workers, teachers and other school officials, day-care or child-care workers, and law enforcement personnel. In some States those required to report include pharmacists, foster parents, clergy, attorneys, day-care licensing inspectors, film or photograph processors (largely to detect cases of sexual exploitation), substance abuse counselors, counselors and staff at children's camps, family mediators, staff and volunteers in child abuse information and referral programs, and "religious healers" (usually Christian Science practitioners) (Besharov 1990, p.24). Each year other professions are added to the list.

*SOURCE: Adapted from Besharov 1990

Everyone must report in some States. About 20 States require a report from any person who has reason to believe that a child is a victim of abuse or neglect, regardless of their professional status or relation to the child. This would include researchers. According to the National Center on Child Abuse and Neglect, as of 1988, the States that required all persons to report were Connecticut, Delaware, Florida, Idaho, Indiana, Kentucky, Maryland, Minnesota, Mississippi, Nebraska, New Hampshire, New Jersey, New Mexico, North Carolina, Oklahoma, Rhode Island, Tennessee, Texas, Utah, and Wyoming.*

Of course, even those persons not legally required to report may do so. In all States, anyone *may* report suspected child abuse or neglect. Anonymous reports also are accepted in all States.

Reporting is an individual as *well as an institutional responsibility.* Most reporting laws do not lift the reporting obligations of staff members when they notify their superior of suspected child maltreatment. Therefore, staff members still may be civilly and criminally liable for not reporting if they knew or should have known that no report was made. Staff members who are falsely told that a report was made will have a defense against liability unless they knew or should have known that this was untrue.

REPORTABLE SITUATIONS

All forms of child maltreatment must be reported. The Federal Child Abuse Prevention and Treatment Act of 1974 requires States to provide for the reporting of all forms of maltreatment to receive special grants[3] The act provides that "child abuse and neglect" means the physical or mental injury, sexual abuse or exploitation, negligent treatment, or maltreatment of a child ...under circumstances which indicate that the child's health or welfare is harmed or threatened thereby . . ."[4]

This definition makes reportable *any parental act or omission that harms* a *child or threatens* to *do* so. As a result, just about every State now requires the reporting of all forms of physical, sexual, and emotional maltreatment. Reportable child maltreatment includes:

- Physical abuse: physical assaults (such as striking, kicking, biting, throwing, burning, or poisoning) that caused or could have caused serious physical injury to the child

- Sexual abuse: vaginal, anal, or oral intercourse; vaginal or anal penetrations; and other forms of inappropriate touching or exhibitionism for sexual gratification

- Sexual exploitation: use of a child in prostitution, pornography, or other sexually exploitative activities

- Physical deprivation: failure to provide basic necessities (such as food, clothing, hygiene, and shelter) that caused or over time would cause serious physical injury, sickness, or disability

- Medical neglect: failure to provide the medical, dental, or psychiatric care needed to prevent or treat serious physical or psychological injuries or illnesses

- Physical endangerment: reckless behavior toward a child (such as leaving a young child alone or placing a child in a hazardous environment) that caused or could have caused serious physical injury

- Abandonment: leaving a child alone or in the care of another under circumstances that suggest an intentional abdication of parental responsibility

- Emotional abuse: physical or emotional assaults (such as torture and close confinement) that caused or could have caused serious psychological injury

- Emotional neglect (or "developmental deprivation"): failure to provide the emotional nurturing and physical and cognitive stimulation needed to prevent serious developmental deficits

- Failure to treat a child's psychological problems: indifference to a child's severe emotional or behavioral problems or parental rejections of appropriate offers of help

- Improper ethical guidance: grossly inappropriate parental conduct or lifestyles that pose a specific threat to a child's ethical development or behavior

- Educational neglect: chronic failure to send a child to school (Besharov 1990, p. 30)

The Federal Child Abuse Act contains an important limitation: Reportable situations are those in which "the child's health or welfare is harmed or threatened thereby." The injury must be sufficiently serious so that there is a danger to the child's health or welfare.[5] This limitation is meant to protect the rights of parents to exercise their best judgment about how to raise children and to protect regional, religious, cultural, and ethnic differences in such beliefs. It

means, for example, that parents who allow their children to watch hours of television are not considered neglectful, although many people think that the children would be better off doing something else. It also means that, absent specific legislation, a parent who is abusing drugs should not be reported unless there is reason to believe that the child is or will be seriously harmed thereby. Thus, for example, use of marijuana on weekends-in a way that does not seem to affect the child-is not generally reportable. (The few States that seem to require reports of such casual or recreational drug use are discussed below.)[6]

"Threatened harm" must be reported. Society does not wait until a child is seriously injured before taking protective action. The Federal Child Abuse Act states that reports and authorizes agency and court intervention *to prevent future harm.* Although statutory provisions vary, they commonly require action if a child "lacks proper parental care," is "without proper guardianship," has parents "unfit to properly care" for him or her, or is in an "environment injurious to his welfare." Such provisions authorize intervention before the child has been seriously injured, and even before he or she has been abused or neglected. Hence, injury is not a prerequisite to a report; abuse must be reported to the authorities if children are in danger of serious injury.

Only "reasonable suspicion" is needed for a report. Because of the difficulty in obtaining information about a child's maltreatment, reporting laws do not require potential reporters to be certain that a child is being abused or neglected or to have absolute proof of maltreatment. In all States, reports are to be made when there is "reasonable cause to suspect" or "reasonable cause to believe" that a child is abused or neglected.[7]

Requiring only reasonable suspicions of abuse relieves potential reporters of the need to make a final or definitive diagnosis of maltreatment, which usually requires a home visit, interviews with parents, and further investigation. After a report is made, the child protective agency is responsible for determining the child's true situation and, if protective intervention is needed, for taking appropriate action.

LIABILITY FOR FAILURE TO REPORT

Almost all States have a specific law making it a crime nor to report suspected child abuse and neglect. Even in those that do not, the failure to report may be a crime under general criminal laws.[8] The criminal penalty is usually of misdemeanor level, with the potential fine ranging from $100 up to $1,000 and/or imprisonment ranging from 5 days up to 1 year in jail. Criminal prosecutions for not reporting have been brought against doctors[9] psychiatrists,[10]

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psychologists," teachers (in one case, a nun),[12] social workers[13] spouses,[14] and friends of the family.[15]

There is also civil liability for failing to report. A specific statute may establish civil liability for the failure to report. Under the common law, the violation of a statutory duty, in this instance the required reporting of suspected abuse and neglect, may be "negligence per se." No legislation specifically creating civil liability is needed: the failure to comply with a statutory mandate establishes the negligence.[16] In other situations, the negligent failure to report may be considered professional malpractice.

