National Institute on Drug Abuse

RESEARCH

MONOGRAPH SERIES

Medications Development for the Treatment of Pregnant Addicts and Their Infants

149

U.S. Department of Health and Human Services • Public Health Service • National Institutes of Health

Medications Development for the Treatment of Pregnant Addicts and Their Infants

Editors:

C. Nora Chiang, Ph.D.

Loretta P. Finnegan, M.D.

NIDA Research Monograph 149
1995

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

ACKNOWLEDGMENT

This monograph is based on the papers from a technical review on "Medications Development for the Treatment of Pregnant Addicts and Their Infants" held on August 26-27, 1993. The review meeting was sponsored by the National Institute on Drug Abuse.

COPYRIGHT STATUS

National Institute on Drug Abuse
NIH Publication No. 95-3891
Printed 1995

NIDA Research Monographs are indexed in the *Index Medicus.* They are selectively included in the coverage of *American Statistics Index, BioSciences Information Service, Chemical Abstracts, Current Contents, Psychological Abstracts,* and *Psychopharmacology Abstracts.*

Contents

Introduction: Medications Development for the Treatment of Pregnant Addicts and Their Infants

C. Nora Chiang and Loretta P. Finnegan

A technical review entitled *Medications Development for the Treatment of Pregnant Addicts and Infants* was held on August 26 and 27, 1993, at the Pooks Hill Marriott in Bethesda, MD. The purpose of this meeting was to review the current strategy for the treatment of pregnant drug-dependent women and their infants, to assess the needs for new pharmacotherapies, and to discuss issues related to the development of new pharmacotherapies, with special emphasis on approaches and methodologies for the design and development of medications with minimal risks to the fetus.

It is the consensus that new and improved medications for the treatment of pregnant drug-dependent women are critically needed. Although methadone has been used for treating opioid addicts since the 1960s the effective use of methadone in pregnancy and the developmental effects on children exposed in utero are still unclear. Therefore, research is needed to define the optimal treatment strategy for using methadone in pregnancy, including a pharmacokinetic and pharmacodynamic study to determine the proper dosage regimen, a study to investigate when and how medically supervised withdrawal can be safely performed, and a followup study to investigate the developmental effects of methadone on the children exposed in utero. Infants suffering from neonatal withdrawal syndrome due to in utero drug exposure can be managed adequately with current medications. However, research on improved formulations, such as transdermal drug delivery systems that are convenient to use, will be encouraged.

Pharmacotherapy for treating pregnant women can be very complicated. As pregnancy advances, pharmacokinetics and pharmacodynamics of a medication can change and necessitate careful monitoring of the effects and adjustment of the dosage regimen. Because there is also concern about the effects of the medication on the developing fetus, neonates must be assessed at the time of delivery. In some cases, followup of

children's development is also required. Additional complications with the treatment of pregnant addicts require a comprehensive intervention program.

Pharmacotherapy serves only as a safe replacement for abused drugs to help maintain pregnant addicts in a health care system. The behavioral intervention and social services provided by addiction-treatment professionals are essential in the successful treatment of addicts. Obstetricians and general health care providers often do not know how to deal with addicts. A top priority for treating this population is to familiarize health care providers with the needs of pregnant drug-dependent women and establish communications between obstetricians and addiction treatment professionals.

Medications development is very complex and requires a multidisciplinary approach. Basic research is necessary for the discovery of potential treatment medications. Pharmacological and toxicological evaluations must be performed in animals before the medications can be advanced to clinical studies. Basic pharmacokinetic and pharmacodynamic information should be obtained in preclinical evaluations and in early clinical trials to guide further clinical development. Prior to the use of a medication by pregnant women, its effects on fetuses throughout the gestational, neonatal, and postnatal periods must be assessed by developmental toxicity studies in animals.

The Food and Drug Administration (FDA) has no established guidelines on how to carry out clinical trials in pregnant women. Communication among FDA, National Institute on Drug Abuse (NIDA), and scientific communities is necessary to clarify issues prior to beginning clinical trials. An integrated effort involving researchers with expertise in obstetrics, addiction treatment, and neonatology is required for the design and execution of the clinical protocol. It is of paramount importance to decide the objectives of the study and then to design the proper outcome measures. When outcome measures include following children's development, pediatricians and epidemiologists must also be included to create a registry and follow the children over time. It is also important to establish a common database for collecting information nationwide across institutes so that data can be collected, analyzed, and disseminated.

There are additional social, economic, and practical issues related to medications development for this population. One issue is who should be responsible for medications development for treating pregnant addicts.

There are ethical concerns as well as fear of litigation about clinical studies in pregnant patients. Therefore, institutional review board (IRB) approval sometimes is difficult. The reluctance of pharmaceutical companies to develop medications for this population probably is due to the concern over financial feasibility and fear of litigation. Orphan drug status could provide some incentive to the industry. Federal Government agencies should encourage research in this area by providing sufficient funds to scientific communities, by facilitating IRB approval, and by actively collaborating with industry and interacting with FDA to advance medications development.

Research is urgently needed to develop treatments for pregnant drug-dependent women and their infants. A multidisciplinary approach is essential for medications development, and a comprehensive treatment program is necessary for the success of the treatment of pregnant addicts.

AUTHORS

C. Nora Chiang, Ph.D.
Project Officer
Medications Development Division

Loretta P. Finnegan, M.D.
Senior Advisor on Women's Issues
Office of the Director

National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

Overview: Medications Development for the Treatment of Drug Abuse

Frank Vocci, C. Nora Chiung, Lee Cummings, and Richard Hawks

INTRODUCTION

In 1988, it was estimated that drug addiction cost Americans at least $58.3 billion each year in health, social, lost productivity, and law enforcement costs. When costs associated with the care of infants born addicted or exposed to illicit drugs, the exacerbation of the AIDS epidemic, and other consequences are considered, the economic costs of drug abuse and addiction may have exceeded $100 billion in 1991 (Rice et al. 1991). Because of the tremendous cost associated with drug addiction, the development of effective treatments for drug addiction is therefore a top priority of the National Institute on Drug Abuse (NIDA). Pregnant women who are addicted to drugs and their infants who suffer adverse effects due to in utero drug exposure are among the people to be treated.

Current treatment programs are a complex mix of medical, psychosocial, and rehabilitation services. An important part of such treatment is the availability of pharmacotherapeutic adjuncts to help stabilize addicts and allow them to succeed in their overall addiction treatment program. At the present time, no medications are available for treating cocaine addiction, and only three medications are available for treating opioid dependence: methadone, naltrexone, and 1-alpha-acetylmethadol (LAAM, which was approved by the Food and Drug Administration [FDA] in July 1993). This scarcity of medications for drug abuse treatment is partly due to factors such as the limited commercial market and the difficulties associated with conducting clinical trials in drug-abusing populations. These factors have historically created a reluctance in the pharmaceutical industry to develop medications for treatment of drug abuse.

Medications development is an extraordinarily complex activity involving a broad range of basic and applied research including chemical

synthesis, pharmacological and toxicological evaluations, formulation and product development, pharmacokinetic and pharmacodynamic studies, clinical trials, and regulatory activities. In order to respond to the unmet needs of treatment communities and to facilitate the transformation of basic research findings into practical treatment applications, NIDA established the Medications Development Program with the goal of ensuring the rapid identification, evaluation, development, and regulatory approval of new and improved pharmacotherapeutic agents. This program works closely with the FDA, other Federal Government agencies, pharmaceutical companies, and academic institutions to achieve this goal.

The Medications Development Program has concentrated on developing medications for heroin (opiate) and cocaine dependence. These drugs were targeted because of the prevalence of their abuse and the high social, criminal, and health care costs including human immunodeficiency virus (HIV) treatment associated with their use.

MEDICATIONS FOR TREATMENT OF OPIOID DEPENDENCE

Unlike the newer phenomenon of epidemic cocaine use, opiate addiction has been well studied in the United States. The basic mechanisms involved in opiate addiction and opiate analgesia are reasonably well understood. The approaches used in designing pharmacotherapeutic agents for opiate addiction can be classified as replacement therapy with opioid agonists to substitute for heroin, such as methadone and LAAM; moderation or elimination of the process of withdrawal; and prevention of relapse after withdrawal either by blocking the behavioral or physiological effects of opioids or by reducing craving for opioids.

Medications Currently Approved for the Treatment of Opioid Addiction

Methadone. An opiate agonist, methadone was the first medication approved by the FDA for the treatment of heroin addiction. It is a maintenance medication and has been used in conjunction with psychosocial treatment since the 1960s (Dole and Nyswander 1965). Methadone is generally administered as an oral dose of 20 to 80 milligrams (mg)/day. Tolerance and dependence develop during the course of therapy. Methadone produces opioid-like subjective effects and is subject to abuse and street diversion. Initially, patients must visit the

clinic every day to receive this medication. Such daily visits are burdensome to the clinic and the individual, and are a contributing factor to low compliance in some individuals.

LAAM. LAAM is a long-acting opiate agonist and is effective at an oral dose of 30 to 100 mg taken every 2 to 3 days (Ling et al. 1980). LAAM is metabolized to the active metabolites nor-acetylmethadol and dinor-acetylmethadol. Because these active metabolites are produced slowly and persist in the body for a long time, LAAM has a slower onset and longer duration of action than methadone. Since LAAM is administered every other day or 3 times per week, it offers an advantage over methadone which requires daily administration. In clinical trials, LAAM has been demonstrated to be effective as an alternative therapy for patients currently taking methadone as well as for initial treatment of patients abusing illicit opiates.

Naltfexone. The narcotic antagonist naltrexone was approved in 1985 for use in patients who have been medically withdrawn from heroin, methadone, or other opiates. Naltrexone at an oral dose of 50 mg daily, or 100 mg Monday and Wednesday and 150 mg Friday, effectively protects patients from readdiction by blocking the effects of opiates. The longer patients can remain on naltrexone treatment, the longer they are able to remain opiate-free after treatment. However, the treatment has been relatively unsuccessful because of poor compliance. Since there is no noticeable effect of taking the drug and no immediate pharmacological consequences for not taking it, incentive to continue daily dosing can only be maintained by very highly motivated patients (Willette and Bamett 1981).

MEDICATIONS DEVELOPMENT FOR OPIOID DEPENDENCE

Clinical Program

New medications based on new chemical entities or improved formulations or delivery systems are needed to fulfill unmet needs and expand the availability of treatment to the broadest possible population base. There is a need to treat withdrawal symptoms with nonopioid adjunct medications, prevent relapse, and convert patients from agonist to drug-free status with antagonist pharmacotherapeutics. For replacement therapy, there are needs for new medications that have a limited addiction potential and are long acting.

Medications Currently Under Clinical Investigation

Buprenorphine. A partial opioid agonist, buprenorphine is being investigated as a maintenance drug for opiate dependence. The pharmacological advantages of buprenorphine include a low level of physical dependence, easy medically supervised withdrawal, low overdose potential, and possibly less abuse liability. Clinical studies have demonstrated that an 8 milligram (mg) sublingual dose of buprenorphine is as effective as a 60 mg dose of methadone (Johnson et al. 1992). NIDA is carrying out a multicenter clinical trial to further establish the efficacy of buprenorphine and plans to file a new drug application (NDA) in mid-1996.

Buprenorphine and naloxone combination product. If buprenorphine's efficacy as an addiction treatment medication is confirmed, NIDA will pursue the development of a "take home" product consisting of buprenorphine combined with naloxone (an antagonist). Naloxone in combination with pentazocine has been shown to effectively reduce the abuse potential for this analgesic product (Legros et al. 1984). Since the bioavailability of naloxone by the sublingual route is considerably less than that of buprenorphine, the efficacy of sublingual buprenorphine in the combination product is not attenuated. However, when administered intravenously (IV), naloxone in such a combination product can precipitate withdrawal in heroin addicts. This effect is expected to greatly reduce its diversion potential and makes this form of treatment potentially available through a wider range of providers than is possible under the current law regarding treatment with narcotic agonist medications with high abuse potential, such as methadone.

Depot nakrexone. Naltrexone is an opioid antagonist currently marketed in an oral dosage form that blocks the effects of opioids such as heroin. However, patient compliance is low. A depot dosage form providing naltrexone-blocking effects for 30 days could potentially improve patient compliance (Willette and Bamett 1981). In the 1970s NIDA developed an implantable 30-day depot dosage form of naltrexone to confirm the feasibility of such a drug delivery system for opioid treatment (Chiang et al. 1985). For ease of use in clinics, a prototype injectable depot system for naltrexone was developed and is currently undergoing a Phase I clinical trial in volunteers.

Currently Marketed and Investigational Medications That Have Been Identified for Clinical Evaluation

- Clonidine alone and in combination with naltrexone appears effective in rapid opiate detoxification. A similar product, lofexidine, marketed in the United Kingdom and Canada for treatment of opiate detoxification symptoms, may also be useful.

- Dynorphin, an endogenous ligand for the kappa opioid receptor, reversed tolerance in morphine (mu agonist)-dependent animals (Takemori et al. 1992; Tulunay et al. 1981) and has been proposed as both a withdrawal treatment and relapse prevention agent.

- Acetorphan, an enkephalinase inhibitor that is related to angiotensin converting enzyme (ACE) inhibitors currently marketed for reduction of blood pressure, may be useful as a nonaddictive opioid treatment medication. There is some indication that it can increase levels of endogenous opioids by inhibiting the enzymes that metabolize them.

PHARMACEUTICAL DEVELOPMENT

Advances in pharmaceutical technology have greatly increased the potential for the development of controlled-release systems or formulations that can improve treatment effectiveness by releasing medications at specified rates. Examples of controlled-delivery systems include implantable or injectable depot systems, transdermal delivery systems, oral sustained-release systems, triggered-release systems, and targeted-delivery systems. The most advanced system is aimed at drug delivery to the site of action. Proper delivery system design can make possible the development of compounds that have desirable pharmacological profiles but are otherwise of limited therapeutic potential because of limited oral bioavailability or short half-lives.

Implantable or injectable controlled-release formulations can be designed to provide effective concentrations for weeks or months. These systems are particularly useful for addiction treatment because they can reduce dosing frequency, minimize diversion, and improve compliance. Buprenorphine depot systems are being considered for development. As mentioned above, a naltrexone depot system is currently under clinical development.

PRECLINICAL DISCOVERY PROGRAM

Efforts are also being directed to discover a second generation of new chemical entities, opioids or nonopioids, for potential treatment of opioid addiction through preclinical evaluation. Compounds are characterized by in vitro opiate receptor subtype binding and evaluated in animals for opioid effects including analgesia, physical dependence, self-administration, drug discrimination, suppression of opioid dependence, and precipitation of withdrawal. Compounds with the desired pharmacological profiles will be identified as lead compounds for clinical evaluations.

Extensive research in the molecular biology of opioids has revealed the existence of a number of receptor subtypes and has led to the recently successful cloning of the subtype receptors mu, delta, and kappa (Chen et al. 1993, Evans et al. 1992, Kieffer et al. 1992, Wang et al. 1993, Yasuda et al. 1993). The emerging information about the role of specific receptors in dependence and tolerance phenomena and the concurrent development of ligands with specific binding characteristics for these receptors may lead to a nonaddicting (or less addicting) medication. Opioids with mixed agonist/antagonist actions (mu/kappa, mu/delta) and those interacting with specific opiate receptor subtypes such as delta or kappa receptors will be investigated as potential opiate treatment medications.

Nonopiate compounds that have been suggested to contribute to the development of opiate dependence, tolerance, or modulation of opiate effects will be investigated for potential treatment of opioid dependence. These compounds include N-methyl-d-aspartate (NMDA) antagonists (including glycine antagonists), nitrous oxide synthetase inhibitors, cholecystokinin (CCK) antagonists, enkephalinase inhibitors, and alpha-2-noradrenergic agonists.

MEDICATIONS DEVELOPMENT FOR COCAINE DEPENDENCE

Medications for the treatment of cocaine addiction are critically needed because of the prevalence of cocaine abuse in the United States. There is no approved treatment medication for cocaine addiction. Therefore, there is neither a reference medication against which new medications can be

designed and tested nor a validated preclinical or clinical testing model or paradigm in which clinical efficacy can be reliably predicted.

Two types of therapeutic approaches that have been postulated are based on therapies that have been successful in the development of opiate addiction pharmacotherapies. In one approach, medications that block the effects of cocaine are identified. In the other, compounds are identified as maintenance medications that are safer, longer acting, and have less abuse liability. These compounds replace cocaine in much the same manner as methadone is used for heroin addiction.

Cocaine is a central nervous system (CNS) sympathomimetic agent that blocks the reuptake of neurotransmitters (serotonin, norepinephrine, and dopamine). The dopamine system is hypothesized to be involved in mediating the reinforcing effects of cocaine (Kuhar et al. 1991). Basic physiological systems on which medications might act to attenuate the effects of cocaine have been hypothesized to include dopamine as well as serotonin receptors, and transporters and receptors for phencyclidine (PCP) and sigma ligands (Gawin 1991; Kuhar et al. 1991).

Clinical and preclinical investigations are ongoing to evaluate compounds acting on these receptors and transporters for their potential in treating cocaine abuse. Compounds acting via different mechanisms that may modify the effects of cocaine are also being tested to identify pharmacological profiles or mechanisms that may predict potentially useful medications. Calcium channel antagonists are an example of such compounds.

Because of the recent cloning of the dopamine transporter receptor and the availability of new brain imaging technologies, now is a promising time to rapidly pursue development of medications for the treatment of cocaine dependence.

CLINICAL DEVELOPMENT

This clinical development program evaluates the clinical efficacy of marketed and investigational compounds for the treatment of cocaine addiction. These compounds either have been suggested to be efficacious based on anecdotal data or are potentially efficacious based on their neuropharmacological activities. These clinical studies not only evaluate the efficacy of the medications but also test the methodology (study

design, outcome measures, etc.) and hypotheses that are directly relevant to medications development for cocaine addiction. On the basis of clinical data, the neuropharmacological basis for cocaine treatment can be investigated to establish a testing model for predicting the clinical efficacy of cocaine dependence pharmacotherapy.

The compounds that have been tested in cocaine-dependent populations can be categorized primarily as those affecting the dopamine system, such as amantadine, desipramine, bromocriptine, buproprion, and mazindol, and those affecting the serotonin system, such as fluoxetine, ritanserin and gepirone. Other hypothetical mechanisms tested include the reduction of cocaine-induced kindling by carbamazepine and decrease of cocaine's subjective effects by blocking calcium channels.

A fourth line of investigation involves the evaluation of potential medications in dually diagnosed populations; e.g., methylphenidate in cocaine-dependent subjects with attention deficit disorder, and buprenorphine in subjects who are both cocaine and opiate dependent.

PRECLINICAL DISCOVERY PROGRAM

New medications are being sought through preclinical testing and evaluation. Compounds identified as dopamine or serotonin transporter ligands, dopamine and serotonin agonists or antagonists, calcium channel antagonists, sigma receptor ligands, and compounds for which clinical efficacy has been suggested are being evaluated in animals. Tests are being conducted to determine whether these compounds may attenuate cocaine's effects. These evaluations include the ability of a test substance to affect cocaine-induced locomotor activity, drug discrimination, and self-administration.