Criminal and civil liability can be based on circumstantial evidence, such as the child's "suspicious" or "apparently inflicted" injuries. In Los Angeles, for example, a doctor-who apparently knew that a 3-year-old child previously had been removed from her mother's custody-was prosecuted for not reporting repeated evidence of severe abuse. According to court documents, the doctor did not report evidence of abuse, which included "old burns on the chest and left leg, and the absence of the nasal . . . septum." His defense was that he wanted to "give the mother a chance" to avoid further contact with social service workers, and that he had attempted to treat the child in his office and at her home. "Thirteen days after [he] began treating her, she died of a massive chest infection resulting from pneumonia."[17] The doctor entered a no contest plea to involuntary manslaughter."[18]

Liability can be extensive and long-lived. Whatever theory of liability is applied, when the person who allegedly failed to report was employed by an agency or organization, the agency or organization also may be sued—and invariably is.[19]

Most nonlawyers know that there is a statute of limitations to the bringing of lawsuits. Generally, an action must be filed within 3 or 5 years of when the harm was done. In all but a few States, however, the statute of limitations usually does not take effect against minor plaintiffs until they reach age 18.[20] Thus, the failure to report the suspected maltreatment of an infant may result in a lawsuit up to 21 years later. Of course, an action may be initiated on behalf of a child who is still a minor if it is brought by a legal representative or a duly appointed guardian.

LEGAL IMMUNITY

All States explicitly grant immunity from civil and criminal liability to persons who report. Except in two or three States, immunity applies only to reports made in *good faith.*[21] There is no protection for reports made maliciously because of prejudice or personal bias or because of reckless or grossly

negligent decisionmaking. To reassure potential reporters even more, about half the States have laws that establish a *presumption of good faith.*

ABROGATION OF PROFESSIONAL CONFIDENTIALITY

Physicians and many social service or mental health professionals, including drug treatment counselors, who are most likely to see abused and neglected children are subject to statutory privileges making their conversations with patients or clients confidential. Ordinarily, they are prohibited from divulging anything told to them within the scope of the privilege, unless the protected person gives permission or the communication involves information about a crime that will be committed in the future.[22] A professional who violates such privileges may be sued by the protected person. Thus, unless the privilege is lifted, many abused children could not be reported.

Professional confidentiality is not a bar to reporting. A legal mandate to report presumably overrides any other law creating a privileged communication—especially if the reporting law was enacted after the law creating the privilege. Nevertheless, to remove any question, most State reporting laws contain specified clauses abrogating statutorily created privileges. Some statutes abrogate only the privileges governing professionals required to report; others abrogate all privileges, even if the professionals involved are not required to report. In addition, almost every jurisdiction has a specific provision abrogating all or some privileges for the purpose of participating in judicial proceedings relating to abuse or neglect.

Federal laws also make some conversations and records confidential for schools,[23] drug treatment programs,[24] and alcohol treatment programs.[25] For each, exceptions have been made for reporting suspected child maltreatment. For example, the statutes concerning drug and alcohol treatment programs specify that "the prohibitions of this section do not apply to the reporting under State law of incidents of suspected child abuse and neglect to the appropriate State or local authorities."[26]

However, the rules concerning the release of information under these statutes are complex and vary from community to community.[27] (For further information on this subject, contact the local child protective agency, the particular Federal agency involved, or the US National Center on Child Abuse and Neglect.)

Families already in treatment must be reported. Some mental health and social service professionals feel that reporting parents already in treatment violates their ethical obligations toward the parents because, throughout their professional training and careers, great emphasis was placed on guarding the

privacy of their clients, They also fear that reporting the parents to a child protective agency and testifying against them in court may reinforce the insecurity and hostility many abusive and neglectful parents feel and may disrupt the treatment already in progress.

Three or four States give mandated professionals limited discretion not to report but only under extremely restricted circumstances.[28] In all the rest, persons mandated to report have no discretion; they must break confidentiality to report suspected child maltreatment.

EXPLICIT REQUIREMENTS TO REPORT PRENATAL DRUG EXPOSURE

Researchers conducting studies of prenatal drug exposure are likely to belong to the professional groups legally required to report suspected child abuse and neglect. Moreover, in about 20 States, all persons-regardless of any professional status-are required to report. So if the researcher is mandated to report, the question is: Must prenatal drug exposure be reported? Depending on the State, the answer is a qualified yes.

In a growing number of States, prenatal drug exposure or parental drug use is explicitly made subject to mandatory child abuse reporting statutes. Of those States having a law, the largest number require reporting of newborns who have been exposed to drugs.[29] In general, these States limit reporting to exposure to illegal substances. Sometimes prescription drugs or drugs taken pursuant to chemical dependency treatment programs are expressly excluded from reporting mandates, but most often the exclusion is accomplished by referencing the State's controlled substance statutes.[30] In all States, this apparently includes marijuana,[31] although child protective agencies rarely accept jurisdiction in such cases. One exception to these general rules is fetal alcohol syndrome, now required to be reported in about four States.

The specified condition of an infant that establishes the duty to report varies among States. Some States require signs of dependence or physical addiction before invoking reporting mandates.[32] This requirement is problematic because of debate about the addictive qualities of cocaine. Others merely require a positive toxicology,[33] which can occur without any signs of dependency. A new development (enacted in one State and pending in others) is a statutory requirement that physicians perform toxicology screens on infants whom they suspect were exposed to drugs.[34]

Parental drug use is the focus of other State laws. Many States have enacted or are considering statutes that identify parental substance abuse as evidence of child abuse or neglect and, therefore, require a report to child protective

agencies.[35] Apparently, no State requires reports of all levels of drug use, no matter how minor. Minnesota, though, requires a physician to:

> administer a toxicology test to a pregnant woman under the physician's care to determine whether there is evidence that she has ingested a controlled substance, if the woman has obstetrical complications that are a medical indication of possible use of a controlled substance for a non-medical purpose. If the test results are positive, the physician shall report the results under Section 5. A negative test result does not eliminate the obligation to report under Section 5, if other evidence gives the physician reason to believe the patient has used a controlled substance for non-medical purposes.[36]

Even if statutory mandates do not exist, many States have court decisions that hold that parental substance abuse is evidence of child abuse and neglect[37]

A growing number of States will accept a report before the child is born to give child protective authorities time to mobilize. At least one State requires such reporting.[38]

IMPLICIT REQUIREMENTS TO REPORT PRENATAL DRUG EXPOSURE

Most States do not have legislation that explicitly addresses reporting of prenatal drug exposure. Even in these States, though, legal analysis indicates that reports of prenatal drug exposure are required when the exposure suggests that the parent is seriously addicted to a debilitating drug.[39] (The phrase "legal analysis" is used deliberately because there are few court decisions on the subject, and the practice seems to vary even within the same community.)

As described above, a mandated reporter must report when there is reasonable cause to suspect that "the child's health or welfare is harmed or threatened." Thus, the operative legal question becomes: Does prenatal drug exposure create reasonable cause to suspect that the child has been seriously harmed or is threatened thereby? The evidence is clear that, at least sometimes, the answer is yes.

Severe parental drug or alcohol abuse is a reportable condition because it can so strikingly impair a parent's judgment and ability to cope that serious harm to the child becomes likely. Parents suffering from such severe drug habits that they cannot care for themselves also cannot care for their children.[40] Moreover, there is evidence that drug use can make parents more violent toward their

children, A Ramsey County Minnesota Department of Human Services report, after reviewing 70 cases of "cocaine-attached" households in mid-1988, found that these parents are "extremely volatile with episodes of 'normal' behavior interspersed with episodes of unpredictable, dangerous and even violent behavior."[41]

In the absence of suitable arrangements for the children of these parents, State intervention is essential no matter how caring such parents may seem. A report should be made, even if the child is not yet harmed and even if the parent has never had custody of the child.[42] To wait until the child shows signs of abuse or neglect would unreasonably endanger many children and, as this chapter describes, may expose the professional to civil or criminal penalties.

There are many degrees of parental incapacity, however, and a prediction of future serious harm to the child—and, therefore, a report—is justified only in cases of regular or continuous drug or alcohol abuse that so severely impairs the parent's judgment or ability to function that future abuse or neglect is likely. Thus, in a statutory construction used in several States, the New York Family Court Act provides that:

> proof that a person *repeatedly uses a drug,* or drugs or alcoholic beverages, to the extent that it has or would ordinarily have the effect of producing in the user thereof a *substantial state* of stupor, unconsciousness, intoxication, hallucination, disorientation, or incompetence, or a substantial impairment of judgment, or a substantial manifestation of irrationality, shall be prima facie evidence that a child [is neglected].[43]

Except in those States where any level of drug addiction must be reported, the parents' participation in a treatment or counseling program does not establish that a report should be made;[44] the parent, perhaps with outside help, may be adequately caring for the child.

Some States consider the harm or threatened harm to the fetus as a form of reportable child abuse. A pregnant woman who continues illicit drug or alcohol use may give birth to a child with severe problems. Untreated neonatal addiction to heroin, for example, can be fatal. The dangers encountered by heroin babies were described 20 years ago in a New York City case:

> [The] baby was born normally without apparent symptoms until 24 hours after birth, [when] the baby began to exhibit unmistakable narcotic withdrawal symptoms; preconvulsive tremors, hyperactivity, incessant crying, ravenousness alternating with

> vomiting. . . . Sedatives (phenobarbital), dark and quiet were required for seven days before the child became physically well. Without careful therapy, the child might have suffered convulsions and death.[45]

Neonatal exposure to heroin and methadone, if treated properly, appears to leave no lasting damage. However, cocaine is different because it constricts the blood vessels in the placenta and the fetus, thus cutting off the flow of oxygen and nutrients and creating a higher probability of miscarriages, stillbirths, and premature and low-birth-weight babies, often with various physical and neurological problems. Some cocaine-exposed babies have deformed hearts, lungs, digestive systems, or limbs: others have what amounts to a disabling stroke while in the womb.[46] Death rates may be twice as high for these babies as for others.

For these reasons, courts have held that prenatal exposure is a form of child neglect because it results in "actual impairment" of the children.[47] As one court held: "A new-born baby having withdrawal symptoms is prima facie a neglected baby."[48]

Basing reports on harm (or threatened harm) to the fetus makes many people uncomfortable because it comes so close to the abortion issue. Hence, it is important to mention that there is a second legal basis for reporting prenatal exposure to drugs: *Prenatal exposure can be circumstantial evidence of severe drug use, which, in turn, would be reportable because of the threat of serious harm to the baby when he or she goes home with the addicted mother.* Thus, prenatal use of dangerous drugs is probative of future neglect.[49] The reasoning behind such a conclusion is that:

> To give rise to such symptoms, the mother must have been regularly using large quantities of heroin (as she substantiated by her history) for considerable time before [the child's birth]; the placenta permits ready transfer of heroin from mother to fetus. Had she injected heroin not habitually but only shortly before child's birth, massive doses may have killed her and the new-born child, or the baby would have been sedated instead of hyperactive and suffering withdrawal. Only a high tolerance (a strong and perhaps sufficient basis for a finding of narcotic addiction without additional history) for both mother and baby would cause the medically observed course of events found here.[50]

Not all babies born to heavy drug users exhibit withdrawal symptoms; anywhere from 30 to 50 percent do not. Although medical studies have yet to develop

specific measures of prediction, it appears that the existence and severity of withdrawal symptoms is a function of the type, dosage, and regularity of drug use. Hence, if there are other reasons to suspect that drug use renders the parent(s) unable to care for the infant, a report should be made.

Demonstrated parental inability to care for a newborn should be reported. Certain specific parental behaviors in the maternity ward provide additional reasons for a report. What parents are unable to do in the hospital, where they have help, they are unlikely to be able to do alone at home. Concrete examples of parental inability to care for a newborn should be reported (see Besharov 1990, pp. 131-133).

The requirement to report "reasonable suspicions" means that there need not be a definitive determination of either the parent's drug abuse or its harmful effect on the child. Some people point to the uncertainty that exists about parental drug use and its effect on children as a reason for not reporting. However, there have been several court cases holding professionals legally culpable for not reporting their reasonable suspicions and, instead, seeking absolute proof of child abuse before making a report.[51] It may be only a matter of time before some local prosecutor or plaintiff in a civil damage suit will use these precedents in a prenatal drug exposure case.

CONCLUSION

In many States, researchers probably are required to report at least some of the prenatal drug exposure revealed in their studies to child protective agencies. First, a growing number of States have laws that expressly require such reports. Second, in many other States, the general child abuse reporting law implicitly requires such reports—at least when there is reasonable cause to suspect that a parent is *seriously addicted to a dangerous or debilitating drug.*

The existence of this requirement to report, though, does not mean that researchers and clinicians should ignore the trusting relationship they may have developed with parents. Unless it appears that doing so will endanger the child, they should prepare the parents for the consequences of the report. The necessity of the report, and the nature of the investigation that will follow, should be described honestly and supportively. If appropriate, the parents should be encouraged to report themselves to the child protective agency.

Reporting child abuse, moreover, does not necessarily mean that the child will be removed from parental custody. In many cases, supportive services provided by the child protective agency or another public or private agency may enable the parents to care for their children. Moreover, researchers can take

steps, such as developing cooperative agreements with child protective agencies, to increase the likelihood that a report will result in the provision of services to the family rather than the child's removal.