Newly synthesized chemical entities, including compounds structurally similar to cocaine, are characterized by an in vitro biogenic amine transporter and receptor assay as well as being tested in animals. The structure-activity relationships will be examined to facilitate better design of compounds for cocaine treatment. Pharmacokinetics will be determined for compounds that show desired pharmacological profiles, and the lead compounds will undergo clinical evaluation.

MEDICATION FOR THE TREATMENT OF PREGNANT ADDICTS

It was estimated that 30,000 to 45,000 drug-affected infants were born in 1987 (Dicker and Leighton 1991). Premature births, low birth weights, pregnancy complications, and neurobehavioral abnormalities have been associated with in utero drug exposure. Neonatal withdrawal syndrome often occurs in neonates born to opiate-abusing mothers. Infants born to cocaine-abusing mothers do not go through withdrawal, but often show signs of neurotoxicity such as irritability. Serious complications such as seizures also occur in both cocaine- and opiate-affected infants (Kandall this volume; Zuckerman et al. this volume).

Methadone is the only medication being used for treating pregnant opioid addicts (21 CFR 291.505, *Drugs Used in the Treatment of Narcotic Addicts).* Women admitted to a methadone treatment program must be warned of the risks associated with the use of or withdrawal from methadone during pregnancy. Infants born to methadone-maintained mothers are larger than those of heroin-using mothers. Nevertheless, methadone, like heroin, produces a neonatal withdrawal syndrome (Finnegan and Kandall 1992). A substitute medication that would produce little or no withdrawal would be an obvious advantage to what is currently available.

Basic research on the design of effective medications for treating pregnant women with minimal harmful effects on the fetus is an area of increasing research opportunity. Such medications could have limited transplacental transport, such as synthetic enkephalin analogs that have analgesic effects in adults but that are not detectable in the fetus (Frederickson 1986).

Alternatively, the development of highly receptor-specific opiate analogs may result in medications devoid of adverse effects in fetuses. Studies to date have shown that the fetal response to certain opiate drugs is different from that of adults partly because of incomplete maturation of specific opiate receptors in the fetus. This receptor asymmetry between mothers and fetuses affords an opportunity for the treatment of pregnant narcotic addicts with minimal effects on fetuses (Szeto, this volume).

Although pharmacotherapies such as paregoric and phenobarbital have been shown to be effective for treating infants suffering symptoms associated with in utero drug exposure (Kandall, this volume), the

development of safer and more effective medications and better dosage forms, such as transdermal drug delivery systems, are of great interest.

SUMMARY

Drug abuse is of great public concern, and effective treatment strategies for opiate and cocaine dependence are urgently needed for the general addict population as well as for pregnant women and their infants. NIDA's effort to develop new pharmacotherapies as an adjunct to the treatment of opiate addiction has already led to the approval of LAAM and an NDA development program for buprenorphine. The momentum achieved by the new Medications Development Program's success with opiate addiction treatment must now be applied to the development of new treatments for cocaine addiction. With recent advances in neuroscience, imaging techniques, and pharmaceutical technology, the development of medications for significantly improving drug abuse treatment in a variety of directions holds real promise.

REFERENCES

Chiang, C.N.; Hollister, L.E.; Gillespie, H.K.; and Foltz, R.L. Clinical evaluation of a naltrexone sustained-release preparation. *Drug Alcohol Depend* 16:1, 1985.

Chen, Y.; Mestek, A.; Liu, J.; Hurley, J.A.; and Yu, L. Molecular cloning and functional expression of a yopioid receptor from rat brain. *Mol Pharmacol* 44:8-12, 1993.

Dicker, M., and Leighton, E.A., Trends in diagnosed drug problems among newborns: United States, 1979-1987. *Drug Alcohol Depend* 28:151-165, 1991.

Dole, V.P., and Nyswander, M. A medical treatment for diacetylmorphine (heroin) addiction. *JAMA* 193:80-84, 1965.

Evans, C.J.; Keith, D.E., Jr.; Morrison, H.; Magendzo, K.; and Edwards, R.H. Cloning of a delta opioid receptor by functional expression. *Science* 258:1952-1955, 1992.

Finnegan, L.P., and Kandall, S.R. Maternal and neonatal effects of alcohol and drugs. In: Lowinson, J.H.; Ruiz, P.; and Millman, R.B., eds. *Substance Abuse, A Comprehensive Textbook.* 2d ed. Baltimore: Williams and Wilkins, 1992. pp. 628-656.

Frederickson, R.C.A. Progress in the potential use of enkephalin analogs. In: Rapaka, R.S., and Hawks, R.L., eds. *Opioid Peptides: Molecular Pharmacology, Biosynthesis, and Analysis.* National Institute on Drug Abuse Research Monograph No. 70. DHHS Pub. No. (ADM) 86-1455. Washington, DC: Supt. of Docs. Govt. Print. Off., 1986.

Gawin, F. H. Cocaine addiction: Psychology and neurophysiology. *Science* 251:1580-1586, 1991.

Johnson, R.E.; Jaffe, J.H.; and Fudala, P.J. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA* 267:2750-2755, 1992.

Kieffer, B.L.; Befort, K.; Gaveriaux-Ruff, C.; and Hirth, C.G. The δ-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. *Proc Natl Acad Sci U S A* 89:12048-12052, 1992.

Kuhar, M. J.; Ritz, M.C.; and Boja, W. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci* 14: 299-302, 1991.

Legros, J.; Khalili-Varasteh, H.; and Magretts, G. Pharmacological study of pentazocine-naloxone combination: Interest as a potentially non abusable oral form of pentazocine. *Arch Int Pharmacodyn Ther* 271: 11-21, 1984.

Ling, W.; Klett, J.C.; and Gillis, R.D. A cooperative clinical study of methadyl acetate. *Arch Gen Psychiatry* 37:908-911, 1980.

Rice, D.P.; Kelman, S.; and Miller, L.S. Economic costs of drug abuse. In: Cartwright, W.S., and Kaple, J.M., eds. *Economic Costs, Cost-Effectiveness, Financing, and Community-Based Drug Treatment.* NIDA Research Monograph No. 113. DHHS Pub. No. (ADM)91-1823. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1991.

Takemori, A.E.; Loh, H.H.; and Lee, N.M. Suppression by Dynorphine A-(1-13) of the expression of opiate withdrawal and tolerance in mice. *Eur J Pharmacol* 221:223-226, 1992.

Tulunay, F.C.; Jen, M.F.; Chang, J.K.; Loh, H.H.; and Lee, N.M. Possible regulatory role of dynorphine on morphine- and endorphine-dependent analgesia. *J Pharmacol Exp Ther* 219:296-298, 1981.

Wang, J. B.; Imai, Y.; Eppler, C.M.; Gregor, P.; Spivak, C. E.; and Uhl, G.R. *mu* opiate receptor: cDNA cloning and expression. *Proc Natl Acad Sci USA* 90:10230-10234, 1993.

Willette, R.E., and Barnett, G., eds. *Narcotic Antagonists: Naltrexone Pharmacochemistry and Sustained-Release Preparations.* National Institute on Drug Abuse Research Monograph No. 28. DHHS Pub. No. (ADM) 81-902. Washington, DC: Supt. of Docs., U.S. Govt Print. Off., 1981.

Yasuda, K.; Raynor, K.; Kong, H.; Breder, C.D.; Takeda, J.; Reisine, T.; and Bell, G.I. Cloning and functional comparison of kappa and δ opioid receptors from mouse brain. *Proc Natl Acad Sci U S A* 90:6736-6740, 1993.

AUTHORS

Frank Vocci, Ph.D.
Deputy Director
Medications Development Division

C. Nora Chiang, Ph.D.
Project Officer

Lee Cummings, J.D.
Chief, Regulatory Affairs Branch

Richard Hawks, Ph.D.
Chief, Chemistry and Pharmaceutics Branch

Medications Development Division
National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

Overview of the Effects of Abuse and Drugs on Pregnancy and Offspring

Barry Zuckerman, Deborah Frank, and Elizabeth Brown

INTRODUCTION

With the rapid increase in cocaine use, substance abuse among pregnant and parenting women has escalated from a relatively small clinical and academic concern to an important public health problem. A U.S. General Accounting Office (1990) report to Congress suggested that each year between 100,000 and 375,000 women use illicit drugs including marijuana during pregnancy. There is currently no national prevalence data regarding prenatal cocaine or other illicit psychoactive substance use. In Rhode Island, 3.4 percent of peripartum urine samples tested positive for cocaine (Griffin et al. 1990). In California in 1992, 1.1 percent of urine samples were positive for cocaine and 1.4 percent for opiates. African-American women had the highest rates: 7.8 percent and 2.5 percent for cocaine and opiates, respectively (Vega et al. 1993).

SOCIAL-POLITICAL ISSUES

Reports in the lay press based on anecdotal evidence resulted in a premature rush to judgment about the impact of in utero exposure to illicit drugs, particularly cocaine, upon the health, behavior, and development of children (Mayes et al. 1992). Children with a history of prenatal cocaine exposure, labeled "crack kids," were portrayed in the media as inevitably and permanently damaged. An article in *The New* York *Times* reported that "parents and researchers say a vast majority of children exposed to significant amounts of drugs in the womb appear to have suffered brain damage which cuts into their ability to make friends, know right from wrong, control their impulses, gain insight, concentrate on tasks, and feel and return love" (Blockner 1990, p. 14). Another article stated that these babies are "like no others, brain damaged in ways yet unknown, oblivious to any affection" (Hopkins 1990, p. 1). These statements are made in spite of the absence of any credible scientific

evidence regarding the sequelae of prenatal cocaine exposure beyond the newborn period.

A very large group of cocaine-exposed children is in danger of being written off. Moreover, a social sentiment has arisen that the loss of these children is entirely attributable to the prenatal effects of cocaine (an irreversible biological factor). Such a conviction works toward exempting society from having to face other possible explanations of the children's plight-explanations such as poverty, community violence, inadequate education, and diminishing employment opportunities. Such explanations require deeper understanding of wider social policy issues.

The labels used to describe drug-exposed children are themselves damaging, since labels have a way of becoming self-fulfilling prophecies (Rosenthal and Rosenow 1979). Minimally, expectations for such children are lowered. The attribution of irremediable damage makes it more difficult to find services for these children, and such services may be geared to custodial care rather than to challenging children's capacities or to effectively remediating. Even more damaging is the difficulty in finding adequate nonbiological homes for such children; potential foster or adoptive parents are often reluctant to assume the care of cocaine-exposed children because of their perceived impairments.

Labels also carry with them a risk for biasing and undermining scientific and clinical decisions. A 1989 report in *Luncet* indicated that abstracts regarding the impact of prenatal cocaine use were more likely to be accepted for presentation at the annual meeting of the Society for Pediatric Research if they reported positive results (i.e., evidence of impairment) than if they failed to show such results, even though the rejected papers with negative findings tended to be methodologically more rigorous (Koren et al. 1989). Clinical decisions are also affected by underlying attitudes. Another study showed that, given an equivalent extent of use of illegal drugs by pregnant women, physicians and clinics are more likely to report African-American women or women on welfare to law enforcement agencies than white or middle-class women (Chasnoff et al. 1990). Prejudice exists, and it can well bias data interpretation, particularly when observers are not blind to study group assignment.

Condemning these drug-exposed children with labels indicating a permanent handicap is premature. Such prophecies of doom lead researchers to overlook what has long been known about the remediating

effects of early intervention. Studies of preterm or ill newborns fail to support biological determinism (Beckwith and Parmalee 1986; Hunt et al. 1988; Werner 1989). Supportive environments contribute significantly to improving the outcome of infants with biological vulnerabilities at birth (Beckwith and Parmalee 1986; Infant Health and Development Program 1990). Even among infants exposed to narcotics prenatally, the home environment is a critical determinant of outcome (Johnson et al. 1990; Lifschitz et al. 1985). Future research is needed to determine if children prenatally exposed to psychoactive drugs suffer behavioral and developmental problems. If problems are identified, the areas of impaired development need to be determined, and the relative effects of prenatal psychoactive substance exposure and postnatal home environment must be assessed.

Methodologic Issues

The authors have recently summarized a number of important methodologic issues that contribute to uncertainty in findings that describe the effects of prenatal psychoactive substance exposure (Frank et al. 1993). These issues include accurate identification of users and determination of dose and gestational timing of exposure; both are difficult to accomplish. Use of biological markers combined with self-report is the most accurate method of identifying users. If users are misclassified as nonusers due to underreporting, identified differences in outcome due to drug exposure may be missed (Zuckerman et al. 1989). The consequences of dose and gestational timing have not been evaluated adequately for most substances and are very difficult to assess in unconfined populations. Sample selection bias is likely if samples involve women in a drug treatment program or women suspected by clinical staff at delivery of using drugs.

Failure to control for confounding variables frequently results in overestimates of the effects of the drug being studied. In one study that controlled for confounding variables, only 25 percent of the 409 gram weight decrement of infants exposed to cocaine could be statistically attributed to cocaine exposure rather than to other factors such as cigarette use (Zuckerman et al. 1989). Lack of blind assessment and appropriate comparison populations impair the validity of findings. Appropriate outcome measures are needed to identify important selective consequences of drug exposure.

There is a growing consensus among researchers that global measures of development may not be sensitive to the effects of cocaine and other psychoactive substances. During preschool and school years, assessment of specific functions such as information processing, attention, activity level, memory, and language function may provide more sensitive indicators of the effects of prenatal psychoactive substance exposure on children's development than global developmental scores.

IMPACT OF SUBSTANCE ABUSE ON PARENTING

The chaotic lifestyle of the addicted mother causes indirect effects on children due to cocaine and opiate exposure. Prenatally these effects include poor nutrition and exposure to infectious diseases; postnatally, the effects involve parenting. Substance abuse and addiction impair parents' caretaking (Bauman and Dougherty 1983; Bernstein et al. 1984; Fiks et al. 1985). Infants develop a sense of security when their caregiver responds appropriately to their needs for comfort, stimulation, and food. Once infants have a sense of security, they can explore the environment and develop other relationships. Addiction prevents a mother from responding to her infant's needs; her primary focus is on her drug of choice, not on her child. Her life is organized around getting the drug, not around taking care of her children. In one of the few published direct observational studies, a reduction in reciprocal behaviors between drug-using mothers with their infants was seen (Bums et al. 1991).

The following case report provides a description of the caregiving capacities of one cocaine-using mother. This description was from a study of young mothers and their children; the observer was unaware that the mother used cocaine (Greer et al., unpublished data).

EJ was the 18-year-old mother of AJ, who was 14 months old at the time of the home visit. They lived in a two-bedroom apartment with EJ's 3-year-old son, her 19-year-old boyfriend (the father of both children), her mother, and four other maternal family members (3 aunts and an 8-year-old cousin). The overwhelming impression upon entering the apartment was one of chaos. One person was sleeping in a room just off the kitchen, another was watching television, and two more people were getting dressed in the same room. EJ was drinking coffee out of a mayonnaise jar and arguing with her boyfriend, who was cooking breakfast. Meanwhile the three children were running around the kitchen trying to obtain food.

EJ appeared depressed and withdrawn, and she demonstrated little tolerance of her son's behavior. At times during the session she shouted at him or appeared hostile to him. In general her involvement and interaction with him was minimal, and the opportunity for positive stimulation appeared limited. As part of this structured observation, EJ was asked to teach her son to make a tower of three blocks. Her teaching consisted of saying "Do this," building a tower of three blocks once, and then returning to her breakfast and cigarette. However, AJ's father and other family members did provide positive stimulation and nurturing to him. For example, AJ's father and maternal grandmother frequently cared for him in his mother's absence. AJ had a variety of appropriate toys, most of which were reportedly supplied by his father or maternal relatives.

Two weeks later, AJ was admitted to the hospital with second and third degree bums on his chin and chest. He had pulled a can filled with hot coffee onto himself from the kitchen table. Following an investigation by the State Department of Social Services, AJ was placed in foster care because of neglect. This case example, empirical studies, and clinical experience show that addiction or substance abuse interferes with parenting and contributes to developmental, behavioral, and health problems.

COCAINE

Pharmacology

Cocaine is a tropane alkaloid that is derived from the leaves of the *Erythroxylon* cocoa plant from the mountain slopes of Central and South America. It affects multiple neurotransmitter systems in the central nervous system (CNS), including the dopaminergic (DA) and norepinephrine (NE) systems. During pregnancy, the NE-mediated vasoactive consequences of cocaine exposure in animals include decreased uterine blood flow and constriction of umbilical arteries (Woods et al. 1987).

Cocaine is highly water and lipid soluble and it has a wide volume of distribution. In addition to its vascular effects, cocaine crosses the placenta and blood brain barrier. Cocaine has been found in the brain in concentrations four times higher than the peak plasma concentration (Farrar and Keams 1989).

Preliminary Data Regarding Effects on Fetal Neurotransmitters

In the fetal brain, neurotransmitters contribute to brain development by influencing neuronal migration and differentiation as well as synaptic proliferation (Lauder 1988). During the prenatal period, neurotransmitters also affect the development of receptor sites (Miller and Friedhoff 1988). Neurotransmitter changes among infants with in utero cocaine exposure were suggested by a pilot study showing blood levels of the NE precursor dihydroxyphenalamine were higher in cocaine-exposed infants than in unexposed newborns (Mirochnick et al. 1991). This finding might be due entirely to chronic stress associated with cocaine-induced vasoconstriction and hypoxia in utero. Another study showed that, when compared with infants not exposed to drugs, 2-month-old infants prenatally exposed to cocaine, narcotics, and other drugs showed elevation of plasma neuroepinephrine but not epinephrine or DA (Ward et al. 1991).

A recent preliminary study, the first in humans, examined CNS neurotransmitter levels by measuring neurotransmitter precursors and metabolites in the cerebrospinal fluid (CFS) of 10 cocaine-exposed and 21 unexposed newborns undergoing spinal taps for a variety of clinical indications. When compared to unexposed infants, cocaine-exposed infants had significantly lower levels of CFS homovanillic acid (HVA), the principal metabolite of DA. Other levels of neurotransmitter precursors and metabolites did not differ significantly between exposed and unexposed neonates (Needleman et al. 1993).

Complications of Pregnancy

Abruptio placentae and placenta previa have been associated with maternal cocaine use, particularly when cocaine use is identified at the time of delivery (Handler et al. 1991). However, when cocaine use is identified by meconium assay, no association with abruptio placentae can be shown. This suggests that the increased risk of abruptio placentae, if any, pertains only when cocaine is used close to delivery (Ostrea et al. 1992).

Fetal Growth

A recent published review has summarized the relationship between prenatal cocaine use and fetal growth (Frank et al. 1993). Maternal

cocaine use has been associated with depressed length, weight, and head circumference for gestational age in many studies. Most of these studies also have found increased rates of low birth weight and prematurity among cocaine-exposed newborns. However, other studies have found no such association. The authors are aware of only five published studies (Chouteau et al. 1988; Gillogley et al. 1990; Handler et al. 1991; Petiti and Coleman 1990; Zuckerman et al. 1989) that have large enough samples to assess cocaine effects on prematurity, low birth weight, and intrauterine growth retardation (IUGR) while statistically controlling for associated risk factors. In spite of methodologic differences, all five studies found an association between maternal cocaine use and IUGR. Four (Chouteau et al. 1988; Gillogley et al. 1990; Handler et al. 1991; Petiti and Coleman 1990) of the five studies also demonstrated an association between maternal cocaine use and increased risk of prematurity. Only in one study (Zuckerman et al. 1989), when 100 percent of the cocaine-using women received prenatal care, was there no association between cocaine use and prematurity. These findings suggest that maternal cocaine use is an independent risk factor for IUGR. In the absence of prenatal care, it appears that cocaine use is also independently associated with prematurity.

Structural Malformations

There is no such entity as a "fetal cocaine syndrome," no consistent pattern of malformations associated with prenatal cocaine exposure. Rare but more serious congenital abnormalities, such as urogenital anomalies (Chavez et al. 1989), distal limb deformities (Hoyme et al. 1990), gastroschisis (Goldbaum et al. 1990), cardiac lesions (Lipshultz et al. 1991) and skull, CNS, and ocular malformations (Bingol et al. 1987; Dominguez et al. 1991) have been noted in clinical series. A meta-analysis of published studies suggested that congenital malformations are independently associated with prenatal cocaine use (Lutiger et al. 1991). However, a subsequent study, the only population-based investigation, did not support this finding. In this study, which assessed trends between 1968 and 1989 for urogenital and other birth defects, no significant change in prevalence of these multiple vascular disruption defects were seen in spite of a large rise in maternal cocaine use over that period (Martin et al. 1992).

Neurologic Findings

An ototoxic effect of prenatal cocaine exposure has been suggested (Shih et al. 1988). Auditory brainstem responses (ABRs) in neonates exposed to cocaine showed prolonged inter-peak latencies and prolonged absolute latencies, which indicate neurologic impairment or dysfunction in the auditory system. Another study (Salamy et al. 1990) also showed delayed auditory brainstem transmission time in cocaine-exposed newborns, which reverted to normal by 3 to 6 months.

Case studies have described 16 infants with seizures in the neonatal period (Kramer et al. 1990). A focal seizure was described in one infant with an infarct on computerized axial tomography (CAT) scan. Six patients continued to have seizures after 6 months of age. One other study reported electroencephalogram (EEG) changes at 1 month of age in a small group of cocaine-exposed infants; EEG changes resolved to normal by 6 months of age (Doberczak et al. 1988). Cocaine use is associated with lowered seizure threshold in adults (Gawin and Kleber 1984). The true incidence of seizures in cocaine-exposed neonates has not been determined; clinical experience suggests that seizures are a relatively rare complication, but may occur in infants with no other risk factors.

Case reports of significant cerebral infarctions associated with prenatal cocaine exposure have been published (Chasnoff et al. 1987a; Kramer et al. 1990). A case report describes congenital, cerebral, and ocular abnormalities in 7 cocaine-exposed neonates that may be attributed to early vascular insult (Dominguez et al. 1991). A more systematic study reported that 41 percent of cocaine-exposed, asymptomatic, term infants undergoing cranial ultrasound in the first 3 days of life showed either echodensities or echolucencies, suggesting CNS vascular injury (Dixon and Bejar 1989). This rate of abnormal findings was comparable to that of ill term infants and much greater than in healthy term newborns. Another study showed a similar rate of ultrasound findings overall among cocaine-exposed and unexposed term newborns (Frank et al. 1992). In order not to miss a finding associated with dose, a subsequent analysis categorized cocaine use as heavy or light. This analysis found increased echodensities among infants with heavy cocaine exposure compared with light exposure (Frank et al. 1994). The clinical significance of ultrasound lesions in term infants, whether cocaine-exposed or not, is unknown; but the existence of these lesions warrants further investigation and followup.

Neurobehavioral Outcomes

Neonatal neurobehavioral abnormalities following cocaine exposure have been reported in some but not all studies. Controlled studies (Chasnoff et al. 1989a, 1989b, 19876; Coles et al. 1992; Eisen et al. 1991; Lester et al. 1991; Mayes et al. 1993; Neuspiel et al. 1990) used the Brazelton Neonatal Behavioral Assessment Score (BNBAS) to assess the neurobehavioral functioning of term infants exposed to cocaine but not opiates. The findings are summarized in table 1 (data from reports by Chasnoff are combined). As the table makes clear, results of these studies are inconsistent regarding the presence or absence of an association between prenatal cocaine use, neurobehavioral dysfunction, and the type of dysfunction identified.

Out of 35 possible outcomes, 9 are significant. However, four of these outcomes occurred in one study (Chasnoff et al. 1989a, b). In this study, subject mothers were enrolled from a drug treatment program. Six outcomes occurred within the first few days following birth, while the other three occurred between 2 and 4 weeks postpartum. There is no consistency among studies in the behavioral cluster associated with prenatal cocaine exposure.

Another study (Lester et al. 1991) using cry characteristics identified two neurobehavioral profiles among cocaine-exposed newborns. One profile, characterized as "excitable," was ascribed to the direct primary effect of cocaine exposure. The other profile, characterized as "depressed," is thought to be due to secondary effects of IUGR. Possible opposite effects of cocaine and IUGR may help explain the variability in newborn behavior seen clinically and in the studies summarized above. It is not known whether alterations in neonatal behavior other than crying will be confirmed with more methodologically rigorous studies.

Findings After the Newborn Period

Sudden Infant Death Syndrome. Probable fetal hypoxia associated with in utero cocaine exposure has raised concerns that such exposure may increase the risk of sudden infant death syndrome (SIDS). These concerns are heightened by reports of respiratory pattern abnormalities in cocaine-exposed infants as compared with methadone-exposed infants (Chasnoff et al. 19896).

TABLE 1. *Cocaine effects on Brazelton Neonatal Behavioral Assessment Score (BNBAS) in term infants not exposed to opiates.*

	Habitu-ation	Orien-tation	Motor	State Range	State Regulation	Autonomic Regulation	Abnormal Reflexes
1) CHASNOFF 94 1989 N = 79	0	+	+	0	+	0	+
2)EISEN 118 1991 N = 52	+	0	0	0	0	0	0
3) NEUSPIEL 119 1991 N = 111	0	0	+*	0	0	0	0
4) COLES 120 1992 N = 107	0	0	0	0	+**	+**	0
5) MAYES 1993 N = 86	+	0	0	0	0	0	0

\+ = less optimal scores in cocaine-exposed

0 = no difference between exposed and unexposed

* = only at 2 weeks of age

++ = only at 14 and 28 days

An early study, using a convenience sample of infants prenatally exposed to cocaine, found that 10 of 66 (15 percent) died of SIDS (Chasnoff et al. 1987b). However, four subsequent studies (Bauchner et al. 1988; Durand et al. 1990; Kandall et al. 1993; Ward et al. 1990) using larger, more representative samples have found only a slightly increased rate of SIDS. In the largest study to date, the adjusted risk ratios are: methadone only, 3:6; heroin only, 2:3; methadone and heroin, 3:2: cocaine only, 1:6; and cocaine and heroin or methadone, 1: 1 (Kandall et al. 1993).

Growth and Developmental Outcome After the Neonatal Period. There are a limited number of published longitudinal studies of the outcome of children prenatally exposed to cocaine and not opiates. In one study, cocaine- and amphetamine-exposed infants scored lower at between 27 and 52 weeks of age on measures of visual recognition memory (Struthers and Hansen 1992). This test evaluates the infant's ability to orient to a novel stimuli in preference to a familiar stimulation, and has been associated with later cognitive development. In a study of growth, children exposed to cocaine achieved expected growth levels by 1 year of age after being smaller at birth (Weathers et al. 1993). In the longest followup study, Chasnoff and colleagues studied three groups of infants from birth to age 2: 106 children exposed to cocaine, alcohol, marijuana, and in a few cases phencyclidine (PCP) and amphetamines, but not opiates; 45 children exposed to marijuana and alcohol, but not cocaine; and 77 children whose mothers abstained from cocaine, alcohol, and marijuana during pregnancy. Women in all three groups smoked tobacco, but use was heavier and more prevalent in the two groups using illegal drugs (Chasnoff et al. 1992).

Both the cocaine-exposed and the alcohol- and marijuana-exposed groups showed catchup from perinatal growth deficits during the early months of life; their attained somatic growth through 18 months did not differ from that of unexposed infants. At 2 years of age, the mean length of the cocaine-exposed infants was significantly shorter than that of the unexposed, but did not differ from alcohol- and marijuana-exposed infants, although a large sample attrition makes this finding difficult to interpret. At all ages, the infants exposed to cocaine, alcohol, and marijuana had lower mean head circumferences than the unexposed infants, but the mean developmental scores for the infants at age 2 did not differ significantly between groups. However, a higher proportion of cocaine-exposed infants than drug-free infants scored greater than one standard deviation below the mean on the Bayley Scales of Infant Development.

A subsequent assessment of this sample at age 3 years showed a four to five point difference on the Stanford-Binet intelligence quotient (IQ) test among cocaine-exposed infants (mean score 94.4), other drug-exposed infants (mean score 93.2), and unexposed infants (mean score 98.5) that is not statistically significant. However, using path analyses of the data collected at 36 months, drug exposure (defined as alcohol, cigarettes, and marijuana with or without cocaine) was directly and indirectly associated with the Stanford-Binet IQ test. The indirect effects were due to smaller head circumference at 3 years of age, poorer environment, and perseverance at tasks (Azuma and Chasnoff 1993). The only other longitudinal investigation of cocaine-exposed infants also included exposure to PCP. Infants in this study showed deficits in unstructured play at 18 months and high rates of insecure, disorganized attachment (Rodning et al. 1991, 1993).

OPIATES

Pharmacology

The opiates comprise a group of naturally occurring opium alkaloids and their chemically related derivatives obtained by drying the milky white exudate of unripe poppy seeds indigenous to Asia Minor. They include morphine, codeine, heroin, and meperidine hydrochloride. Although the chemical structure of methadone is different from that of the opiates, the pharmacological properties are similar. In adults, the half-life of heroin is 4 hours and that of methadone, 23 hours. The half-life of methadone in newborns is 32 hours. The opiates work in the CNS, binding at specific sites that are associated with nerve synapses and normally bind natural neurotransmitters, the endogenous opioids (Brown and Zuckerman 1991).

The opiates produce analgesia, lowered anxiety, improved mood, drowsiness, and a clouding of the sensorium. They also cause respiratory depression, peripheral vasodilatation, and decreased intestinal peristalsis. Tolerance (the need for an increased dose of drug to achieve the same effect) and physiologic dependence resulting in a withdrawal syndrome occur with long-term opiate use. Only a small proportion of any opiate dose crosses the blood-brain barrier; most is concentrated in kidney, lung, liver, and spleen. Opiates are metabolized in the liver and excreted in the urine after glucuronidation. Opiates cross the placenta and affect the fetus directly (decreased somatic growth, neonatal abstinence syndrome).

Newborn Outcome

There is no convincing evidence that exposure to narcotics in utero results in an increased rate of congenital malformations in either animal or human pregnancies. Some animal studies have shown teratogenic effects, but only at extremely large doses. Many of these studies did not control for the effects of anorexia and decreased caloric intake seen in most animals given narcotics (Hutchings 1982). Studies that have used doses more closely approximating human usage and that have taken nutritional intake into account have not demonstrated an increased rate of malformations. In humans, no consistent pattern of anomalies has been described in infants, nor has the rate of malformations been greater than that seen in the general population (Zuckerrnan and Brown 1993).

The primary effects of maternal narcotic use on the fetus are IUGR and neurobehavioral dysfunction. Numerous studies have documented low birth weight for gestational age in infants exposed to narcotics in utero (Glantz and Woods 1993; Zuckerman and Brown 1993). Although participation in a methadone maintenance program during pregnancy improves birth weight, the infants are still significantly growth-retarded relative to drug-free controls (Kandall et al. 1976). In a summary of data from controlled studies, Glantz and Woods (1993) reported that risk of low birth weight appears to be 41 to 45 percent for heroin users, 24 to 26 percent for methadone users, and 12 to 19 percent in drug-free controls. However, other confounding factors among narcotic-using pregnant women complicate drawing a firm conclusion regarding a causal relationship between opiate use and low birth weight. When outcomes were controlled for differences in race, adequacy of prenatal care, weight gain during pregnancy, prenatal risk score, maternal education, and maternal smoking, no differences in birth weight were seen between drug-exposed (heroin or methadone) and drug-free infants (Lifschitz et al. 1985).

Studies evaluating the relationship between opiate use and prematurity do not control for associated risk factors, which prevents firm conclusions from being drawn (Glantz and Woods 1993). Among premature infants, narcotic-exposed infants are less likely to experience respiratory distress syndrome (Glantz and Woods 1993). This may be due to earlier pulmonary maturity secondary to heroin exposure and associated stress. Meconium in amniotic fluid associated with narcotic use was 21 to 46 percent compared with 12 to 14 percent in drug-free controls and 6 to 17 percent in methadone-maintained women (Glantz and Woods 1993).

Low Apgar scores at 5 minutes are no more frequent in infants of narcotic-exposed mothers compared with controls (Glantz and Woods 1993). A higher rate of stillbirth associated with prenatal narcotic use is reported in some but not all studies. It is possible that the risk of stillbirth is related to intermittent narcotic withdrawal in utero rather than a direct effect of drug exposure per se.

There is growing evidence that in utero exposure to narcotic drugs may result in abnormal structural organization of the fetal brain (Sakellaridis et al. 1986; Smith et al. 1977; Zagon and McLaughlin 1984;). Morphine decreases the packing density of neurons in the medial and lateral preoptic areas of the hypothalamus, and in all layers of the cerebral cortex (Hammer et al. 1989). Since receptors affect dendritic growth and mature at different rates in different parts of the brain, prenatal exposure could produce different effects depending on timing of the exposure. Thus, the neurobehavioral abnormalities seen in narcotic-exposed infants may be attributable, in part, to underlying structural changes in brain development.

Neurochemical alterations resulting from prenatal opiate exposure may be expressed in a variety of ways. Herzlinger and colleagues (1977) reported a 1.2 percent incidence of seizures for heroin-exposed infants and 7.8 percent for methadone-exposed infants. A 1 -year followup study of infants with abstinence-related seizures showed that most early EEG and neurological abnormalities associated with abstinence-related seizures were transient (Doberczak et al. 1988). By 8 to 16 months of age, results of all neurological exams were normal; none of the infants developed a seizure disorder. It is possible that the cause of abstinence-related seizures may be the depletion of neurotransmitters (McCinty and Ford 1980; Roseman and Smith 1972; Smith et al. 1977), which if restored over time would result in improved neurological function.

The most common neurological complication seen in narcotic-exposed infants is the presence of a neonatal abstinence syndrome. During in utero exposure to narcotics, a fetus develops drug dependency, including tolerance for narcotics. After delivery, the infant develops symptoms of irritability, tremulousness, sweating, stuffy nose, difficulty in feeding, diarrhea, and vomiting. The neurochemical pathways underlying drug withdrawal symptoms are poorly understood. Finnegan (1990) developed a scoring system commonly used to quantify the severity of withdrawal symptoms, to determine when pharmacotherapy is indicated, and to guide therapy once it is begun.

The onset of symptoms depends on the type of narcotic. Heroin has a short half-life (4 hours), so that withdrawal symptoms are apparent on the first day. Methadone, on the other hand, has a very long half-life (32 hours in the newborn), so that the drug stays in the newborn's system for days. Therefore, withdrawal symptoms seldom occur before 24 to 48 hours, and can occur as late as 7 to 10 days after birth. Methadone is excreted in the infant's urine for 10 to 14 days after birth (Kreek 1979), which may account for the very prolonged withdrawal period seen with methadone-exposed infants. In addition, a subacute withdrawal syndrome characterized by restlessness, agitation, tremors, and sleep disturbance may last 3 to 6 months after birth and may be a reflection of the prolonged metabolism and excretion of methadone (Hutchings 1982).

Infants exposed to heroin and cocaine are more likely to show withdrawal symptoms; these signs occur earlier than for infants only exposed to heroin. Other studies have found no difference in type and frequency of withdrawal symptoms between infants exposed to methadone and those exposed to both methadone and cocaine (Doberczak et al. 1988; Ryan et al. 1987). Withdrawal symptoms occur less often in premature infants. When symptoms are seen they are less severe, and fewer premature infants require pharmacologic treatment. This may be related to decreased fat stores of methadone (Doberczak et al. 1991) or lack of development of receptor sites.

Long-Term Outcome

Growth. Followup of narcotic-exposed infants at 3 years of age found that the growth of the drug-exposed infants is no more impaired than that of a control group of infants from a similar socioeconomic status (SES), although mean scores for height, weight, and head circumference were below the 50th percentile (Lifschitz et al. 1983). The multiple risk factors in the lifestyle of drug-abusing pregnant women appear to be major factors in the poor growth reported both prenatally and postnatally for this group of infants.

Developmental Outcome. There is no convincing evidence that exposure to narcotics in utero results in developmental delay when exposed infants are compared to appropriate controls of similar SES. The major studies of children 2 years or older are reviewed in table 2. Only one study showed any significant differences in global developmental

TABLE 2. *Cognitive function in narcotic-exposed infants and children.*

Author	Study Age (Years)	Methadone/ Heroin-Exposed Group	Control Group
Chasnoff et al. (1986)	2	98.7	96.2
Kaltenbach et al. (1979)	2	91.0	95.0
Hans (1989)	2	92.0	95.8
Wilson (1989)	3-5	90.4	89.4
Kaltenbach and Finnegan (1989a)	4	106.51	106.5
Strauss et al. (1979)	5	86.8	86.2

cognitive function between narcotic-exposed and control infants. Hans (1989) found no overall differences in cognitive function; however, methadone-exposed children raised at the lowest SES level fared worse than control infants at the same low SES, suggesting that in utero methadone exposure may produce a biological vulnerability that is added to the stress of being raised in a disadvantaged social environment. The exacerbation of a biological vulnerability by nonresponsive caretaking or social disadvantage has been described in other studies.

In a preliminary study of school performance of older heroin-exposed children, a different picture emerged. As many as 40 percent required special educational classes, and 25 percent needed to repeat one or more

grades (Wilson 1989). Behavioral dysfunction in the classroom was reported by teachers of 75 percent of the schoolage children. Teachers reported inattention and poor self-discipline in half the students. Deficits in attention among schoolage children exposed to methadone prenatally have also been described (Hans, in press). These preliminary observations, if replicated, suggest at least two possibilities. First, prenatal narcotic exposure may impair specific CNS-associated learning functions. Autonomic system regulating mechanisms also may be impaired, but may be difficult to identify until school age. Alternatively, childrearing by addicted or recovering mothers may be more dysfunctional than that of SES-matched mothers; over time, this may lead to the problems described above. It is also possible that both mechanisms play a role, illustrating the potential double jeopardy experienced by drug-exposed infants.