However, State laws vary, and they change almost constantly; therefore, it is impossible to provide definitive guidance here. And, although the State or local child protective agency may be of help in planning a response to child abuse reporting responsibilities, the issues are sufficiently complex, State laws sufficiently ambiguous, and the cost of a wrong decision sufficiently high that prudence dictates an early consultation with an attorney specializing in such matters.

NOTES

1. E.g., Applebaum, P.S. *Informed Consent: Legal Theory and Clinical* Practice. New York: Oxford University Press, 1987; Morrissey, J.M. *Consent* and *Confidentiality in the Health* Care *of Children and Adolescents: A* Legal Guide. New York: Free Press, 1986; Barber, B. *informed Consent in Medical Therapy and Research. New* Brunswick, NJ: Rutgers University Press, 1980; *Rosoff,* A.J. *Informed Consent: A Guide for Health Care Providers.* Rockville, MD: Aspen Systems Corp., 1980; Sharpe, S. B. *Informed Consent: Its* Basis *in Traditional Legal Principles.* Toronto: Butterworths, 1979; Ludlam, J.E. *Informed Consent.* Chicago: American Hospital Association, 1978; Annas, G.J. *Informed Consent to Human Experimentation: The Subject's Dilemma.* Cambridge, MA: Ballinger, 1977; Hershey, N. *Human Experimentation and the* Law. Germantown, MD: Aspen Systems Corp., 1976.

2. Clearinghouse on Child Abuse and Neglect Information. *State Statutes Related to Child Abuse and Neglect: 1988,* passim. U.S. Department of Health and Human Services, Office of Human Development Services, Administration for Children, Youth and Families, Children's Bureau, and National Center on Child Abuse and Neglect. June 1989.

3. See generally Besharov, D. The need to narrow the grounds for state intervention. In: Besharov, D. *Protecting Children from Abuse and Neglect: Policy and* Practice. Springfield, IL: Charles C. Thomas, 1988. pp. 47, 50 et seq.

4. Child Abuse Prevention and Treatment Act of January 31, 1974, codified as amended at 42 U.S.C. § 5102(1) (Suppl.1989).

5. For the definitive exposition of how severity of injury affects—and should affect—child protective decisionmaking, see Giovannoni, J.M., and Becerra, R.M. *Defining Child Abuse. New* York: Free Press, 1979. Reflecting the need to specify the level of severity, the National Center on Child Abuse and Neglect provides the following definitions: (1) "Physical injury" means death, or permanent or temporary disfigurement or impairment of any bodily organ or function and (2) "mental injury" means an injury to the intellectual or psychological capacity of a child as evidenced by an observable and substantial impairment in his ability to function within his normal range of performance and behavior, with due regard to his culture. National Center on Child Abuse and Neglect. *Child* Protection: *A Guide for State Legislation,* subsections 4(h) and (i) (Draft 1983).

6. See the text at note 38, infra.

7. Although there is a small, technical difference between the two phrases, most legal authorities have concluded that they are fundamentally equivalent and have the same impact on reporting decisions. [E.g., Op.Ill.Attorney General, S-1298 (October 6, 1977); Op.Mass.Attorney General 74/75-66 (June 16, 1975).] Since "reasonable cause to suspect" is the more common phraseology, it is adopted in this chapter.

8. For example, the failure to report may be misprision of a felony. Cf. *Pope v. State,* 38 Md.App.520, 382 A.2d 880 (1978); *modified,* 284 Md.309, 396 A.2d 1054 (1979) dismissed because the state's child abuse law did not apply and because there was no crime of misprision of felony in Maryland.

9. "Doctor, Parents Charged in Death of Abused L.A. Child." *Los Angeles Times,* December 3, 1983. Pt. 1, p. 1, col. 5; "MD Charged With Not Reporting Child Abuse." *Toronto Star,* June 2, 1983. p. A16, col. 1.

10. E.g., *Groff* v. *State,* 390 So.2d 361 (Fla. Dist.Ct.App. 1980), *State v. Groff* 409 So.2d 44 (Fla. Dist.Ct. App. 1981), ultimately dismissed on the grounds that the Florida reporting mandate was limited to "any person ... serving children," and, therefore, did not apply to the defendant psychiatrist who was treating the father, not the child and, in fact, had never met her.

11. *People v. Poremba, 7 Family Law Repotter* p. 2142 (1/1/81) (Denver County Court 12/17/80).

12. E.g., *People* v. *Sok* (for punching and pushing two children) and *People v. Molitor* (for not reporting the abuse) mentioned in, "Monk Seeks $60 Million Damages for Lawsuit's Allegations of Racism." Los *Angeles Times,* June 23, 1982. Pt. 2, p. 12, col. 1. According to the Los Angeles District Attorney, both cases resulted in convictions.

13. E.g., "People v. Noshay." *NASW* News, February 1984. p. 21, and April 1984, p. 7, a case, later dismissed, charging the social worker for failing to report "immediately" because she worked with the victim's family for 5 weeks before a report was made by the family.

14. E.g., "2 Found Guilty of Not Reporting Child-Abuse Case." *Providence Journal,* December 4, 1981. p. A-3, col. 3. On appeal, the case was dismissed on procedural grounds. (The case was tried in the wrong *court.) State v. Boucher and Flinkfelt,* 468 A.2d 1227 (R.I. 1983).

15. E.g., *Pope v. State,* supra n. 8.

16. See Keeton, W.P., and Prosser, W.L. *Prosser and Keeton on Torts.* 5th ed. St. Paul/Minneapolis: West, 1984. p. 220.

17. All information and quotations from "Doctor, Parents Charged in Death of Abused L.A. Child," supra n. 10.

18. Metro section, *Los Angeles Times,* December 1, 1984. p. 1.

19. Such vicarious liability is based on the legal doctrine of "respondeat superior," under which the tortious conduct of a staff member may be imputed to the employer. See generally Keeton and Prosser, supra n. 16, at Chapter 12, p. 499, "Imputed Negligence." See also Note, "Agency: Liability of a hospital for negligent acts of a physician—employee," *Oklahoma Law Rev* 18:77, 1965; annotation, *American Law Reports 2d* 69:30, 1960.

20. A full discussion of these issues can be found in: Horowitz, R. "The Child Litigant." In: *The Legal Rights of Children* § 3.04; "Statutes of Limitation" (Horowitz, R., and Davidson, H., eds., *1984); American Jurisprudence 2d ed.,* "Limitations of Actions," 51:§§ 181-185 (1970 and Suppl. 1981).