REFERENCES

Azuma, SD., and Chasnoff, I.J. Outcome of children prenatally exposed to cocaine and other drugs: A path analysis of three-year data. *Pediatrics* 92:396-402, 1993.

Bauchner, H.; Zuckerman, B.S.; McClain, M.; Frank, D.; Fried, L.E.; and Kayne, H. Risk of sudden infant death syndrome among infants with in utero exposure to cocaine. *J Pediatr* 113:831-4, 1988.

Bauman, P., and Dougherty, F. Drug-addicted mothers: Parenting and their children's development. *Int J Addict* 18:291-302, 1983.

Beckwith, W., and Parmalee, A. EEG patterns in preterm infants, home environment, and later I.Q. *Child Dev* 57:777-789, 1986.

Bernstein, V.; Jeremy, R.J.; Hand, S.; and Marcus, J.A. Longitudinal study of offspring born to methadone-maintained women: Dyadic interaction and infant behavior at four months. *Am J Drug Alcohol Abuse* 10:161-193, 1984.

Bingol, N.; Fuchs, M.; and Diaz, V. Teratogenicity of cocaine in humans. *J Pediatr* 110:93-96, 1987.

Blockner, S. "Crack Babies." *The New York Times,* August 19, 1990. p. 14.

Brown, E., and Zuckerman, B. The infant of the drug abusing mother. *Pediatr Ann* 20:555-563, 1991.

Bums, K.; Chethik, L.; Bums, W.J.; and Clark, R. Dyadic disturbances in cocaine abusing mothers and their infants. *J Clin Psychol* 47:316-319, 1991.

Chasnoff, I.J.; Bussey, M.E.; and Savich, R. Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 111:571-578, 1987a.

Chasnoff, I.J.; Bums, K.A.; and Bums, W.J. Cocaine use in pregnancy: Perinatal morbidity and mortality. *Neurotoxicol Teratol* 9:291-293, 1987b.

Chasnoff, I.J.; Griffith, D.R.; and MacGregor, S. Temporal patterns of cocaine use in pregnancy. *JAMA* 261:1741-1744, 1989a.

Chasnoff, I.J.; Hunt, C.E.; and Kletter, R. Prenatal cocaine exposure is associated with respiratory pattern abnormalities. *Am J Dis Child* 143:583, 1989b.

Chasnoff, I.J.; Griffith, D.R.; and Freier, C. Cocaine/polydrug use in pregnancy. *Pediatrics* 89:284-289, 1992.

Chasnoff, I.J.; Landress, H.; and Barett, M. The prevalence of illicit drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. N *Engl J Med* 322:1202-1206, 1990.

Chavez, G.F.; Mulinare, J.; and Cordero, J.F. Maternal cocaine use during early pregnancy as a risk factor for congenital urogenital anomalies. *JAMA* 262:795-798, 1989.

Chouteau, M.; Namerow, P.B.; and Leppert, P. The effect of cocaine abuse on birth weight and gestational age. *Obstet Gynecol* 72:351-354, 1988.

Coles, C.D.; Platzman, K.A.; and Smith, I. Effects of cocaine and alcohol use in pregnancy on neonatal growth and neurobehavioral status. *Neurotoxicol Teratol* 14:23-33, 1992.

Dixon, S.D., and Bejar, R. Echoencephalographic findings in neonates associated with maternal cocaine and methamphetamine use: Incidence and clinical correlates. *J Pediatr* 115:770-778, 1989.

Doberczak, T.M.; Kandall, S.A.; and Wiletts, I. Neonatal opiate abstinence syndrome in term and preterm infants. *J Pediatr* 118:933-937,1991.

Doberczak, T.M.; Shanzer, S.; and Senie, R.T. Neonatal neurologic and electroencephalographic effects of intrauterine cocaine exposure. *J Pediatr* 113:354-358, 1988.

Dominguez, R.; Vila-Coro, A.A.; and Slopis, J.M. Brain and ocular abnormalities in infants with in utero exposure to cocaine and other street drugs. *Am J Dis Child* 145:688-695, 1991.

Durand, D.J.; Espinoza, A.M.; and Nickerson, B.G. Association between prenatal cocaine exposure and sudden infant death syndrome. *J Pediatr* 117:909-911, 1990.

Eisen, L.N.; Field, T.F.; and Bandstra, S.E. Perinatal cocaine effects on neonatal stress behavior and performance on the Brazelton Scale. *Pediatrics* 88:477-480, 1991.

Farrar, H.C., and Keams, G.L. Cocaine: Clinical pharmacology and toxicology. *J Pediatr* 115:665-675, 1989.

Fiks, K.; Johnson, H.; and Rosen, T. Methadone-maintained mothers: Three-year follow-up of parental functioning. *Int J Addict* 20:651-660, 1985.

Finnegan, L.P. Neonatal abstinence. In: Nelson, N.M., ed. *Current Therapy in Neonatal-Perinatal Medicine.* Vol. 2. Philadelphia: B.C. Docker, 1990.

Frank, D.A.; Bresnahan, K.; and Zuckerman, B. Maternal cocaine use: Impact on child health and development. *Adv Pediatr* 40:65-99, 1993.

Frank, D.A.; McCarten, K.; and Cabral, H. Cranial ultrasounds in term newborns: Failure to replicate excess abnormalities in cocaine-exposed. *Pediatr Res* 31:247A, 1992.

Frank, D.; McCarten, K.; Cabral, H.; Levenson, S.; and Zuckerman, B. Association of heavy in utero cocaine exposure with caudate hemorrhage in term newborns. *Pediat Res* 35:269A, 1994.

Gawin, F.H., and Kleber, H.D. Cocaine abuse treatment. *Arch Gen Psychiatry* 41:903-909, 1984.

Gillogley, K.M.; Evans, A.T.; and Hansen, R.L. The perinatal impact of cocaine, amphetamine, and opiate use detected by universal intrapartum screening. *Am J Obstet Gynecol* 163:1535-42, 1990.

Glantz, J.C., and Woods, J.R. Cocaine, heroin, and phencyclidine: Obstetric perspectives. In: Pitkin, R.M., and Scott, J.R., eds. *Clin Obstet Gynecol* 36:279-301, 1993.

Goldbaum, G.; Daling, J.; and Milham, S. Risk factors for gastroschisis. *Teratology* 42:397-403, 1990.

Griffin, J.F.; Scott, H.D.; and Burke, M.E. Statewide prevalence of illicit drug use by pregnant women in Rhode Island. *Morb Mortal Wkly Rep* 39:225-227, 1990.

Hammer, R.P.; Rocalde, A.A.; and Seatriz, J.V. Effects of opiates on brain development. *Neurotoxicology* 19:475-484, 1989.

Handler, A.; Kistin, N.; and Davis, F. Cocaine use during pregnancy: Perinatal outcomes. *Am J Epidemiol* 133:818-825, 1991.

Hans, S.L. Developmental consequences of prenatal exposure to methadone. *Ann N Y Acad Sci* 562:195-207, 1989.

Hans, S. Prenatal drug exposure: Behavioral functioning in late childhood and adolescence. In: Finnegan, L., ed. *Behaviors of Drug-Exposed Offspring.* National Institute on Drug Abuse Research Monograph. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., in press.

Herzlinger, R.A.; Kandall, S.R.; and Vaughn, H.G. Neonatal seizures associated with narcotic withdrawal. *J Pediatr* 91:638-641, 1977.

Hopkins, E. Childhood's End. *Rolling Stone,* October 18, 1990. p. 1.

Hoyme, H.E.; Jones, K.L.; and Dixon, S.D. Prenatal cocaine exposure and fetal vascular disruption. *Pediatrics* 85:743-747, 1990.

Hunt, J.V.; Cooper, B.A.B.; and Tooley, W.H. Very low birth weight infants at 8 and 11 years of age: Role of neonatal illness and family status. *Pediatrics* 82:596-603, 1988.

Hutchings, D.E. Methadone and heroin during pregnancy: A review of behavioral effects in human and animal offspring. *Neurobehav Toxicol Teratol* 4:429-434, 1982.

Infant Health and Development Program. Enhancing the outcome of low birth weight, premature infants: A multisite randomized trial. *JAMA* 263:3035-3042, 1990.

Johnson, H.; Glassman, M.; Fiks, K.; and Rosen, T. Resilient children: Individual differences in developmental outcome of children born to drug abusers. *J Genet Psychol* 151:523-539, 1990.

Kandall, S.R.; Albin, S.; Lowenson, J.; Berle, B.; Eidelman, A.I.; and Gartner, L.M. Differential effects of maternal heroin and methadone use on birth weight. *Pediatrics* 58:681-685, 1976.

Kandall, S.R.; Gaines, J.; Davidson, G.; and Jessop, D. Relationship of maternal substance abuse to subsequent sudden infant death syndrome in offspring. *J Pediatr* 123:120-126, 1993.

Kandall, S.; Gaines, J.; Habel, L.; Davidson, G.; Jessop, D.; Struthers, J.; and Hanson, R. Visual recognition memory in drug exposed infants. *J Dev Behav Pediatr* 13:108-111, 1992.

Koren, G.; Graham, H.; Shear, H.; and Einarson, T. Bias against the null hypothesis: The reproductive hazards of cocaine. *Lancet* 2:1440-1442, 1989.

Kramer, L.D.; Locke, G.E.; and Ogunyemi, A. Neonatal cocaine-related seizures. *J Child Neural* 5:60-64, 1990.

Kreek, M.J. Methadone disposition during the perinatal period in humans. *Pharmacol Biochem Behav* 11:7-13, 1979.

Lauder, J.M. Neurotransmitters as morphogens. *Prog Brain Res* 74:365, 1988.

Lester, B.M.; Corwin, M.J.; and Sepkoski, C. Neurobehavioral syndromes in cocaine-exposed newborn infants. *Child Dev* 62:694-705, 1991.

Lifschitz, M.H.; Wilson, G.S.; and Smith, E.O. Fetal and postnatal growth of children born to narcotic-dependent women. *J Pediatr* 102:686, 1983.

Lifschitz, M.H.; Wilson, G.S.; and Smith, E.O. Factors affecting head growth and intellectual function in children of drug addicts. *Pediatrics* 75:269-274, 1985.

Lipshultz, S.E.; Frassica, J.J.; and Orav, E.J. Cardiovascular abnormalities in infants prenatally exposed to cocaine. *J Pediatr* 118:44-51, 1991.

Lutiger, B.; Graham, K.; and Einarson, T. Relationship between gestational cocaine use and pregnancy outcome: A meta-analysis. *Teratology* 44:405-414, 1991.

Martin, M.L.; Khoury, M.J.; and Cordero, J.F. Trends in rates of multiple vascular disruption defects, Atlanta, 1968-1989. *Teratology* 45:647-653, 1992.

Mayes, L.C.; Granger, R.H.; Bornstein, M.H.; and Zuckerman, B.S. The problem of prenatal cocaine exposure: A rush to judgement. *JAMA* 267:406-408, 1992.

Mayes, L.C.: Granger, R.H.; Frank, M.A.; Schottenfeld, R.; and Bomstein, M.H. Neurobehavioral profiles of neonates exposed to cocaine prenatally. *Pediatrics* 91:778-783, 1993.

McCinty, J.F., and Ford, D.H. Effects of prenatal methadone on rat brain catecholamines. *Dev Neurosci* 3:224-234, 1980.

Miller, J.C., and Friedhoff, A.J. Prenatal neurotransmitter programming of postnatal receptor function. In: Boer, G.J.; Feenstra, M.G.P.; and Mirmiran, M., eds. *Progress in Brain Research. New* York: Elsevier Science Publishers, 1988.

Mirochnick, M.; Meyer, J.; Cole, J.; Herren, T.; and Zuckerman, B. Circulating catecholamine concentrations in cocaine-exposed neonates: A pilot study. *Pediatrics* 88:481-485, 1991.

Needleman, R.; Zuckerman, B.S.; Anderson, G.; Mirochnick, M.; and Cohen, D.J. CSF monoamine precursors and metabolites in human neonates following in utero cocaine exposure. *Pediatrics* 92:55-60, 1993.

Neuspiel, D.R.; Hamel, S.C.; and Hochberg, E. Maternal cocaine use and infant behavior. *Neurotoxicol Teratol* 13:229-233, 1990.

Ostrea, E.M.; Brady, M.; and Gause, S. Drug screening of newborns by meconium analysis: A large scale, perspective, epidemiologic study. *Pediatrics* 89:107-113, 1992.

Petiti, D.B., and Coleman, C. Cocaine and the risk of low birth weight. *Am J Public Health* 80:25-28, 1990.

Rodning, C.; Beckwith, L.; and Howard, J. Quality of attachment and home environments in children prenatally exposed to PCP and cocaine. *Develop Psychopath* 3:351-366, 1991.

Rodning, C.; Beckwith, L.; and Howard, J. Characteristics of attachment organization and play organization in prenatally drug-exposed toddlers. *Develop Psychopath* 1:277-289, 1993.

Roseman, S.J., and Smith, C.B. C-Catecholamine synthesis in mouse brain during morphine withdrawal. *Nature* 240:153-155, 1972.

Rosenthal, R., and Rosenow, R. *Behavioral Research. New* York: Academic Press, 1969. pp. 181-277.

Ryan, I.; Ehrlich, S.; and Finnegan, L. Cocaine abuse in pregnancy: Effects on the fetus and newborn. *Neurobehav Toxicol Teratol* 9:295-299, 1987.

Sakellaridis, N.; Mangoura, D.; and Veradakis, A. Effects of opiates on the growth of neuron-enriched cultures from chick embryonic brain. *Int Devl Neurosci* 4:293-302, 1986.

Salamy, A.; Eldgredge, L.; and Anderson, J. Brain-stem transmission time in infants exposed to cocaine in utero. *J Pediatr* 17:627-629, 1990.

Shih, L.; Cone-Wesson, B.; and Reddix, B. Effects of maternal cocaine abuse on the neonatal auditory system. *Int J Pediatr Otorhinolaryngol* 15:245-251, 1988.

Smith, A.A.; Hui, F.W.; and Crofford, H.J. Inhibition of growth in young mice treated with dl-methadone. *Eur Pharmacol* 43:307-309,1977.

Struthers, J.M., and Hansen, R.L. Visual recognition memory in drug-exposed infants. *J Dev Behav Pediatr* 13: 108-22, 1992.

U.S. General Accounting Office. Drug Exposed Infants: A Generation at Risk. Report to the Chairman, Committee on Finance, U.S. Senate. Washington, DC: Supt. of Docs., U.S. Gov. Print. Off., 1990.

Vega, W.A.; Kolody, B.; Hwang, K.; and Noble, A. Prevalence and magnitude of perinatal substance exposure in California. *N Engl J Med* 329:850-854, 1993.

Ward, S.D.; Bautista, D.; and Chan, L. Sudden infant death in infants of substance abusing mothers. *J Pediatrics* 117:876-881, 1990.

Ward, S.; Schuetiz, S.; and Wachsman, L. Elevated plasma norepinephrine levels in infants of substance-abusing mothers. *Am J Dis Child* 145:44-48, 1991.

Weathers, W.T.; Crane, M.M.; Sauvain, K.J.; and Blackhurst, D.W. Cocaine use in women from a defined population: Prevalence at delivery and effects on growth in infants. *Pediatrics* 91:350-354, 1993.

Werner, G. Children of the Garden Island. *Sci Am* 106:111, 1989.

Wilson, G.S. Clinical studies of infants and children exposed prenatally to heroin. *Ann N Y Acad Sci* 562:183-194, 1989.

Woods, J.R., Jr.; Plessinger, M.A.; and Clark, K.E. Effect of cocaine on uterine blood flow and fetal oxygenation. *JAMA* 257:957-961, 1987.

Zagon, IS., and McLaughlin, P.J. Naltrexone regulates body and brain development in rats: A role for endogenous opioids in growth. *Life Sci* 35:2057-2064, 1984.

Zuckerman, B., and Brown, E. Maternal substance abuse and infant development. In: Tsang, R., ed. *Handbook of Infant Mental Health.* New York: Guilford Press, 1993. pp. 143-158.

Zuckerman, B.S.; Frank, D.; Hingson, R.; Amaro, H.; Levenson, S.M.; Kayne, H.; Parker, S.; Vinci, R.; Aboagye, K.; Fried, L.E.; 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.

AUTHORS

Barry Zuckerman, M.D.
Professor and Chairman
Department of Pediatrics
Boston City Hospital

Deborah Frank, M.D.
Associate Professor of Pediatrics
Boston University School of Medicine
and
Director of Growth and Development Program
Boston City Hospital

Elizabeth Brown, M.D.
Associate Professor of Pediatrics
Boston University School of Medicine
and
Director of Newborn Medicine
Boston City Hospital

818 Harrison Avenue, T214
Boston. MA 02118

Clinical Management of Drug Dependency in Pregnancy

James R. Woods, Jr.

INTRODUCTION

The urgency of substance abuse treatment in pregnancy is underscored by current estimates of substance usage. Alcohol abuse and cigarette smoking are widespread; cocaine's decline has plateaued; marijuana use remains prevalent; and there now appears to be a resurgence in heroin use, which is due to both enhanced purity of this illicit drug and its greater availability (Gregg et al. 1988).

Despite the debate regarding cause and effect, certain adverse obstetric outcome measures consistently appear in conjunction with substance abuse during pregnancy. Preterm births, small-for-gestational-age babies, meconium aspiration, and newborn irritability and tremulousness have each been associated with alcohol, heroin, cocaine, and marijuana (Bresnahan et al. 1991; Cohen et al. 1991; Day et al. 1991; Lutiger et al. 1991; Roland and Volpe 1989; Spence et al. 1991; Zuckerman et al. 1989). Moreover, the fact that in some communities substance abuse has been detected by questionnaire or screening in over 10 percent of the obstetric study population makes drug addiction among the most common disease entities identified in maternal-fetal medicine (Glantz and Woods 1993).

The personal and financial costs of substance abuse are substantial. One study found that an estimated $500 million would be saved in the cost of obstetric and newborn care if cocaine abuse alone could be controlled (Phibbs et al. 1991). Abating adverse effects of alcohol and heroin could compound this savings even more.

Formulating solutions to this widespread, largely unaddressed problem in obstetrics requires a clear understanding of *barriers to care* for pregnant substance abusers. The three most relevant barriers are the attitudes and behavior of substance-abusing women, the attitudes and lack of understanding of the pregnant addict by obstetric care providers, and the lack of coordination between obstetric care providers and those professionals involved in mental health and drug abuse treatment.

Attitude of Substance Abusers

Focus group discussions with pregnant substance abusers reveal a personality profile of the addicted woman and her opinions of the health care system (table 1). When asked how it feels to be a pregnant substance abuser, this group expresses embarrassment, impatience, and apprehension. They complain that they get little respect and that the clinics are overbooked, hastily run, and not compatible with their schedules. When asked their opinion of drug treatment (table 2), they acknowledge that they have to hit bottom before they can consider seeking help. Moreover, they feel a lack of self-esteem each time they use drugs. They are deterred from attempting to overcome substance addiction by long waiting lists for entry into drug treatment, fear of the loss of custody of their children, and a lack of child care and transportation. Some women admit that they time their obstetric visits around their drug use in order to test drug free. Overall, they believe that obstetric care providers do not understand addiction or their personal problems.

From these descriptions, a picture emerges of women who are suspicious of the health care system, impatient with the clinic arrangements, and limited in their activities by the lack of child care and transportation. The strongest motive for them to remain within the health care system is fear of losing custody of their children. A major deterrent to seeking intensive drug treatment during pregnancy is awareness that many drug treatment programs do not allow them to bring children into the facility overnight.

TABLE 1. *Opinions of pregnant substance abusers.*

How does it feel to be a pregnant substance abuser?	
Worried I'll lose my kids	Embarrassed
Impatient	Apprehensive
No respect	Brushed aside
I'm different if I'm Medicaid	

Attitudes of Care Providers

A number of barriers to care of the pregnant substance abuser reside within the attitudes and skills of care providers themselves. Few obstetric-gynecology (OB-GYN) residencies teach techniques of substance abuse history taking and directive counseling when there are affirmative answers to questions regarding substance abuse. Consequently, OB-GYN care providers remain insecure in this area of treatment and are likely to avoid direct questioning out of fear that they will be unable to respond appropriately to the answers.

TABLE 2. *Opinions of pregnant substance abusers.*

How do you really feel about drug treatment?

Must hit bottom to seek help	Self-esteem is gone when I shoot up
I hate the chaos of the clinic	Want to see the same person again
I time my drugs around clinic visits	I have no phone
I have no transportation	Don't take my kids away, please

An additional problem is lack of knowledge by OB-GYN care providers about community-based resources. Few are aware of available drug or alcohol treatment programs or how to establish a linkage with these programs, if a patient so desires. As a consequence, obstetric care remains isolated from alcohol or drug-abuse treatment, and there is little coordination of care.

Care providers' attitudes also remain a major obstacle to improving access to care for pregnant substance abusers (table 3). Beliefs that substance abuse is a "hopeless condition of helpless people," that "substance abuse is a chronic problem and may even be more a crime than a disease," and that "substance abuse is a problem of the poor and not middle class" limit intervention by OB-GYN care providers in this form of primary care (Chasnoff et al. 1990). Some professionals may also struggle with distinctly conflicting personal attitudes regarding illicit

TABLE 3. *Physician attitudes.*

Why OBs don't get involved.	
Drug abuse is a chronic problem	Hopeless condition by helpless people
Substance abuse is a crime, not a disease	I'm not trained to handle this
It doesn't occur in my office (NIMO)	

drugs, such as heroin and cocaine, and licit drugs, such as alcohol and cigarettes.

DEVELOPING A COMPREHENSIVE APPROACH TO SUBSTANCE ABUSE PREVENTION AND TREATMENT DURING PREGNANCY

The ability to structure a successful perinatal program for substance-abusing women is within the domain of most community health organizations. Accomplishing this goal, however, requires coordination of many health care systems that may, under most situations, function independently of one another. It is this coordination of services, the creation of formal ties, that is the very foundation of a community-wide perinatal substance abuse program (DeLeon and Jainchill 1991; Giles et al. 1989) (table 4).

Pregnancy Should Be Thought of as an Important Entry Point into Health Care for Substance Abusers

Within the field of substance abuse treatment, some care providers view pregnancy as an abbreviated period on a much longer continuum involving drug and alcohol abuse and treatment. However, for many women, pregnancy is often the first contact with the health care system since childhood. Although the reasons for seeking health care during pregnancy are undoubtedly diverse, maternal concern that substance abuse early in pregnancy may have damaged or endangered the developing baby must be recognized as a powerful motivation. Moreover, peer pressure to seek prenatal care often is present, even when

TABLE 4. *Important Elements of a Comprehensive Substance Abuse Program for Pregnant Women.*

CHALLENGES	OUTCOME
Use pregnancy as entry into health care	Improved chances of recovery
Improve community-based outreach	Early pregnancy detection and increased clinical attendance
Enhance systems for transportation and child care	Better compliance
Educate OB care providers and clinic staff on: I. Addiction 2. Medical signs of substance abuse	Better rapport between addict and care provider Better clinic flow
Standardize obstetric care	Decreased chance that health problems will be missed/overlooked
Continuity of care	Improved compliance
Network OB services with drug treatment and mental health programs	Quicker access to needed services
Build flexibility into an integrated outpatient-residential treatment program	System is ready when patient is ready
Identify and close gaps in health care	Reduce potential for losing women from substance abuse treatment programs
Acknowledge mother-baby bond	Fewer dropouts; better parenting
Contraception and GYN care	Better control over addict's life decisions
Combine medical programs with career training resources in addict's neighborhood	Fewer no-shows Establishes a future direction

concerns regarding other health care issues appear lacking in the community. In table 5 many initial entry sites into prenatal care are illustrated. Because commencing early prenatal care may represent the single most important factor in reducing perinatal mortality, the

TABLE 5. *Sites of entry into prenatal care.*

Child protective services	School nurses
Self-referral	Prison/jail
Settlement houses	Residential treatment
Outpatient treatment	Mental health clinics
Emergency rooms	Homeless shelters
Halfway houses	HIV programs
STD clinics	

importance of linking these community-based programs to obstetric services cannot be overstated.

Community-Based Outreach Must Be Formalized and Expanded

Although the value of facilitating entry of pregnant substance abusers into the health care system is uniformly accepted, methods for accomplishing this task differ among communities. Unfortunately, in many communities such protocols are nonexistent. This responsibility in the past has fallen to social service and nursing outreach personnel who identify and introduce this population into a health care system. Some communities have strengthened their outreach efforts by mobilizing former addicts as neighborhood or block leaders who identify pregnant substance-abusing women and facilitate their access to health care (Allen and Sandler 1993).

Women with a history of substance abuse who have successfully negotiated pregnancy and substance abuse treatment to become drug free appear to offer a substantial resource to perinatal drug abuse intervention. These women often exhibit an earnest desire to participate in the same social system that enabled their recovery. Their impact as peers to other substance-abusing women during pregnancy can be enormous. Health

care professionals cannot accomplish this task without community support. Through schools, churches, and community organizations, a large army exists of willing nonprofessional participants in perinatal substance abuse treatment. The challenge for each community is to identify and organize these resources.

Systems for Transportation and Child Care Must Be Expanded, and Locations for Prenatal Care Should Be Centralized

Late entry into and poor compliance during prenatal care represent the greatest obstacles to adequate obstetric management (Knisely et al. 1991). In many communities, pregnant substance-abusing women, particularly if they are single with other children and of low socioeconomic status, find that multiple bus transfers are sufficiently difficult obstacles as to render access to prenatal care impossible. If sites for prenatal care of substance-abusing women were established in these women's neighborhoods, the need for elaborate transportation systems could be reduced and the compliance to health care increased.

At these community-based sites, the effort to concentrate services for high-risk obstetric care and pediatric care logically would enhance the motivation of pregnant women to seek these types of resources. As described in a later section of this chapter, ultrasound and antepartum fetal surveillance as well as social support and nutritional counseling are only a few of many services which, if located at one comprehensive site, could enhance prenatal care of the substance-abusing woman.

Obstetric Care Providers and Clinical Staff Must Be Educated in Addiction Medicine and Medical Signs of Substance Abuse

Residency education in obstetrics and gynecology traditionally has concentrated upon technical procedures and medical management and has not emphasized counseling skills applicable to sensitive areas such as substance abuse, miscarriage, battering, or sexual abuse. OB-GYNs complete their training insecure in these areas. Thus, they are likely to choose, consciously or unconsciously, to avoid asking questions that reveal substance abuse or risks of physical or emotional abuse. For many obstetricians, their greatest fear is that a pregnant woman will say "yes" when asked if she uses drugs. If OB-GYNs examined their attitudes carefully, the importance of counseling for substance abuse and emotional or physical abuse would be obvious. Unfortunately, many

OB-GYNs hold attitudes that limit their ability to participate fully in this important area of high-risk obstetrics (Klein et al. 1993).

The distinction between illicit drugs such as marijuana, cocaine, and heroin, and licit drugs such as nicotine and alcohol may create conflicts for the care provider: socially acceptable drugs may be a part of the care provider's lifestyle. It is evident that smoking and alcohol abuse constitute the greatest risk to the developing fetus, both by sheer number and by documented impact upon the intrauterine environment and the fetus (Streissguth et al. 1983; Williamson et al. 1989). By tacitly condoning alcohol use and cigarette smoking even while condemning the use of illicit drugs, the care provider takes an ineffectual approach to major health risks and may, in fact, miss an important opportunity to engage in corrective actions that would benefit both the fetus and the pregnant woman. By improving the knowledge base from which care providers understand addiction, it is anticipated that they will diminish their image as unskilled in this area.

The failure to engage OB-GYNs' efforts in the field of substance abuse is best illustrated by the fact that during three consecutive annual meetings of the American College of Obstetrics and Gynecology, postgraduate courses in substance abuse were offered. Invited speakers were nationally known, and the materials provided were appropriate and well developed. Despite these efforts, only 30 to 40 participants attended each of the three annual postgraduate courses. Yet other meeting rooms devoted to the technology of OB-GYN were filled to capacity with standing room only.

In the June 1993 issue of *Clinical Obstetrics and Gynecology,* one-half of the volume was dedicated to substance abuse in pregnancy. Contributors included experts in the field of marijuana, heroin, cocaine, and alcohol, and the collective results were both substantive and educational. However, when these individuals were asked to contribute each was reluctant, not because of lack of commitment to this field, but because they felt that OB-GYNs were not interested in this topic and would not read such contributions. The experts viewed their contributions as ceremonial but not substantive. In the end, they provided a significant resource in this area.

In 1994, the fifth edition of *Precis* (a comprehensive text in obstetrics and gynecology for practicing clinicians preparing for recertification) for the first time included a primary and preventive health care section. As part

of this edition, a small section on counseling for substance abuse and corrective measures is included. While only a beginning, this addition to mainstream education in obstetrics and gynecology marks an important new commitment by the American College of Obstetrics and Gynecology to substance abuse issues.

Obstetric Care of the Substance Abuser Must Be Standardized

Appropriate prenatal care of substance-abusing women requires that care providers recognize important risk factors in these women's lives. Polydrug use is to be expected (Little et al. 1991). Moreover, many women contract one or more sexually transmitted diseases (STDs). Antepartum fetal monitoring and ultrasound evaluation of fetal growth may offer early identification of fetal risks for intrauterine growth retardation (IUGR), a recognized sequela resulting from use of cocaine, heroin, methadone, alcohol, or nicotine during pregnancy.

In many institutions, a standardized approach (figure 1) to screening for these risk factors has resulted in a reduction in missed opportunities and overlooked care measures. As noted in figure 1, the emphasis is placed on those risk factors that are most specific to substance-abusing women. Early screening for STDs is a mainstay of this type of management (Nanda et al. 1990; Williams 1990). Additionally, with continued prenatal visits, the importance of drug screening emerges. Negative drug-screening results may be utilized by the care providers as a positive incentive to remain drug free and serves as evidence of the program's success. Positive drug-screening results may be used to direct counseling and mobilize additional resources to respond to this evidence of dysfunctional lifestyles.

In this standardized approach, attention is directed to assessing fetal health and growth throughout the remainder of the pregnancy. Ultrasound provides the most available clinical method for tracking fetal growth. Estimated fetal weight as well as measurements of individual body parts (length of femurs, head and abdominal circumference) can be plotted and fetal growth monitored. Additionally, a number of tests are now available to assess the health of the fetus. Routinely, from 33 weeks until delivery, substance-abusing women may be followed with nonstress fetal heart rate testing as the simplest and most cost-effective triage method for assessing fetal health. In this test, the fetal heart rate is

FIGURE 1. *Special Care OB Clinic for Chemically Dependent Women Management Flow Sheet.*

INTERVENTION	8-12	14	16	18	20	22	24	26	28	30	32	33	34	35	36	37	38	39	40	42
SERUM			A.F.P.					GLUCOLA & HCT							RPR					
ROUTINE LABS	X																			
HEP B	X																			
HIV			X												X					
URINE																				
CHEM DEP SCR	——	——	——	——	——	——	——	——	——	——	——	——	——	——	——	——	——	——	——	->
Culture & Sens.	X								X											
CERVICAL CULT.														Only if Positive						
G C	X								X						X					
B STREP	X								X						X					
HERPES	As Indicated																			
CHLAMYDIA	X								X						X					
BIOPHYSICAL																				
U/S	X			X								X								
NST												X	——	——	——	——	——	——	——	->
DOPPLER	As Indicated by NST or U/S																			
OTHER																				
TB TEST	X														X					

recorded for a period of 20 minutes using a monitor placed on the maternal abdomen. During that period, a healthy fetus should exhibit at least two accelerations of fetal heart rate in conjunction with fetal movement. Figure 2 illustrates normal nonstress test results. This test is usually repeated on a weekly basis until delivery.

When a nonstress test is not reassuring (i.e., when accelerations of the fetal heart are not seen during the 20 minutes of monitoring), fetal surveillance should be followed by one of several more intensive methods for scrutiny. The oxytocin challenge test represents one assessment of placental function and oxygen delivery to the fetus. When oxytocin is administered intravenously (IV) to the woman, most women respond with increased uterine contractions. An oxytocin challenge test requires that three uterine contractions be generated over a lo-minute period, during which time the fetal heart rate is monitored. Decelerations (slowing) of the fetal heart rate linked to each contraction represent an abnormal (or positive) oxytocin challenge test, an indication of fetal hypoxemia (low oxygen) or decreased placental reserve.

An alternative test to the oxytocin challenge test is the biophysical profile. As is shown in table 6, this test consists of five measures of fetal function, each assessed by ultrasound during a 30-minute period. A cumulative score of 8 or 10 is consistent with acceptable fetal health. A biophysical profile score in the range of four to eight represents a borderline condition; if such a score is obtained near term, this indicates the need for delivery. If such a score is obtained earlier in pregnancy (30 to 36 weeks), the patient may be monitored continuously and a followup biophysical profile obtained within the following 12 hours. If a repeat test is again abnormal, consideration should be given to delivery. Finally, if the score for the biophysical profile is under four, irrespective of gestation, delivery should be considered.

A new ultrasound technique, ultrasound Doppler measurement, has been developed within the past few years in which the velocity of blood flow through the umbilical artery (the artery carrying blood from the fetus to the placenta) can be assessed. Normally, blood flows from the fetus through the placenta during the systolic phase (contraction or beating) of the fetal heart cycle at a rapid rate and at a slower rate during the diastolic (filling or resting) phase of the fetal heart cycle. Continuous blood flow through the placenta allows transport of oxygen and nutrients to the fetus and removal of carbon dioxide (CO,) and other cellular waste products from the fetal circulation.

FIGURE 2. *A Reactive Nonstress Test. Note that fetal heart rate accelerations (top panel) occur during fetal movement (lower panel).*

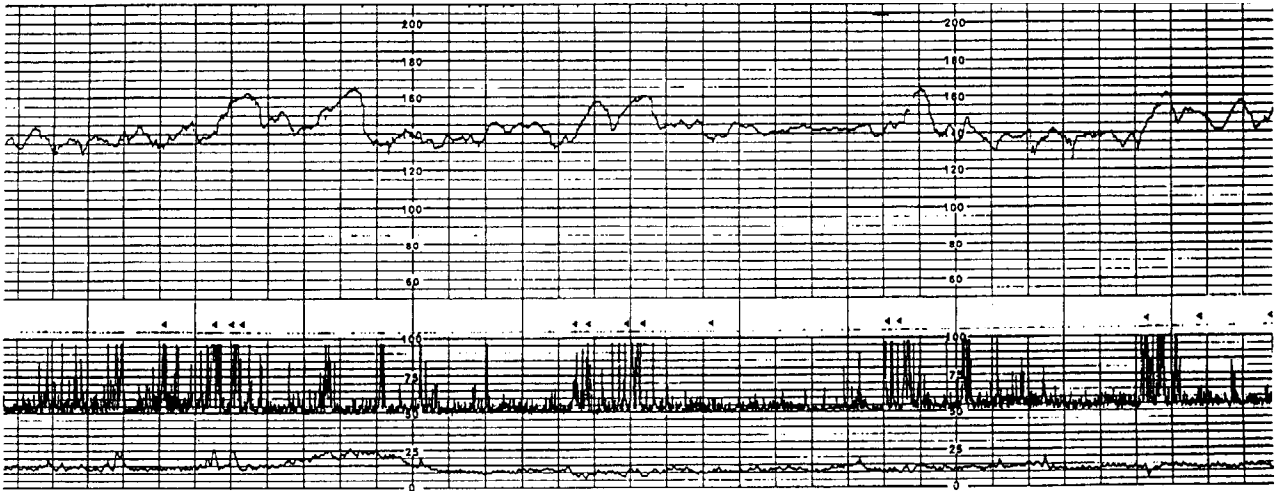


TABLE 6. *Biophysical profile.*

Biophysical Variable	Normal Score	Abnormal (Score = 0)
Fetal breathing movements	At least I episode of FBM of at least 30 sec duration in 30 min observation	Absent FBM or no episode of ≥30 sec in 30 minutes
Gross body movement	At least 3 discrete body/ limb movements in 30 min (episodes of active continuous movement considered as single movement)	2 or fewer episodes of body/limb movements in 30 min.
Fetal tone	At least 1 episode of active extension with return to flexion of fetal limb(s) or trunk. Opening and closing of hand considered normal tone	Either slow extension with return to partial flexion or movement of limb in full extension or absent fetal movement with fetal hand held in complete or partial deflection
Reactive fetal heart rate	At least 2 accelerations of the fetal heart rate≥15 beats/minute of 15 seconds duration	Less than 2 accelerations or decelerations < 15 beats/ minute of 15 seconds duration
Qualitative amniotic: fluid volume	At least a pocket of 2cm in 2 perpendicular planes	No fluid or a pocket less than 2cm in 2 planes

Many clinical conditions such as poor nutrition, hypertension, and cigarette smoking are believed to adversely affect placental blood flow. Oxygen and nutrient exchange from maternal to fetal circulations are restricted, causing IUGR. Ultrasound Doppler measurement can detect these changes in placental blood flow, alerting the clinician to the risks of intrauterine fetal growth impairment. Since IUGR is the fetal condition most frequently associated with abnormal tests of fetal well-being and increased perinatal mortality, new techniques such as ultrasound Doppler are important additions to current tests of fetal health.

Continuity of Care in the Clinic Setting Should Be Maintained

Focus groups of recovered addicts indicate that compliance with prenatal care can be enhanced if the pregnant substance abuser is able to see the same or only a small group of care providers during her prenatal care. This patient/care provider relationship establishes a level of confidence and trust that is often absent in large inner-city clinics, where care providers and patients remain strangers.

It is true that the pregnant substance abuser often lacks the patience or even tolerance for treatment in large clinic settings. This fact must be used to reexamine and then reorganize the manner in which care is provided for substance-abusing women throughout pregnancy. Seeing a variety of doctors or other care providers with a range of abilities in addiction medicine is both disruptive and obstructive to the woman. Increased utilization of nurse practitioners and midwives with skills in interpersonal relations with substance abusers, in conjunction with physician supervision and direct participation, offers an appropriate model to enhance the opportunity for substance-abusing women to seek prenatal care and to continue their care throughout the pregnancy.