21. See Besharov, supra n. 3, p. 46.

22. See generally *Wigmore on Evidence* 8:§ 2380 (Suppl. 1981); *McCormick's Handbook of the Law of Evidence* § 95 (2d ed., E. Cleary 1972).

23. Family Educational Rights and Privacy Act of 1974 (FERPA), codified at 20 U.S.C. § 1232g(b)(1)(I) (1978).

24. Public Health Service Act, § 527, codified at 42 U.S.C.§ 290ee-3 (1988 and Suppl. 1990).

25. Public Health Service Act, § 523, codified at 42 U.S.C.§ 290dd-3 (1988 and Suppl. 1990).

26. 42 U.S.C. § 290dd-3(e); 42 U.S.C. § 290ee-3(e).

27. For a further discussion of these issues, see U.S. Public Health Service, Proposed regulations on confidentiality of alcohol and drug abuse patient records, *Fed Register* 48:38758, *38767* et seq, 1983, codified at 42 C.F.R. 2 (1985); National Center on Child Abuse and Neglect, *Impact of Federal Law on Provision of Child Protective and Related Services,* p. 16 et seq. (DHHS 1981); "Iowa Attorney General Issues Opinion On Dilemma In Child Abuse Reporting," *10 Family Law Reporter* 1123 (January 3, 1984), discussing Iowa Attorney General's Opinion No. 83-11-3, November 9, 1983.

28. Maine mandates reports from therapists but requires the child protective agency to meet with the therapist and to consider the abuser's willingness to seek treatment before deciding what to do. [Me. Rev. Stat. Ann. tit. 22, § 4011 (1-A)(C) (Suppl. 1988).] Note that, before deciding not to report, the professional must determine that there is "little threat of serious harm to the child," a difficult decision in many cases and one that creates the threat of criminal and civil liability for not reporting. Maryland exemption is limited to health practitioners who specialize in psychiatric treatment of pedophilia. A report is not required if the report would be based solely on the statement of an abuser made while in treatment for past abuse. [Md. Fam. Law Code Ann. § 5-704 (Suppl. 1988).] See also Or. Rev. Stat. § 418.750 (1987), where mental health professionals, clergy, and attorneys are not required to report if such a report would disclose privileged communications, and Utah Code Ann. § 78-3c-4 (1987), abrogating the privilege between a victim and a sexual assault counselor at the counselor's discretion as established by statutory guidelines.

29. Generally, reports are required for any suspected child abuse or neglect, as defined in each state's statute; these statutes then specifically mention drug exposure in their definitions. E.g., Fla. Stat. Ann. § 415.503(7)(a) (Suppl. 1988). (Child abuse or neglect includes "physical dependency of a newborn infant upon any drug controlled in Schedule II of § 893.03 . .. ."); Hawaii Rev. Stat. § 587-2 (1985). (Abuse includes "any case where the child is provided with dangerous, harmful, or detrimental drugs as defined by § 712-1240."); Ill. Rev. Stat. ch. 23, § 2053 (Smith-Hurd 1990). (Neglected children include "any newborn infant whose blood or urine contains any amount of a controlled substance as defined in subsection (9 of Section 102 of the Illinois Controlled Substance Act . . . ."); Ind. Code Ann. § 31-6-4-3.1 (Burns 1987). (A child is in need of services if he or she is "born with fetal alcohol syndrome or an addiction to a controlled substance or a legend drug .. . ."); Mass. Gen. Laws Ann. ch. 119, § 51A (West Suppl. 1988). (A report is mandated for any infant ". . . who is determined to be physically dependent upon an addictive drug at birth."); Minn. Stat. Ann. § 626.556(4)(2) (1988). ("Neglect includes prenatal exposure to a controlled substance ..."); Okla. Stat. tit. 21, § 846(A) (Suppl. 1989). (A report must be made for "a child who appears to be a child born in a condition of dependence on a controlled dangerous substance . . . ."); Utah Code Ann. § 78-36-3.5 (Cum. Suppl. 1989). (A report is mandated when a child "at the time of birth, has a fetal alcohol syndrome or fetal drug dependency.")

30. E.g., Hawaii Rev. Stat. § 587-2 (1985). (Harm to a child occurs in "any case where the child is provided with dangerous, harmful, or detrimental drugs, as defined by Section 712-1240 . . . ."); Ill. Ann. Stat. ch. 37, § 802-3(1) (Smith-Hurd 1989). (Neglected children include "any newborn infant whose blood or urine contains any amount of a controlled substance as defined in subsection (9 of Section 102 of the Illinois Controlled Substance Act . . . .")

31. Ind. Code Ann. § 31-6-4-3 (Burns 1987). (A child is in need of services if "the child is born with fetal alcohol syndrome . . . . "); Nev. Rev. Stat. § 201.090 (1987). (A child is neglected if he or she "habitually uses intoxicating liquors . . . ."); Utah Code Ann, § 78-3b-8 (1),(6) (1987). (The agency shall investigate "an oral or written report of alleged abuse, neglect, fetal alcohol syndrome, or dependency . . . .")

32. Fla. Stat. Ann. § 415.503(8)(a)(2) (West Suppl. 1988). ("physical dependency of a newborn infant"); Mass. Gen. Laws Ann, Ch. 119 § 51A (West Suppl. 1989). ("physically dependent on an addictive drug at birth"): Okla. Stat. Ann. tit 21, § 846(A) (West Suppl. 1988). ("born in a

condition of dependence on a controlled substance"): Utah Code Ann. § 78-36-3.5 (Cum. Suppl. 1989). ("at the time of birth has a fetal alcohol syndrome or fetal drug dependency".)

33. Ill. Ann. Stat. ch. 37, § 802-3(1) (1990). ("any newborn infant whose blood or urine contains any amount of a controlled substance . . . or metabolite of a controlled substance, with the exception of. . . such substances, the presence of which in the newborn infant is the result of medical treatment administered to the mother or the newborn infant."); Minn. Stat. Ann. § 626.5562(2) (West Suppl. 1990). (Physicians are required to report as neglect the positive results of any toxicology tests.)

34. Minn Stat. Ann. § 626.5562(6)(2) (1988). This section also requires a physician to report to the child protective agency even when the drug test is negative, if "other medical evidence of prenatal exposure to a controlled substance" exists.

35. Minn. Stat. Ann. § 626.5562(1) (West Suppl. 1990). (A report is required if "a woman is pregnant and uses a controlled substance for a non-medical purpose. . . ."); R.I. Gen. Laws § 40-11-2 (2), (3) (Suppl. 1988). (Evidence of an abused or neglected child includes parental "use of a drug, drugs or alcohol to the extent, that the parent . . . loses his ability or is unwilling to properly care for the child . . . ."); Nev. Rev. Stat. § 128.106 (1987). ("In determining neglect by or unfitness of a parent, the court shall consider. . . excessive use of intoxicating liquors, controlled substances or dangerous drugs which renders the parent consistently unable to care for the child."); N.Y. Fam. Ct. Act § 1012(e) (McKinney 1983 and Suppl. 1989). (A parent may neglect his child "by misusing a drug, or drugs; or by misusing alcoholic beverages to the extent that he loses self-control of his actions.")

36. Minn. Stat. Ann. § 626.5562(1) (1989).

37. *In Re Baby X,* 293 N.W.2d 736, 97 Mich. App. 111 (1980); *In Re Troy D.* 215 Cal. App. 3d 889, 263 Cal. Rptr. 869 (Ct. App. 1989); *In Re Stefanel C.,* N.Y. App. Div. 1st Dept., May 29, 1990; NYLJ May 31, 1990. Additional cases exist in Illinois, Alaska, Georgia, South Dakota, Montana, and Nevada. See Horowitz, R. Testimony before Subcommittee on Human Resources, Committee on Ways and Means, U.S. House of Representatives, April 3, 1990.

38. Minn. Stat. Ann. § 626.5561 (1989). (Physicians must report any pregnant women whom they suspect of using drugs. Child abuse

includes “prenatal exposure to a controlled substance used by the mother for a non-medical reason . . . .”); (Delaware has a similar bill pending, H.B. 571, which would require reporting of “any woman suspected of using a controlled substance during pregnancy.“)

39. See generally English, A. Prenatal drug exposure: Grounds for mandatory child abuse reports?” *Youth Law News* X1(1):3-8, 1990.

40. E.g., Ward, P., and Krone, A. Deadly deals: Child abuse and chemically dependent families. *Focus on Chemically Dependent Families* 10(6):16-17, 34-35, 1987; Coleman, E. Family intimacy and chemical abuse: The connection. *J Psychoactive Drugs* 14(1-2):153-158, 1982; Jones, C., and Lopez, R. “Direct and Indirect Effects on the Infant of Maternal Drug Use.” In: *Component Report on Drug Abuse.* Expert Panel on Prenatal Care. U.S. Department of Health and Human Services and the National Institutes of Health. Pub. No. 7161M, July 15, 1988; Finnegan, L.P.; Oehlberg, S.M.; Regan, D.O.; and Rudrauff, M.E. “Evaluation of Parenting, Depression and Violence Profiles in Methadone Maintained Women.” Paper presented at the Third International Congress *on* Child Abuse and Neglect, 1981.

41. Clement, D. Babies in trouble. *Minnesota Monthly* March:49, 1989.

42. E.g., *Roberts v. State,* 941 Ga. App.268, 233 S.E.2d 224 (1977) where a baby born to a mentally retarded, 14-year-old mother was placed in foster care immediately after birth. Despite the absence of any “history of deprivation,” the court held that, under the circumstances, parental rights could be terminated on the grounds that the child would suffer deprivation if the mother were given custody of him.

43. N.Y. Fam. Ct. Act § 1046(a)(iii)(McKinney 1988) (emphasis added).

44. E.g., N.Y. Fam. Ct. Act § 1012(e) (McKinney 1983 and Suppl. 1989) (‘Where the respondent is voluntarily and regularly participating in a rehabilitative program, evidence that the respondent has repeatedly misused a drug or drugs or alcoholic beverages to the extent that he loses self-control of his actions shall not establish that the child is a neglected child in the absence of evidence that the child’s physical, mental or emotional condition has been impaired or is in imminent danger of becoming impaired . . . .”)

45. *In the Matter of John Children,* 61 Misc.2d 347, 353, 306 N.Y.S.2d 797, 805 (Fam.Ct., N.Y.Co., 1969).

46. E.g., Zuckerman, B.; Frank, D.; Hingson, R.; Amaro, H.; Levenson, S.; Parker, S.; Vinci, R.; Aboagye, K.; Fried, L.; Cabral, H.; Timperi, R.; and Bauchner, H. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med* 320:762-768, 1989.

47. *In Re Stefanel C.,* N.Y. App. Div. 1st Dept; May 29, 1990, NYLJ May 31, 1990; see also *In Re Ruiz,* 500 N.E.2d 935 (Ohio Ct. Comm. Pls. 1986).

48. *In the Matter of Vanesa F.,* 76 Misc.2d 617,620,351 N.Y.S.2d 337,340 (Surr.Ct., N.Y.Co. 1974).

49. *In Re Troy D.,* 215 Cal. App. 3d 889, 263 Cal. Rptr. 869 (Ct. App. 1989), basing its decision on "prognostic deprivation"; *In Re Baby X.,* 293 N.W.2d 736, 739, 97 Mich. App. 111 (1980), stating that "prenatal treatment can be considered probative of a child's neglect."

50. In the Matter of *John Children,* supra n. 46, 61 Misc.2d at 354, 306 N.Y.S.2d at 805.

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Discussion: Effect of Legal Stipulations on the Conduct of Treatment and Prevention Research

Judy Howard

INTRODUCTION

This chapter discusses the divergent viewpoints expressed by Ellen Marie Weber, Legislative Counsel for the Legal Action Center of New York City, Inc., in her chapter (this volume) "Alcohol and Drug-Dependent Pregnant Women: Laws and Public Policies That Promote and Inhibit Research and the Delivery of Services," and by Douglas J. Besharov, Resident Scholar at the American Enterprise Institute for Public Policy Research, in his chapter (this volume) "Mandatory Reporting of Child Abuse and Research on the Effects of Prenatal Drug Exposure." The issues addressed by these two legal experts span a continuum that ranges from protecting the privacy rights of women and men in drug treatment to reporting suspected child abuse and neglect in instances where parents are chronic substance abusers. Both authors express the need to balance treatment for substance-abusing parents with the provision of an environment for their children that is safe from harm.

The two views expressed in these chapters regarding the need to report prenatally substance-exposed infants and to maintain confidentiality of information related to parental chemical dependency reflect the controversies and issues that professionals and policymakers must face and resolve if treatment programs for chemically dependent families are to be improved and legislation enacted that is appropriately guided by research findings. It is my belief that only through close collaboration-in which clinicians and researchers from the fields of health, social services, and alcohol and other drug treatment work together with legislators and policymakers-can meaningful public policy be enacted that will benefit this population.