Obstetric Services Must Be Networked Formally with Drug Treatment and Mental Health Programs

Since many substance abusers suffer from impaired mental health, rapid access to treatment and counseling programs through appropriate community networking is essential. Unfortunately, most obstetricians are unaware of the impact of complex and multilayered interaction by social service personnel and other health care providers on patients who suffer from impaired mental health. Nevertheless, substance abuse and impaired mental status are linked by more than coincidence (James et al. 1991), and formal liaisons between obstetric and mental health services should be created to facilitate communication across these professional disciplines.

Flexibility Must Be Built into the Continuum of Outpatient and Residential Substance Abuse Treatment Programs

Many substance abusers will not contemplate entering residential treatment or even intensive same-day treatment until they essentially have hit rock bottom. That decision is further complicated if the woman is pregnant and expecting to care for a newborn. It is evident from focus

group discussions with former substance abusers that the health care provider is not in the position to dictate that moment when a woman is capable of entering residential treatment for substance abuse. The relationship between outpatient substance abuse treatment programs and residential drug treatment programs therefore must be aligned carefully to capitalize on that moment when the woman is receptive to this type of intervention. Success in this endeavor will come about via careful and cooperative efforts between obstetric care providers and substance abuse treatment programs that allow the woman immediate access into residential treatment.

Systems Gaps in Care of the Pregnant Substance Abuser Must Be Identified and Closed

Despite attempts to offer comprehensive health care to pregnant substance abusers, gaps in care exist. Examples of these "systems errors" are as follows:

- A pregnant heroin user wishes to end her addiction. There is no consensus as to how the fetus should be monitored to identify fetal withdrawal (Allen 1991; Hutchings 1990; Thornton et al. 1990; Wittmann and Segal 1991; Wolman et al. 1989; Zuspan et al. 1975).

- A pregnant heroin addict is hospitalized and placed on methad one. Upon discharge, openings in outpatient methadone programs are limited, and the woman is placed on a waning list. Despite efforts to provide priority to methadone-using pregnant women, coordination between inpatient and outpatient methadone programs remains complex.

- A pregnant heroin user on methadone is confined to jail. During that confinement, she is unable to receive her methadone due to restrictions regarding narcotics use in the penal system. She may be forced to withdraw from methadone without any monitoring of fetal health.

The Power of the Maternal/Baby Bond Must Be Appreciated and Applied to Health Care

Recovered addicts have helped the health care community to understand that one of their greatest fears is that their baby would be taken away

from them. Residential day treatment programs should be designed to allow a woman to bring her newborn into the residential treatment environment in order to access this level of intense substance abuse treatment. It is clear that there is a revolution in care of pregnant substance-abusing women: the value of the maternal/baby bond is finally being recognized. This recognition is also an opportunity to enhance the effectiveness of substance abuse treatment while the patient is pregnant.

Continuing treatment in the postpartum period while also making it possible for the woman to keep her baby with her is an initial step in strengthening the parenting skills that will be required over the next few years. Programs that focus upon only pregnant or postpartum women without their babies, disregarding the major significance of having a baby, will find that the recidivism rate is high and the numbers of successful encounters few. Most programs are not capable of allowing a woman to keep older children with her over a 24-hour period. Some, however, have developed successful visitation programs or day-care programs to emphasize the importance of the parent/child relationship in the overall scheme of substance abuse treatment.

Contraception and Gynecological Care Must Be Available as Part of an Integrated Program for Pregnant Substance-Abusing Women

Since an unexpected subsequent pregnancy is the worst outcome of drug treatment during a target pregnancy, programs should be developed to help case managers guide postpartum patients to use an effective contraceptive program. This approach provides the woman with control over her reproductive health and timing of any subsequent pregnancy, thus helping prevent pregnancy if she chooses, not if health care and contraceptive counseling have failed.

Career Training Programs Must Be Established at Locations Adjacent to Health-Care Programs

It is evident that women who are substance abusers have dysfunctional lifestyles and poor self-esteem. They frequently lack basic skills that would permit them to enter the workforce as contributing members of society. Drug abuse does not arise in a vacuum. Likewise, substance abuse treatment cannot succeed effectively in a vacuum. It must, instead, be linked to other support systems that are designed to help the woman establish a stable lifestyle, a sense of responsibility, and a means to

become self-sufficient. Colocating pregnancy and substance abuse treatment with facilities capable of providing onsite schooling, child care, and career development courses enhances the possibility that this comprehensive approach will succeed. For many women who overcome substance abuse, a drug-free life is hindered by low self-esteem and lack of professional skills. Linking health care centers with career training programs is important in offering a life path for these women.

SUMMARY

In summary, the pregnant substance abuser challenges formal coordination between community-based programs in obstetrics, pediatrics, drug and alcohol treatment, and mental health. Moreover, since substance abuse often is a manifestation of a dysfunctional lifestyle, medical treatment must be linked to education and ultimately, career planning. Some wish that the problem would just go away. Others may feel that the problem is too enormous or too vague for solutions. Neither of these attitudes is appropriate. Identifying and mobilizing the pregnant substance abuser into health care is truly a window of opportunity. Successful rehabilitation into a drug-free lifestyle for the woman and her baby is the reward for this effort.

REFERENCES

Allen, P.M., and Sandler, M. Critical components of obstetric management of chemically dependent women. In: Woods, J.R., ed. *Drug Abuse in Pregnancy. Clin Obstet Gynecol* 36:347-360, 1993.

Allen, M.H. Detoxification considerations in the medical management of substance abuse in pregnancy. *Bull NY Acad Med* 67:270-276, 1991.

Bresnahan, K.; Brooks, C.; and Zuckerman, B. Practical cocaine use: Impact on infants and mothers. *Pediatr Nus* 17:123-129, 1991.

Chasnoff, I.J.; Landress, H.J.; and Barrett, M.E. The prevalence of illicit drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. N *Engl J Med 322:* 1202, 1990.

Cohen, H.R.; Green, J.R.; and Crombleholme, W.R. Peripartum cocaine use: Estimating risks of adverse pregnancy outcome. *Int J Gynaecol Obst* 35:51-54, 1991.

Day, N.; Sambamoorthi, U.; Taylor, P.; Richardson, G.; Robles, N.; Jhon, Y.; Scher, M.; Stoffer, D.; Cornelius, M.; and Jasperse, D. Perinatal marijuana use and neonatal outcome. *Neurotoxicol Teratol* 13:329-334, 1991.

DeLeon, G., and Jainchill, N. Residential therapeutic communities for female substance abusers. *Bull NY Acad Med* 67:277-290, 1991.

Giles, W.; Patterson, T.; Sanders, R.N.; Batey, R.; Thomas, D.; and Collins, J. Outpatient methadone program for pregnant heroin using woman. *Aust NZ J Obstet Gynaecol* 29:225-229, 1989.

Glantz, J.C. and Woods, J.R. Cocaine, heroin, and phencyclidine: Obstetric perspectives. *Clin Obstet Gynecol* 36:279-301, 1993.

Gregg, J.E.M.; Davidson, D.C.; and Weindling, A.M. Inhaling heroin during pregnancy: Effects on the baby. *Br Med J* 296:754, 1988.

Hutchings, D. Issues of risk assessment: Lessons from the use and abuse of drugs during pregnancy. *Neurotoxicol Teratol* 12:183-189, 1990.

James, M.E.; Rubin, C.P.; and Willis, S.E. Drug abuse and psychiatric findings in HIV-seropositive pregnant patients. *Gen Hosp Psychiatry* 13:4-8, 1991.

Klein, R.F.; Friedman-Campbell, M.; Tocco, C.; and Tocco, R. History taking and substance abuse counseling with the pregnant patient. In: *Drug Abuse in Pregnancy. Clin Obstet Gynecol* 36:338-346, 1993.

Knisely, J.S.; Spear, E.R.; Green, D.J.; Christmas, J.T.; and Schnoll, S.H. In: Harris, L., ed. *Problems of Drug Dependence, 1990. Substance Abuse Patterns in Pregnant Women.* National Institute on Drug Abuse Research Monograph No. 105. DHHS Pub. No. (ADM)91-1753 Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1991.

Little, B.B.; Snell, L.M.; Gilstrap, L.D.; and Johnson, W.L. Patterns of multiple substance abuse during pregnancy. Implications for mother and fetus. *South Med J* 83:507-509, 1990.

Lutiger, B.; Graham, K.; Einarson, T.R.; and Koren, G. Relationship between gestational cocaine use and pregnancy outcome. A meta analysis. *Teratology* 44:405-414, 1991.

Nanda, D.; Feldman, J.; Delke, I.; Chinlalapally, S.; and Minkoff, H. Syphilis among parturients at an inner city hospital: Association with cocaine use and implications for congenital syphilis rates. *NY State J Med* 90:485-486, 1990.

Phibbs, C.S.; Bateman, D.A.; and Schwartz, R.M. The neonatal costs of maternal cocaine use. *JAMA* 266:1521-1526, 1991.

Roland, E.G., and Volpe, J.J. Effect of maternal cocaine use on the fetus and newborn: Review of the literature. *Ped Neurosci* 15:88-94, 1989.

Spence, M.R.; Williams, R.; Digregorio, G.J.; Kirby-McDonnell, A.; and Polansky, M The relationship between recent cocaine use and pregnancy outcome. *Obstet Gynecol* 78:326-329, 1991.

Streissguth, A.P.; Darby, B.L.; Barr, H.M.; Smith, J.R.; and Martin, D.C. Comparison of drinking and smoking patterns during pregnancy over a six-year interval. *Am J Obstet Gynecol* 145:716-724, 1983.

Thornton, L.; Clune, M.; Maguire, R.; Griffin, E.; and O'Connor, J. Narcotic addiction: The expectant mother and her baby. *Ir Med J* 83:139-142, 1990.

Williams, A.B. Reproductive concerns of women at risk for HIV infection. *J Nurse Midwifery* 35:292-298, 1990.

Williamson, D.F.; Serdula, M.K.; Kendrick, J.S.; and Brinkin, N.J. Comparing the prevalence of smoking in pregnant and nonpregnant women, 1985 to *1986. JAMA* 261:70-74, 1989.

Wittmann, B.K., and Segal, S. A comparison of the effects of single and split-dose methadone administration on the fetus: Ultrasound evaluation. *Int J Addict* 26:213-218, 1991.

Wolman, I.; Niv, D.; Yovel, I.; Pauser, D.; Geller, E.; and David, M.P. Opioid-addicted parturient, labor and outcome: A reappraisal. *Obstet Gynecol Surv* 44:592-597, 1989.

Zuckerman, B.; Frank, D.A.; Hingson, R.; Amaro, H.; Levenson, S.M.; Kayne, H.; Parker, S.; Vinci, R.; Aboagye, K.; Fried, L.F.; 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.

Zuspan, F.P.; Gumpel, J.A.; Mejia-Zelaya, A.; Madden, J.; and Davis, R. Fetal stress from methadone withdrawal. *Am J Obstet Gynecol* 122:43-46, 1975.

AUTHOR

James R. Woods, Jr., M.D.
Professor of Obstetrics and Gynecology
Director of Obstetrics and
Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
University of Rochester School of Medicine and Dentistry
Strong Memorial Hospital
601 Elmwood Avenue
Rochester, NY 14642-8668

Methadone Use During Pregnancy

Margaret A.E. Jarvis and Sidney H. Schnoll

INTRODUCTION

Since methadone was first reported as a treatment for opioid-dependent addicts it has been associated with considerable controversy and with loyal supporters and detractors. The use of methadone in pregnant opioid-dependent women has been at least as controversial. The controversy has become even more critical as the number of addicts with human immunodeficiency virus (HIV) infection has increased, and is heightened by the fact that over 70 percent of pediatric acquired immunodeficiency syndrome cases occur in children born to drug-using women or women who have sexual relations with drug-using men. Therefore, it is increasingly important to employ all methods available to reduce drug use in pregnant women in order to reduce the risk for HIV infection, and ultimately to reduce the risk for transmission of HIV to the fetus and newborn.

This chapter explores issues around the use of methadone in pregnant opioid addicts by reviewing research on the use of methadone and also describes methods of placing women on methadone, altering the dose during pregnancy, and, when appropriate, how to withdraw women from methadone during pregnancy.

METHADONE MAINTENANCE

Methadone is the only medication currently used for the treatment of pregnant opioid addicts. As a result of studies done in the late 1960s and early 1970s, methadone maintenance is the standard of care for the pregnant opioid addict. Much of this work was performed in centers offering comprehensive services: obstetric, medical, and psychiatric care; case work; and individual, group, and family counseling. Studies done at the Philadelphia General Hospital's Family Center showed that birth weights were increased and the incidence of preeclampsia was reduced in opioid addicts placed on methadone doses sufficient to suppress craving (Finnegan 1978). These women received good prenatal care compared with those receiving no chemical dependency treatment. The incidence of low birth weight in the groups of addicts treated with methadone was

not significantly different from nonaddicted controls. The incidence of neonatal withdrawal was reduced in the methadone-maintained group; however, of the infants who went through withdrawal, a higher percentage of the neonates of methadone-maintained mothers underwent moderate withdrawal as compared with the untreated addicts whose infants went through severe or mild withdrawal (Connaughton et al. 1975, 1977; Finnegan 1978).

A study at the Albert Einstein Hospital in New York involving patients whose prenatal care and chemical dependency counseling were provided in different institutions demonstrated that methadone-maintained women tended to get more prenatal care than those on heroin, though less care than the nonaddicted controls. Mothers taking either heroin or methadone during pregnancy tended to give birth to lower birth weight infants than nonaddicted mothers. There was no difference in the infants' Apgar scores, although there was increased meconium staining in the infants born to heroin-dependent mothers. While the total number of infants exhibiting neonatal withdrawal did not differ between heroin- and methadone-taking groups, those born to mothers on methadone had more diarrhea and significantly more seizures. This was not found to be related to maternal methadone dose, however (Kandall et al. 1977).

A report from the Illinois Drug Abuse Program compared women taking heroin with women on methadone maintenance and a variety of psychosocial supports. The incidence of fetal wastage (stillbirth, abortion) was much higher in the group that received only methadone, even in comparison with heroin-complicated pregnancies. The group of infants born to heroin-dependent women had a significantly greater incidence of low birth weight than other groups. The incidence of neonatal withdrawal requiring treatment increased significantly with higher maternal methadone dose. Importantly, the authors reported higher treatment retention in the groups receiving increased psychosocial support (Davis et al. 1975).

A similar study in Australia revealed increased duration of gestation in methadone-maintained women when compared with heroin users. The treatment did not increase the number of antenatal visits that the addicted women kept, nor did it cause any substantial increase in the size of the babies or decrease the medical and obstetrical complications that the addicted mothers suffered. It is not clear how much psychosocial support was offered in the program (Giles et al. 1989).

The available clinical studies demonstrate that methadone maintenance at an appropriate dose, when combined with prenatal care and a comprehensive program of support for the pregnant addict, can significantly improve fetal and neonatal outcome.

EFFECTS ON OFFSPRING

Animal Studies

Though methadone maintenance is the treatment of choice for the pregnant opioid addict, there are potential physiological, teratological, and psychological consequences that can result from its use. In contrast, the effects of continued heroin use, often in conjunction with other drugs such as cocaine, alcohol, nicotine, and marijuana, and the lifestyle associated with addiction can result in more severe consequences such as fetal demise. Little of the research in defining the effects of methadone and other drugs on the fetus has been done in humans; therefore, results from animal studies are presented here.

Elaborate surgical means have been used to study the effect of intoxication and withdrawal in pregnant ewes. Infusion of morphine into pregnant ewes did not alter heart rate, blood pressure, or arterial blood gasses in either ewe or fetus. Naloxone was then infused separately into the maternal and fetal circulations. This precipitated abstinence caused an increase in fetal systolic and diastolic blood pressures, decreased fetal heart rate, decreased fetal arterial oxygen partial pressure (pO_2), and decreased arterial pH and meconium staining of amniotic fluid. Injection of naloxone into the mother produced similar changes in the fetus, although these responses followed injection by several minutes (Cohen et al. 1980). Umans and Szeto (1985) demonstrated that morphine infusion into the fetus altered fetal function, but the most severe alterations resulted from naloxone-precipitated abstinence. Morphine at low doses caused a desynchronization of the electroencephalogram (EEG), increased nuchal and body tone, increased body and eye movement, increased heart rate, and increased variability of heart rate. Higher doses reduced all of these parameters below normal except body movements. Naloxone-precipitated abstinence from low doses of morphine caused desynchronization of the EEG, reduced heart rate, and increased rate and depth of breathing. After high doses of morphine, naloxone infusion induced increased diastolic and systolic blood pressures, increased pulse pressures, and decreased heart rate and meconium staining of the

amniotic fluid. A second precipitated abstinence was attempted 24 hours after the first with similar but less severe results.

Fertilized chicken eggs have also been used for similar studies. The chorioallantois was injected with N-desmethyl-L-α-acetylmethadol (NLAAM), an active metabolite of L-or-acetylmethadol (LAAM), on the third day of incubation. On day 19 of incubation, the egg was injected with either saline or naloxone. Treatment with naloxone alone or NLAAM alone had no effect on the hatchability of eggs, but naloxone treatment after NLAAM administration reduced hatchability. Fetal movements were recorded and revealed that fetuses treated with NLAAM showed less movement than controls while treatment of the same fetuses with naloxone caused increases in movement compared to controls (Kuwahara and Sparber 1981).

A similar paradigm using morphine instead of NLAAM showed a difference between precipitated and gradual withdrawal. Fetuses were treated with morphine and allowed to withdraw gradually by stopping the morphine doses or underwent precipitated withdrawal by treatment with naloxone. Gradual withdrawal caused no change in motility or hatchability, while precipitated withdrawal did increase mobility. After hatching, morphine-tolerant chicks did not exhibit altered frequency of distress vocalization upon morphine treatment, but both morphine-naive and withdrawn chicks showed a reduction in distress vocalization with morphine treatment (Newby-Schmidt and Norton 1983).

A study of rats exposed to opioids in utero showed both low birth weight and reduced litter size in rats withdrawn from opioids. One group of females rats received LAAM starting 3 weeks before mating, and another group was started at conception; naloxone was then administered subcutaneously starting at day 14 of gestation. In rats who received naloxone, the birth weight and total body length of the pups was reduced, and the total litter size was reduced, as compared with rats that did not receive naloxone (Blinick et al. 1969). In rats exposed to varying doses of methadone and buprenorphine before breeding and during gestation, the rate of conception was decreased as compared with controls. There was decreased neonatal survival in the litters exposed to buprenorphine. The pups born of these pregnancies were decapitated at age 21 days and the levels of Met- and Leu-enkephalin were measured. The only drug effect noted was a decrease in striatal content of both enkephalins in the rats exposed to high doses of methadone in utero (Tiong and Olley 1988).