As a developmental pediatrician based at a university medical center, I have been involved since 1981 in clinical and research programs serving chemically dependent parents and their offspring. In addition, I have served as medical

director of the University of California, Los Angeles (UCLA) Suspected Child Abuse and Neglect (SCAN) Team and chair of the hospital's Child Abuse Policy Committee for 8 years. Within UCLA Medical Center, the SCAN Team functions as a consulting resource for mandated reporters of suspected child abuse and neglect, and since 1977, SCAN Team members have formally reviewed all such cases occurring in the Medical Center. This interdisciplinary team is composed of university professionals from the fields of medicine, nursing, social work, pharmacology, dentistry, law, and law enforcement. in our work with families at UCLA Medical Center we routinely collaborate with a range of community-based professionals in Los Angeles County from child protective services, public health nursing, alcohol and other drug treatment, the office of the county counsel (representing the child in the civil courts), and the office of the district attorney (prosecuting the alleged perpetrator in the criminal courts). Last year, 277 cases of suspected child abuse and neglect were reviewed. Approximately 23 percent (64) of these cases involved infants with prenatal drug exposure, and 42 percent (116) involved parental substance abuse.

Thus, this discussion of the issues raised by Weber and Besharov is based on a decade of experience in both research and clinical intervention with chemically dependent women and their children. However, whether one approaches the issue of perinatal substance abuse from a purely clinical stance or from that of a researcher, it is true that there has been a paucity of prevention and treatment efforts on behalf of chemically dependent pregnant women and women with children. It is also true that-despite a lack of information regarding the effectiveness of various treatment methods, a lack of thoughtful, organized approaches to developing programs for rehabilitating chemically dependent pregnant women or women with young children, and a lack of existing treatment resources overall-there appears to be a widespread trend toward criminalizing the act of using drugs during pregnancy.

It is within this emotionally charged arena—in which the reporting of suspected child abuse and neglect remains controversial—that clinicians and researchers are asked to maintain subject confidentiality and to protect children from harm. Weber and Besharov raise four issues that influence the ability to meet both these requirements while simultaneously providing effective clinical services and conducting meaningful research. The issues identified relate to confidentiality, whether child abuse laws deter women from seeking treatment, the question of serious harm, and the effect of reporting on research paradigms.

CONFIDENTIALITY

The critical issue of confidentiality is acknowledged by both authors. As Weber notes, when a suspected child abuse or neglect report is made by a scientific

researcher or by an alcohol and other drug treatment program staff member, Federal regulations regarding the exemption for confidentiality apply only to the initial report and not to requests for followup information. This regulation presents several potential conflicts for research projects that incorporate the provision of clinical services. Initially, there is the potential for discord between researchers and community agencies if the researchers appear to be withholding requested followup information on cases that already have been reported. Over time, lack of availability of information or unwillingness to share information may foster a climate of distrust, since it is possible that community agency representatives would perceive such action on the part of the research staff to be uncooperative. In turn, for the researcher it could become difficult to recruit future study subjects who are involved with these community systems.

At UCLA, compliance with basic requests for information relevant to a child's situation always has been considered necessary, and a recent California Court of Appeals decision' seems to support this position. In this case, it was determined that a mandated reporter could provide followup information to the county counsel and to child protective services. The UCLA programs have incorporated within the research design provisions for a carefully monitored exchange of information to ensure safety for the child and to develop a more appropriate and realistic intervention plan for the entire family.

DETERRENT TO TREATMENT

A second area of concern for Weber and Besharov relates to potentially adverse consequences when strict confidentiality is not maintained-specifically to the possibility that reporting of alcohol or other drug use by pregnant women may be a deterrent to their obtaining prenatal care and/or drug treatment for their chemical dependency.

Because health care behaviors are influenced by multiple factors, to understand deterrents to care, more information and research are needed regarding those specific variables that facilitate the chemically dependent woman's seeking and following through with prenatal care and chemical dependency treatment programs, In fact, pregnant, substance-abusing women may have a variety of reasons for not making and keeping appointments. Although these reasons may include fear of losing their children, they also may be related to the lack of a user-friendly environment in which to receive care, long waits before appointments, the scarcity of child care facilities for other children during prenatal visits, the insensitivity of some health care professionals, and difficulty in arranging transportation to and from appointments. Just as important, the effects of chronic and severe addiction may interfere with the chemically dependent woman's ability to plan ahead and to keep scheduled appointments.

Furthermore, just as researchers lack information about what deters women from seeking prenatal care, information also is lacking relative to the impact of child abuse reporting. No solid data are available indicating that the potential referral to child protective services agencies at the time of birth has deterred a significant number of women from either seeking prenatal care or entering drug treatment programs. In fact, the opposite may be true. Indeed, at UCLA many pregnant women have entered and complied with drug treatment and prenatal care programs specifically to increase their chances of keeping their babies should child protective services agencies become involved.

In two research projects at UCLA, one involving 20 and the other 41 families, clients have been tracked over a course of 3 years. These projects have involved a home-based intervention component staffed by a competent, caring professional staff of social workers, public health nurses, and/or early childhood specialists. At the time of subject recruitment, each client was informed that a referral to child protective services would be filed in the event that the newborn demonstrated symptoms of prenatal substance exposure and/or had a positive urine toxicology screen or if there was any subsequent evidence of child abuse or neglect. In addition, it was made clear that the project staff would continue to provide services and advocate on behalf of the mother's and infant's needs even if child protective services should become involved. We believe this forthright approach helped build trust and establish clear expectations for the client's behavior.

In following subjects over the course of 3 years, we have made reports to child protective services for approximately 30 percent of these families in cases where we believed a child was in imminent harm or had been abused or neglected. Admittedly, some mothers became angry and threatened to leave the project or even personally threatened project staff members. However, a skillful, consistent, patient, and unambivalent stance can be effective in these situations. When staff members are honest with families about the reasons for making a report and when they continue to follow and maintain contact with families after a report has been filed, the families can learn that they will not be abandoned and that they can trust the staff from the research project to help them weather the crisis We stay in touch with the family throughout the investigative and dispositional process and advocate for services as indicated. The attrition rate in both these projects has been less than 5 percent.

When the health care and research team operates under the assumption that addiction is a chronic, relapsing disease characterized by denial, the identification of a chemically dependent client has the goal of providing the substance-abusing mother with the structure and the impetus that she is unable to provide for herself. From a child neglect standpoint, as Dr. Donald Bross has

stated in the *Denver University Law Review,* ". . . in cases in which the parent suffers from mental illness, it is appropriate to view drug addiction or alcoholism as a capacity issue, rather than one of blame. Since the civil court process involves determining the child's status, 'guilt' or 'innocence' of the parent is not at issue" (Bross 1988).

Rather than supporting criminal sanctions, this view advocates treatment for children and families that is backed by the legal clout of the civil court. In the *Harvard Mental Health Letter,* Richard S. Schottenfeld stated that there is considerable evidence that some kind of leverage almost always is needed to counter the denial that is frequently present in drug and alcohol addiction. "Coercion at the start often helps drug and alcohol abusers realize they need treatment" (Schottenfeld 1990).