The effects of methadone maintenance on neurotransmitters and receptors in fetal brain have been examined in rats. Wang and colleagues gave pregnant rats methadone or water, and the pups were then fostered to dams who were also implanted with either water or methadone pumps; this treatment produced changes in hypothalamic and cortical expression of adrenergic receptors in the pups. Methadone exposure before or after birth caused decreased numbers of a,-receptors in the cortex. Methadone exposure before birth caused decreased numbers of δ and μ opioid receptors in the hypothalamus and decreased δ opioid receptors in the cortex. If methadone exposure was continued after birth, an additional decrease in μ receptors was seen in the cortex. No change in hypothalamic α-adrenergic receptors was seen as a result of methadone exposure (Wang et al. 1986).

A study of the effects of methadone maintenance on the development and activity of ß-adrenergic receptors revealed the presence of both $ß_1$- and $ß_2$-receptors in rat placenta and maternal cortex. Term fetal whole brain (with the exception of cerebellum) was found to contain only $ß_1$-receptors. There were no changes in B-receptor population or function in any of the organs after methadone exposure for 13 days (Darmani et al. 1991). A similar study in which neurotransmitters were measured in 4-day-old rats exposed to methadone in utero showed a decrease in striatal acetylcholine in all exposed pups. There were some gender-specific changes, with drug-exposed male rats having an increase in striatal serotonin and hindbrain acetylcholine and drug-exposed female rats having increased hippocampal acetylcholine (Guo et al. 1990). Rats exposed to methadone in utero showed an increase in analgesic response to morphine at the fourth day of life as compared with controls, but at day 21 the analgesic response was decreased (Enters et al. 1991).

The presence of naloxone has been shown to exacerbate significantly the effects of hypoxia on fetal heart rate, blood pressure, ventricular output, and placental blood flow in the opioid-naive fetal lamb (LaGamma et al. 1982), suggesting that endogenous opioids may normally serve to protect against hypoxia.

Fetal lambs were exposed to varying doses of morphine (0.75 milligrams per hour [mg/hr]-80 mg/hr) for 2 hours, and the breathing movements were monitored. The breathing rates exhibited a biphasic curve, with doses of morphine 1.5-2.5 mg/hr causing increased breathing movements and doses over 2.5 mg/hr causing decreased breathing movements. At

the highest dose, 80 mg/hr, all subjects experienced apnea (Szeto et al. 1988b).

Tachycardia has been observed during exposure to varying doses of morphine in the fetal lamb. The percentages of the population responding with tachycardia as a function of dose described a Gaussian distribution. The authors showed that either a functional antagonism model or a noncompetitive inhibition model could be invoked to explain these results (Zhu and Szeto 1989).

Taken together, these findings support the conclusion that opioids protect against the response to hypoxia by causing increased heart rate and fetal breathing movements. This effect only occurs at low doses, however, and at high doses bradycardia and hypopnea result, perhaps due to some change in interaction of opioid with opioid receptor.

A study of sleep-wake cycles in fetal lambs showed that an initial response to chronic morphine exposure was an increase in the time spent in arousal; this phenomenon attenuated with continued exposure, and there was a return to cyclicity within 7 days. Withdrawal also resulted in increased arousal (Szeto et al. 1988a).

These studies demonstrate the need for further investigation of opioids' effects on the developing fetus. However, it is clear that the most devastating consequences of opioid use during pregnancy occur with repeated episodes of intoxication and withdrawal. This lends support to the importance of stabilization on a dose of a long-acting narcotic to prevent wide fluctuations in blood levels.

Human Studies

Many gaps exist in researchers' knowledge of the effects of methadone on pregnancy and the fetus. The animal studies are sparse, and there are even fewer human studies. Zuspan and colleagues (1975) published a clinical case report of elevations of amniotic fluid epinephrine and norepinephrine levels during a slow withdrawal. It should be noted that this report described only one case, and it is not clear how accurately amniotic fluid levels reflect fetal distress.

Solish and colleagues (1976) investigated the effects of methadone maintenance and withdrawal on several markers of maternal-fetal

well-being in humans. The level of placental heat-stable alkaline phosphatase as measured in blood (which increases with stress and rises normally during the third trimester) showed no statistically significant differences between methadone-maintained pregnancies, controls, and a small number of withdrawn mothers. There was some indication, however, that heat-stable alkaline phosphatase may be elevated in women who receive methadone doses greater than 60 mg/day.

A study of the endocrine effects of methadone maintenance in pregnancy showed that the early morning dehydroepiandosterone sulphate (DHEAS) level was reduced in methadone-maintained pregnant women as compared with nondrug-using pregnant women. The circadian fluctuation of DHEAS levels was observed only in the second and third trimesters during methadone maintenance. In methadone-maintained women, the third trimester level of estriol was reduced compared with controls. No differences in levels of cortisol or human chorionic somatomammotropin were seen. This suggested that adrenal function is disturbed by opioid use and that the fetal adrenal gland is more disturbed than the maternal adrenal gland (Facchinetti et al. 1986). The authors suggested that estriol levels therefore may not be a useful marker of fetal well-being in opioid-exposed pregnancies.

Very little is known about the pharmacokinetics of methadone during pregnancy in humans. Kreek and colleagues (1974) published studies of one woman and her infant that suggested that methadone metabolism might be accelerated during late pregnancy. This study was expanded to nine more patients in 1984, and the finding of accelerated methadone metabolism was confirmed (Pond et al. 1985). The authors suggested that increasing the dose of methadone might be necessary to prevent withdrawal symptoms late in pregnancy.

Methadone Withdrawal

At the Family and Maternity Care Program of the State University of New York, a small number of heroin addicts were treated with withdrawal or methadone during pregnancy. This program offered intense psychosocial support and several modalities of methadone maintenance and detoxification. Approximately half of the patients refrained from illicit drug use during and after treatment. Six of 5 1 women were withdrawn from opioids by the time of delivery. Obstetrical and medical complications were well controlled. There was a significant incidence of low birth weight infants and almost universal neonatal

withdrawal (94 percent), except in the withdrawn women. There was no correlation between methadone dose and the severity of neonatal withdrawal, nor was there any mention in the report of how methadone withdrawal compared with maintenance in outcome of pregnancy (Harper et al. 1974).

In the methadone maintenance treatment program of the Bernstein Institute in New York, the incidence of low birth weight was lower in infants born to methadone-maintained mothers as compared with infants born to mothers who underwent withdrawal. The doses of methadone given were intended to prevent craving and were in the range of 80 to 140 mg per day. Approximately two-thirds of the infants underwent mild or moderate withdrawal. Fourteen of these children were followed for 4 years and were found to be developing normally physically. It is unclear how much psychosocial support was offered by the program (Blinick et al. 1969; Wallach et al. 1975).

A study at the University Hospital Rudolph Virchow, Free University of Berlin reported on outcomes of 75 pregnancies: 17 untreated opioid addicts, 58 treated. Of the 58 treated addicts, 17 were completely withdrawn by the time of delivery and had not relapsed in their drug use. They were withdrawn over a 2- to 8-week period as outpatients, with daily contact during that time. The level of psychosocial support was not addressed in the report. The incidence of neonatal abstinence was decreased significantly by participation in the withdrawal program. In addition, treatment resulted in increased length of gestation, with resulting normalization of intrauterine growth (Maas et al. 1990).

It is clear that any treatment of opioid addiction positively influences the outcome of pregnancy. It is possible that higher doses of methadone result in increased severity of neonatal withdrawal, making low-dose treatment or abstinence preferable for those addicted mothers who can tolerate these treatments. Little has been done to investigate the specific effects of tapered withdrawal on the fetus and infant, and thus the treatment options for these women have been limited. The difficulty that addicts have in remaining drug-free has been an impediment to tapered withdrawal, but some motivated addicts are capable of abstinence (Harper et al. 1974; Maas et al. 1990). Intense psychosocial support seems to be helpful in all of these processes (Harper et al. 1974; Panepinto et al. 1977). If psychosocial support is not offered, there is a tendency to lose women from the program (Blinick et al. 1969).

Although abstinence from drug use during pregnancy may seem to be an ideal goal, it is evident that most pregnant addicts cannot remain drug-free after withdrawal. Relapse could result in a continual cycling from intoxication to withdrawal with wide variation in the blood levels of opioids and other drugs. This cycling, along with the effects of multiple drug use, appears to have severe consequences for fetal development. The return to street drug use also increases the risk of infection with HIV, hepatitis, other sexually transmitted diseases (STDs), and numerous other medical complications resulting in the potential for adverse effects on the fetus. Methadone maintenance at the appropriate dose prevents this cycling and reduces the risk of the medical consequences of street drug use.

Postnatal Effects of Prenatal Exposure

All of the commonly used opioids can produce a neonatal abstinence syndrome in infants born to addicted mothers. The neonatal abstinence syndrome combines the symptoms of the adult withdrawal syndrome with irritability, poorly coordinated sucking and, in the most severe cases, seizures and death. However, if abstinence is appropriately recognized, assessed, and treated promptly, severe complications such as dehydration and seizures occur rarely, and infant mortality should not occur.

With the doses used to suppress craving and withdrawal, methadone can cause a moderately severe syndrome. This syndrome generally has been found to be more severe than the syndrome seen in infants of heroin addicts, but it is most likely that this is a function of the impurity of the heroin available on the streets rather than a true pharmacologic difference between the two drugs. At methadone doses of less than 20 mg per day, little or no incidence of neonatal abstinence is seen (Madden et al. 1977). However, the consequences of administering adequate methadone doses to eliminate illicit heroin use (a major factor in contracting infectious diseases such as HIV and hepatitis) may be less risky than the inadequate pharmacological doses of methadone often provided to pregnant women.

The most recent work investigating the relationships between blood levels and withdrawal symptoms showed that there are significant correlations between maternal dose and plasma level 16 hours postpartum, between the maternal postpartum level and the infant's plasma level on day 1 of life, and between the rate of decline of methadone level in the fetal blood and the severity of neonatal

withdrawal symptoms in the central nervous system (i.e., seizures, irritability) (Doberczak et al. 1993).

Earlier studies had similar results. Offidani and colleagues (1986) found correlations between umbilical cord plasma methadone level and severity of neonatal withdrawal, umbilical cord plasma methadone level and maternal plasma methadone level, and maternal methadone dose and the severity of neonatal withdrawal. No neonatal withdrawal was seen if mothers were drug-free by delivery. Harper and colleagues (1977) saw that severity of withdrawal was positively correlated with total maternal methadone ingestion in the final 12 weeks of pregnancy, the daily dose at delivery, and maternal serum level at delivery. There was no correlation found between severity of withdrawal and drug levels in fetal urine or cord blood.

There has been speculation that substance abuse during pregnancy may result in sudden infant death syndrome (SIDS). A 1990 report based on the Los Angeles County Population found an incidence of 8.87 per 1,000 for SIDS in infants born to mothers who used any combination of phencyclidine, amphetamines, cocaine, or opioids as compared with an incidence of 1.22 per 1,000 in infants born to nonsubstance-using women. The variability in SIDS incidence due to gender, race, and season that was seen in infants of nonsubstance-abusing women disappeared in the exposed infants. In addition, exposed infants were reported to have had more premorbid apnea than unexposed infants (Ward et al. 1990). A less powerful study showed increased rates of SIDS in infants born to both polysubstance-abusing women and methadone-maintained women when compared with infants of nonabusers (Rosen and Johnson 1988). The etiologies that have been ascribed to SIDS are myriad, and while substance abuse may contribute, no cause-and-effect relationship has been defined.

A comparison of two groups of children with differing severity of neonatal withdrawal syndrome showed no significant difference in cognitive functioning as measured with the Bayley Scale of Mental Development at 6 months of age. In those children who had severe withdrawal, treatment was implemented with any of several medications, and withdrawal was controlled. Comparison of the childrens' development based on the medication used to control withdrawal also revealed no significant differences (Kaltenbach and Finnegan 1986).

When compared to nondrug-exposed children, the development of children exposed to methadone in utero is not fully delineated at this time. At age 6 months, there was no significant difference found between the two groups of children on the Bayley Scale of Mental Development (Kaltenbach and Finnegan 1987). At age 2 years, however, measurements on the Bayley Scale of Mental Development, Bayley Scale of Psychomotor Development, and Infant Behavior Record showed that the drug-exposed children were smaller and more tense, with poor psychomotor development (Hans 1989). The effects of maternal intelligence quotient, socioeconomic status, and medical/obstetrical complications were controlled statistically and were found to cause variation in components of development (Hans 1989). Some evidence has been found to suggest that strabismus may occur more frequently in children exposed to methadone in utero than in unexposed children (Nelson et al. 1987).

CLINICAL CARE OF THE METHADONE-MAINTAINED PREGNANT ADDICT

It has been well documented that the most effective treatment for pregnant addicts is delivered in well-coordinated, multidisciplinary treatment settings, In addition to methadone and other treatment for the addiction, good obstetrical and medical care should be provided. Education about nutrition, parenting, and the need for strong, healthy psychosocial support systems are considered important components of treatment, as are individual, group, and family counseling. Social service advocacy is also critical. There are indications that, without these extensive services, the outcome of treatment will be less than satisfactory. However, there are no studies documenting the efficacy of these additional services. Research opportunities exist for investigating the nature and the efficient use of essential support services.

In addition to the concern about opioid use, it has become increasingly apparent that women who are abusing any one drug during pregnancy are also likely to be using other drugs with dependence liability. Thus, these patients should be monitored for use of alcohol, cocaine, nicotine, benzodiazepines, other sedative-hypnotics, and the other myriad drugs with abuse potential. All of these can have potential effects on pregnancy and neonatal outcome.

Medical care should be provided to ensure adequate progression of the pregnancy. There should be routine examination for STDs, including hepatitis and HIV infection. In most instances, prenatal care should be provided in an obstetrical setting where there is easy access to advanced technology and expertise in diagnosis and treatment. As in all pregnancies in general, addicted pregnant women should receive thorough physical examinations with complete medical histories and comprehensive laboratory studies. If the pregnancy occurs while a woman is already in a methadone maintenance program, then the use of methadone should be continued throughout the pregnancy. However, it may be the necessary to alter the dose of methadone later in pregnancy, as described later in this chapter.

If an addicted pregnant woman presents for care and has not been on methadone, it is necessary to determine the appropriate dose of methadone to block withdrawal and reduce her craving. This can often be a difficult process and may take several weeks before the appropriate dose of methadone is achieved on an outpatient basis. If it is possible to hospitalize the patient for a brief time, the dose of methadone can be established more rapidly. Upon entering the hospital, the woman should be assessed very carefully for any signs of opioid withdrawal as outlined in table 1. A careful history of the previous 24 hours' use of opioids will give some information as to the average dose of opioids being taken on the street and the time at which the last dose was taken. This information is helpful in establishing the maintenance dose and predicting withdrawal response. Opioid withdrawal can appear within 6 to 12 hours of the last dose taken. If the patient has reported the last use of short-acting opioids over 6 hours ago and is not showing significant signs of withdrawal, then it can be anticipated that the withdrawal syndrome will be mild. On the other hand, if the withdrawal symptoms are beginning to appear within 6 hours, then there may be a more severe withdrawal syndrome.

By monitoring the patient for the signs and symptoms described in table 1, the amount of methadone necessary to suppress withdrawal can be determined. If the total score is 4 or less, no methadone is given. For a score of 5, 5 mg methadone is administered. Higher scores require an equivalent dose of methadone (e.g., a score of 8 = 8 mg methadone). After 24 hours the total amount of methadone administered is determined, and identical doses of methadone are given during the second 24-hour period. At the end of the second 24-hour period, a tapered withdrawal may be initiated by reducing subsequent 24-hour total doses by 10 percent of the total dose given in the first 24 hours (e.g., if a total of

TABLE 1. *Objective rating of opioid withdrawal signs used to calculate methadone dosage every 6 hours.*

SIGNS OF WITHDRAWAL	NOT PRESENT (0)	MILDLY PRESENT (1)	STRONGLY PRESENT (2)
Pupillary dilation			
Rhinorrhea			
Lacrimation			
Piloerection			
Nausea or vomiting			
Diarrhea			
Yawning			
Cramps			
Restlessness			
Subjective evaluation			

50 mg was given in the first 24 hours, 45 mg may be administered over the third 24-hour period, 40 mg during the fourth 24-hour period, and so forth).

Once the amount of methadone necessary to block withdrawal is determined, the dose of methadone is increased to full blocking dose. This dose increase can occur while the woman is an outpatient, though the patient should be monitored daily to determine the dosage adjustments.

There has been considerable discussion of the merits of high-dose versus low-dose methadone treatment of opioid dependence. Philosophical differences have been presented; however, the evidence currently available seems to indicate that higher doses are more efficacious in the reduction of illicit drug and needle use. These factors are especially

important for the reduction of HIV infection. However, there is some evidence that lower doses of methadone can result in less neonatal abstinence.

Methadone maintenance is traditionally given in once-daily dosages. This regimen seems to be sufficient to block withdrawal in most individuals. However, there is evidence that this may not be the case in pregnant women, particularly in later states of pregnancy. Szeto and colleagues (1982a) have demonstrated in animals, and Kreek and colleagues (1974) and Pond and colleagues (1985) have shown in humans, that the methadone blood levels fall more rapidly in the later stages of pregnancy, resulting in the onset of an abstinence syndrome prior to the next dose of methadone. It has, therefore, been recommended that the appropriate approach to this change in blood levels is to increase the dose of methadone in the later stages of pregnancy. However, more recent evidence (Wittman and Segal 1991) demonstrated that splitting the dose of methadone into a twice-daily schedule produced better results by reducing fetal stress and increasing the comfort of the pregnant woman. The authors' clinical experience has indicated that split doses can be very effective in offsetting the altered metabolism of methadone in the latter stages of pregnancy.

WITHDRAWAL FROM METHADONE DURING PREGNANCY

In recent years, there has been mounting pressure by regulatory agencies and others to limit the amount of time that an individual can be on methadone, therefore encouraging withdrawal from methadone. These pressures have produced intense discussion regarding the efficacy of withdrawal of pregnant women from methadone. As previously stated, there are limited studies of the outcome of this approach, its appropriate implementation, and whether it should be implemented at all. The current belief among most practitioners involved in the treatment of pregnant addicts is that methadone should be maintained throughout pregnancy to reduce the possibility of return to drug use and, in particular, to reduce the risk of HIV infection. In addition, the use of methadone during pregnancy enables the practitioner to remain in much more frequent contact with the pregnant woman than would normally occur if she were not on methadone. However, extenuating circumstances may require a woman to be withdrawn from methadone during pregnancy. There are four reasons to consider withdrawal of the pregnant addict from opioids.

1. The patient refuses to be placed on methadone maintenance;

2. The patient lives in an area where methadone maintenance is not available;

3. The patient has been stable during treatment and requests withdrawal from methadone prior to delivery; and

4. The patient has been so disruptive to the treatment setting that the treatment of other patients is jeopardized, necessitating the removal of the patient from the treatment setting.