Thus, at UCLA Medical Center, we do not view the reporting of suspected child-endangering situations as punitive-to continue to permit a mother to endanger her own health and that of her child would be a terrible disservice. Indeed, my staff members and I have seen children permanently removed from their mothers' custody without any real attempt made to effect family reunification, and we have seen children receive serious injuries or even die while in their mothers' care. If constructive intervention can be made before such irreversible damage occurs, then everyone's best interest—the parent's, the child's, and society's—will be better served.

SERIOUS HARM

Besharov and Weber agree that mandatory reporting of suspected child abuse and neglect in cases of prenatal substance abuse appears to be contingent on ability to demonstrate harm. In the absence of specific legislation, Besharov notes that chemically dependent parents should not be reported unless there is reason to believe "that the child is or will be *seriously* harmed thereby." He goes on to comment that chronic, severe substance abuse interferes with the adult's alert state, and if there is a dependent child within the home, imminent harm to the child is a real consideration.

In a recent California appellate decision, specific testimony by one expert witness detailed the cycle of parental addiction, which included a description of the behavioral effects of a drug on the adult's alert state and a description of how the parents, who used drugs together, "would be out of commission frequently at the same time." According to this testimony, the ability of chemically dependent parents to prioritize their children's needs over their own "literally disappears as the length of time between the last dosage and what is currently needed by the individual increases."[2]

However, for those engaged in research with chemically dependent families, it is often difficult to draw the line between what constitutes chronic, severe substance abuse and occasional, recreational use of illegal substances. **It** is well known that chemically dependent adults tend not to be reliable historians in reporting their own substance abuse patterns. Besharov states that such differentiation is necessary to help interpret correctly the child abuse reporting law as it pertains to perinatal substance abuse, but how does a researcher make educated, informed decisions about the frequency and nature of drug use or even about the specific substances abused?

RESEARCH PARADIGMS

Conducting research with chemically dependent families is complicated by statutory regulations, legal requirements, and professional ethics. However, the decision regarding whether to make a referral of suspected child abuse or neglect to a child protective services agency is only one facet of conducting research with this population. Once a chemically dependent family has been identified and it has been determined that the children are in imminent danger and/or have been abused, professionals involved in the care of these families—whether through research projects or clinical programs—need to recognize that the family is part of a much larger system over which the researcher has minimal control. For instance, the child protective services worker, in conjunction with the juvenile court, may recommend special programs to address the unique needs of the immediate family as well as of the extended family members and foster parents who may be caring for the children. Thus, the experimental and control groups within a research project may swell in size and in complexity of required services: conversely, group sizes may diminish because some children will be moved to distant locations.

Conforming to a research paradigm, which usually is not a difficult task with non-substance-abusing families, can become a real challenge in studying this population. Because the legal disposition of a given case cannot be predicted or controlled, research studies have to be carefully and flexibly designed to allow for multiple contingencies. Attachment behaviors, parenting skills, and the effects of prenatal drug exposure on a child's long-term development are all difficult to determine in a "moving target" population involving multiple caretaking environments for the child, multiple drug treatment programs for the parent, and in some cases, episodes of parental incarceration.

In designing a research project, professionals have the option to study populations who are participating in the program voluntarily or populations whose participation is mandated by the court. If a decision is made to solicit subjects who have been mandated to enroll in a treatment program to maintain

custody of their children or to regain custody, it has been our experience that this official court order may create the crisis that motivates a family toward change. Over time, as skilled staff members have worked with families whose participation has been mandated, the majority of them have remained in our projects, even after the initial order has been terminated, as a result of the positive relationships that have been established with the project staff. On the other hand, those chemically dependent parents who have participated voluntarily in our research projects have been easier to engage in program services and have been more open about their substance abuse and family problems, Yet, over the long haul, they can prove as resistant to significant change as families who are mandated to participate. Finally, because the voluntary or mandated status of a subject may change during the course of a longitudinal research project, the research staff needs to understand this possibility, be knowledgeable about dealing with either contingency, and be aware of how this affects the research design.

When recruiting pregnant, substance-abusing women or chemically dependent mothers of young children into a study, the research staff has the responsibility to describe to the subjects the manner in which cases of suspected child abuse and neglect will be reported. As previously stated, an unambiguous, informed, and caring approach to this topic on the part of the professional staff is essential. Also, it may be useful to include on the project staff those professionals who are familiar with community services that may be required in the event a child abuse report is made. In addition, whether project services will be ongoing in the event a child is removed from parental custody should be made clear at the onset.

Furthermore, it may be helpful for research projects involving chemically dependent families to have two professional staffs: one to serve the clinical needs of the families and a second to perform the research activities. It has been our experience that such a staffing pattern can help alleviate the extra burden placed on the researcher who may be unfamiliar with the multiple agencies and systems that become involved with these families once a report of suspected child abuse or neglect has been filed.

Finally, when designing research that involves chemically dependent parents, it seems imperative that each participant—whether assigned to the experimental or the control group—receive care that is at least at the level of “standard of practice” within the community. Under such circumstances, randomization of subjects into experimental or control groups will not jeopardize a subject’s ethical right and access to treatment. If the proposed research is designed to compare a new treatment approach to an established one, the control subjects still will receive the “standard of practice” care.

CONCLUSION

Longitudinal research is possible with this difficult-to-follow population of chemically dependent families, and it can be conducted in compliance with the child abuse reporting law. However, a successful project depends to a great extent on staff knowledge and expertise in the area of child abuse and neglect. To retain subjects who have been reported, staff members not only need to be comfortable with and unambivalent about the need for reporting but also need to stand by the family throughout the process. Furthermore, the research design needs to have the flexibility to deal with a population of families in which there are frequent changes in status with regard to caretaking responsibility, family residence, and legal involvement. In those situations when information deemed confidential must be shared to observe the law and protect a child from harm, this process need not be viewed as a punitive measure but rather as part of the early intervention and treatment plan for the family. The child abuse reporting law need not be viewed as an obstacle to conducting research with this population. Rather, one can simultaneously comply with the law, protect children, retain subjects in a study, and increase knowledge in the field of substance abuse.

NOTES

1. John Ferraro et al., Plaintiffs-Appellants, v. David L. Chadwick, M.D., et al., Defendants-Respondents. 90 Daily Journal Daily Appellate Report 6582. CA Courts of Appeal, 14 June 1990.

2. In re: Stephen, W., a Person Coming Under the Juvenile Court Law. Butte County Child Protective Services, Petitioner and Respondent, v. Rayla, W., Defendant and Appellant. Daily Opinion Service. CA Courts of Appeal, 22 June 1990.

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