In the case of the woman who meets one of these criteria, the risks of withdrawal should be clearly explained prior to the initiation of withdrawal, particularly the risk of returning to drug use and its consequences. The conventional wisdom has been that women should only be withdrawn during the second trimester of pregnancy, that withdrawal during the first trimester will result in spontaneous abortions, and that withdrawal in the third trimester may result in premature delivery. Despite these widely held beliefs, there are no reports in the literature to document or support these contentions.

Recent anecdotal reports from a number of centers, including the work of one of the authors (SHS), indicate that withdrawal can occur during any trimester of pregnancy without undue risk to mother or fetus if carried out in a controlled fashion. It is important to keep in mind that if a woman is to be withdrawn, withdrawing her, placing her back on methadone, and then potentially withdrawing her again may be more detrimental to the fetus than either maintaining her on methadone or, if she can remain abstinent, keeping her in a drug-free state. As previously described, cycling on and off of the drug is more detrimental than the maintenance of constant blood levels, whatever that level may be.

As with all withdrawals from drugs of abuse, it is strongly recommended that this be done in a blind fashion so the patient is not aware of the dose or the speed at which the dose is reduced. This can be accomplished by providing the medication in liquid form in a fixed volume, diluted with juice or some other vehicle so that the patient receives the same volume of liquid each day throughout the withdrawal period.

When a decision has been made to withdraw a pregnant woman, it is important to provide intensive psychosocial support during this period to

deal with any discomforts, fears, or concerns that may arise. In an inpatient setting where more intense support can be provided, withdrawal can proceed at a rate of 2.5 mg decrease in dose of methadone per day. In an outpatient setting where less support is available, it is recommended that the withdrawal proceed at a rate of no more than 10 mg decrease in dosage per week. The patient should be monitored daily for signs of withdrawal and any changes in fetal activity or heart rate, and the rate of withdrawal should be adjusted to meet changing clinical situations.

Again, it should be emphasized that although it is possible to withdraw women from methadone during pregnancy, it is not the recommended therapeutic intervention at this time.

CONCLUSIONS

Methadone has shown to be an effective treatment for pregnant women who are using opioids during pregnancy. Methadone provides stabilization when the level of methadone is brought up to full blocking doses; however, these dosage levels may result in low birth weight for gestational age, and the newborn may go through withdrawal following delivery. For the woman on methadone maintenance during pregnancy, it is important to monitor the dose carefully and adjust the dose as necessary to provide the best outcome. This may include splitting the dose, particularly later in pregnancy when the metabolism of methadone is altered by the pregnancy. In rare cases when the woman meets specific criteria, it is possible to withdraw her from methadone, but this is discouraged except in extenuating circumstances.

REFERENCES

Blinick, G.; Wallach, R.C.; and Jerez, E. Pregnancy in narcotics addicts treated by medical withdrawal. *Am J Obstet Gynecol* 105:997-1003, 1969.

Cohen, M.S.; Rudolph, A.M.; and Melmon, K.L. Antagonism of morphine by naloxone in pregnant ewes and fetal lambs. *Dev Pharmacol* 1:58-69, 1980.

Connaughton, J.F.; Finnegan, L.P.; Schut, J.; and Emich, J.P. Current concepts in the management of the pregnant opiate addict. *J Addict Dis* 2:21-35, 1975.

Connaughton, J.F.; Reeser, D.; Schut, J.; and Finnegan, L.P. Perinatal addiction: Outcome and management. *Am J Obstet Gynecol* 129: 679-686, 1977.

Darmani, N.A.; Schnoll, S.H.; Fuchs, B.; and Martin, B.R. Does chronic prenatal methadone exposure affect B-receptor subtypes in placental, fetal and maternal brain homogenates? *Neurotoxicol Teratol* 13:43-48, 1991.

Davis, R.C.; Chappel, J.N.; Mejia-Zelaya, A.; and Madden, J. Clinical observations on methadone-maintained pregnancies. *J Addict Dis* 2:101-112, 1975.

Doberczak, T.M.; Kandall, S.R.; and Friedmann, P. Relationships between maternal methadone dosage, maternal-neonatal methadone levels and neonatal withdrawal. *Obstet Gynecol* 81:936-40, 1993.

Enters, E.K.; Guo, H.; Pandey, U.; Ko, D.; and Robinson, S.E. The effect of prenatal methadone exposure on developmental and nociception during the early postnatal period of the rat. *Neurotoxicol Teratol* 13:161-166, 1991.

Facchinetti, F.; Comitini, G.; Petraglia, F.; Volpe, A.; and Genazzani, A.R. Reduced estriol and dehydroepiandosterone sulphate plasma levels in methadone-addicted pregnant women. *Eur J Obstet Gynecol Reprod Biol* 23:67-73, 1986.

Finnegan, L.P. Management of pregnant drug-dependent women. *Ann N Y Acad Sci* 311:153-146, 1978.

Giles, W.; Patterson, T.; Sanders, F.; Batey, R.; Thomas, D.; and Collins, J. Outpatient methadone programme for pregnant heroin using women. *Aust N Z J Obstet Gynaecol* 29:225-229, 1989.

Guo, H.; Enters, K.; McDowell, K.P.; and Robinson, S.E. The effect of prenatal exposure to methadone on neurotransmitters in neonatal rats. *Brain Res Dev Brain Res* 57:296-298, 1990.

Hans, S.L. Developmental consequences of prenatal exposure to methadone. *Ann N Y Acad Sci 562:* 195-207, 1989.

Harper, R.G.; Solish, G.I.; Purow, H.M.; Sang, E.; and Panepinto, W.C. The effect of a methadone treatment program upon pregnant heroin addicts and their newborn infants. *Pediatrics* 54:300-305, 1974.

Harper, R.G.; Solish, G.; Feingold, E.; Gersten-Woolf, N.B.; and Sokal, M.M. Maternal ingested methadone, body fluid methadone, and the neonatal withdrawal syndrome. *Am J Obstet Gynecol* 129:417-424, 1977.

Hoegerman, G., and Schnoll, S. Narcotic use in pregnancy. *Clin Perinatol* 18:51-76, 1991.

Kaltenbach, K., and Finnegan, L.P. Neonatal abstinence syndrome, pharmacotherapy and developmental outcome. *Neurobehav Toxicol Teratol* 8:353-355, 1986.

Kaltenbach, K., and Finnegan, L.P. Perinatal and developmental outcome of infants exposed to methadone *in-utero*. *Neurotoxicol Teratol* 9:311-313, 1987.

Kandall, S.R.; Albin, S.; Gartner, L.M.; Lee, K.; Eidelman, A.; and Lowinson, J. The narcotic dependent mother: Fetal and neonatal consequences. *Early Hum Dev* 1:159-180, 1977.

Kreek, M.J.; Schecter, A.; Gutjahr, C.L.; Bowen, D.; Field, F.; Queenan, J.; and Merkatz, I. Analysis of methadone and other drugs in maternal and neonatal body fluids: Use in evaluation of symptoms in a neonate of mother maintained on methadone. *Am J Drug Alcohol Abuse* 1:409-419, 1974.

Kuwahara, M.D., and Sparber, S.B. Prenatal withdrawal from opiates interferes with hatching of otherwise viable chick fetuses. *Science* 212:945-947, 1981.

LaGamma, E.F.; Itskovitz, J.; and Rudolph, A.M. Effects of naloxone on fetal circulatory responses to hypoxemia. *Am J Obstet Gynecol* 143:933-940, 1982.

Maas, U.; Kattner, E.; Weingart-Jesse, B.; Schafer, A.; and Obladen, M. Infrequent neonatal opiate withdrawal following maternal detoxification during pregnancy. *J Perinat Med* 18:111-118, 1990.

Madden, J.D.; Chappel, J.N.; Zuspan, F.; Gumpel, J.; Mejia, A.; and Davis, R. Observation and treatment of neonatal narcotic withdrawal. *Am J Obstet Gynecol* 127:199-201, 1977.

Nelson, L.B.; Ehrlich, S.; Calhoun, J.H.; Matteucci, T.; and Finnegan, L.P. Occurrence of strabismus in infants born to drug-dependent women. *Am J Dis Child* 141:175-178, 1987.

Newby-Schmidt, M.B., and Norton, S. Drug withdrawal prior to hatch in the morphine tolerant chick embryo. *Pharmacol Biochem Behav* 18:817-820, 1983.

Offidani, C.; Chiarotti, M.; De Giovanni, N.; and Falasconi, A.M. Methadone in pregnancy: Clinical-toxicological aspects. *Clin Tox* 24:295-303, 1986.

Panepinto, W.; Amon, D.; Silver, F.; Orbe, M.; and Kissin, B. Detoxification from methadone maintenance in a family-oriented program. *Br J Addict* 72:255-259, 1977.

Pond, S.M.; Kreek, M.J.; Tong, T.G.; Raghunnath, J.; and Benowitz, N.L. Altered methadone pharmacokinetics in methadone-maintained pregnant women. *J Pharm Exp Ther* 233:1-6, 1985.

Rosen, T.S., and Johnson, H.L. Drug-addicted mothers, their infants and SIDS. *Ann N Y Acad Sci* 553:89-95, 1988.

Solish, G.I.; Harper, R.G.; and Feingold, E. Prenatal studies of infants in methadone maintained women. In: Ford, D.H., and Clouet, D.H., eds. *Tissue Responses to Addictive Drugs.* New York: Spectrum Publications, Inc., 1976. pp. 653-665.

Szeto, H.H.; Umans, J.G.; and Rubinow, S.I. The contribution of transplacental clearances and fetal clearance to drug disposition in the ovine maternal-fetal unit. *Drug Metab Dispos* 10:382-386, 1982a.

Szeto, H.H.; Umans, J.G.; Umans, H.R.; and McFarland, J.W. The relationship between maternal and fetal plasma protein binding of methadone in the ewe during the third trimester. *Life Sci* 30:1271-1279, 1982b.

Szeto, H.H.; Zhu, Y.S.; Amione, J.; and Clare, S. Prenatal morphine exposure and sleep-wake disturbances in the fetus. *Sleep* 11:121-130, 1988a.

Szeto, H.H.; Zhu, Y.S.; Umans, J.G.; Dwyer, G.; Clare, S.; and Amione, J. Dual action of morphine on fetal breathing movements. *J Pharmacol Exp Ther* 245:537-542, 1988b.

Tiong, G.K.L., and Olley, J.E. Effects of exposure *in utero* to methadone and buprenorphine on enkephalin levels in the developing rat brain. *Neurosci Lett* 98:101-106, 1988.

Umans, J.G., and Szeto, H.H. Precipitated opiate abstinence in utero. *Am J Obstet Gynecol* 151:441-444, 1985.

Wallach, R.C.; Jerez, E.; and Blinick, G. Comparison of pregnancies and birth during methadone detoxification and maintenance. *Pediatr Ann* 4:46-61, 1975.

Wang, C.; Pasulka, P.; Perry, B.; Pizzi, W.J.; and Schnoll, S.H. Effect of perinatal exposure on brain opioid and α_2-adrenergic receptors. *Neurobehav Toxicol Teratol* 8:399-402, 1986.

Ward, S.L.D.; Bautista, D.; Chan, L.; Derry, M.; Lisbin, A.; Dunfee, M.J.; Mills, K.S.C.; and Keens, T.G. Sudden infant death syndrome in infants of substance-abusing mothers. *J Pediatr* 117(6):876-881, 1990.

Wittman, B.K., and Segal, S. A comparison of the effects of single- and split-dose methadone administration on the fetus: Ultrasound evaluation. *Int J Addict* 26:213-218, 1991.

Zhu, Y.S., and Szeto, H.H. Morphine-induced tachycardia in fetal lambs: A bell-shaped dose-response curve. *J Pharmacol Exp Ther* 249:78-82, 1989.

Zuspan, F.P.; Gumpel, J.A.; Mejia-Zelaya, A.; Madden, J.; and Davis, R. Fetal stress from methadone withdrawal. *Am J Obstet Gynecol* 122:43-46, 1975.

AUTRORS

Margaret A.E. Jarvis, M.D.
Hoff Fellow

Sidney H. Schnoll, M.D., Ph.D.
Chairman

Division of Substance Abuse Medicine
Medical College of Virginia
Box 109
Richmond, VA 23298

Treatment Options for Drug-Exposed Infants

Stephen R. Kandall

INTRODUCTION

Despite the fact that women have been closely associated with drug use and drug addiction in the United States since the middle of the 19th century, little attention was directed at drug-related problems of women for more than 100 years. In the 1960s, however, it became increasingly obvious that maternal drug use during pregnancy was associated with a growing list of problems in the pregnant woman, fetus, neonate, and young infant. Although a small number of anecdotal reports had been published throughout the earlier part of the century, more scientifically grounded observations and studies on the perinatal effects of heroin began to be published only in the 1960s and 1970s. These studies more carefully delineated the perinatal impact of maternal use of illicit opiates such as heroin as well as maintenance medication such as methadone. These same scientific and clinical methodologies were subsequently applied to studies of the effects of maternal use of stimulants such as amphetamines in the 1960s and 1970s and cocaine, which had a resurgence in use in the 1970s and again, as "crack" cocaine, in the 1980s.

Delineation of the perinatal effects of specific individual drugs was hampered, however, by the increasing tendency of women to use multiple drugs during pregnancy. Polydrug use continues to be a common practice today, and since the clinical sequelae stemming from different maternal drugs may appear similar in the neonate, the appropriate treatment of drug-exposed newborn infants must rest on the accurate determination of the pattern of intrauterine drug exposure.

This determination is far from easy, however, as highlighted by Dicker and Leighton (1991), who compared studies that sought to determine the extent of intrauterine drug exposure in the United States in 1988 and 1989. The authors found that these estimates varied quite widely, ranging from a low of 14,000 to a high of about 700,000, with intermediate figures of 30,000 to 50,000, 100,000, and 375,000. Dicker and Leighton, using the National Hospital Discharge Survey and a multi-

plicative adjustment factor of three for underreporting, estimated the number to be close to 38,000 infants, approximately one-tenth of the most frequently cited figure (Chasnoff et al. 1989).

Difficulties in establishing accurate data are due in part to the unreliability of maternal histories of drug use, failure of obstetric care providers to fully question women regarding drug habits, fear by women that they may face repercussions in the legal and child welfare arenas if they admit to drug use, and the limitations imposed by both clinical observations and "snapshot" testing such as urine toxicologies in establishing the diagnosis of drug exposure.

Another reason for the widely disparate estimates of intrauterine drug exposure is the lack of uniform policies that govern drug testing of mothers and neonates. Hospitals employ a wide range of criteria, ranging from universal testing to selective testing based on combinations of maternal self-report, behavior, lifestyle indices, and obstetric conditions, as well as nonspecific neonatal conditions such as prematurity, intrauterine growth retardation (IUGR), poor feeding, and neurologic dysfunction. These practices have resulted in truncation of the total sample of drug-exposed infants and the selective identification of infants who should be considered at risk for reasons other than intrauterine drug exposure.

Confusion also arises from terminology that often equates two vague terms, "drug-exposed" and "drug-affected" (Dicker and Leighton 1991). "Drug-exposed" denotes infants who have been exposed to one or more drugs during part or all of the pregnancy and may or may not show obvious effects of that exposure in the newborn period. In contrast, "drug-affected" infants are defined as only those infants who have been diagnosed by hospital staff in the neonatal period as having suffered the effects of intrauterine drug exposure.

Despite obvious shortcomings, epidemiological data from throughout the United States consistently indicate that maternal drug use increased markedly in the 1980s. Threefold to fourfold increases in the number of drug-exposed newborn infants during the mid- to late-1980s were reported by many cities, including New York, Dallas, Denver, Oakland, Philadelphia, and Houston (U.S. Department of Health and Human Services 1993). Although most data originate from low-income urban populations, it has become apparent that the problem of drug use during

pregnancy crosses all racial, ethnic, geographic, and socioeconomic boundaries.

This chapter reviews clinical aspects of the neonatal abstinence syndrome following exposure to opiates and other depressants and the neurotoxicity seen in newborn infants following exposure to stimulants such as cocaine and amphetamine, details the widely accepted and more controversial therapeutic regimens currently being used in the treatment of drug-exposed infants, and outlines research questions for future consideration regarding the treatment of these infants.

NEONATAL OPIATE ABSTINENCE SYNDROME

The neonatal opiate abstinence syndrome is a generalized disorder characterized by dysfunction of the central nervous system (CNS), autonomic nervous system, gastrointestinal (GI) tract, and respiratory system.

Infants of mothers who are dependent on opioids during their pregnancy may be born with a passive dependency on those same agents. These drugs include powerful opiates such as heroin, morphine, and methadone, as well as less potent opioids such as codeine, pentazocine, and propoxyphene hydrochloride. In addition, other substances such as alcohol, barbiturates, chlordiazepoxide, diazepam, diphenhydramine, ethchlorvynol, and imipramine may produce a similar picture of neonatal abstinence. Since these substances cross the placenta, the fetus biochemically adapts to these drugs. When the umbilical cord is cut, the supply of drug is abruptly terminated. Approximately 75 percent of infants with chronic intrauterine exposure to narcotics develop an abstinence syndrome in the days or weeks after birth.

Since fetal exposure to these drugs varies based on the amount of the drug used by the mother, purity of the drug (if used illicitly), and length of usage, the occurrence, time of onset, and severity of abstinence symptomatology is not totally predictable. Abstinence symptoms from heroin and other short-acting opioids usually manifest within 48 to 72 hours after birth. Although the same is generally true for longer-acting opioids such as methadone, abstinence symptoms may appear later in some cases because methadone is stored in fetal tissue, and its rate of tissue clearance and excretion postnatally is quite variable. Abstinence symptoms are believed to appear when neonatal serum levels of

methadone drop to a certain level (Rosen and Pippenger 1976). In a few cases, usually when a mother has been treated with dosages of methadone exceeding 100 milligrams (mg) daily, the onset of major signs of the neonatal abstinence syndrome may be delayed up to 1 or 2 weeks (Kandall and Gartner 1974).

Controversy still exists as to the relationship between neonatal abstinence symptoms, maternal drug dosages, and serum levels of those drugs. A recent study found that a spectrum of relationships does exist between these variables (Doberczak et al. 1993), strengthening the general impression that lower maternal drug dosages are associated with reduced severity of neonatal abstinence symptoms. It is important to stress, however, that reduction of the maternal methadone dose may lead to an increase in use of street drugs, with an attendant increase in the risk of adverse health conditions such as human immunodeficiency virus (HIV) acquisition. Maternal methadone dosages, therefore, should be individualized and should be adequate to ensure maternal comfort and fetal well-being.

The neonatal opiate abstinence syndrome occurs in about 60 to 80 percent of heroin-exposed infants and methadone-exposed infants (Finnegan and Ehrlich 1990; Kandall et al. 1977). Individual symptoms occur with the same frequency in the two groups of infants, and severity of abstinence symptoms from methadone and from heroin cannot be compared on a milligram (mg)-to-mg basis. One study found that, probably because of differing pharmacokinetics, methadone-exposed infants required treatment more frequently, with higher dosages of medication over longer periods of time, than heroin-exposed infants (Kandall et al. 1977). Again, benefits and risks of illicit heroin use versus methadone maintenance and provision of comprehensive services must be considered when making comparisons.

Signs of neonatal abstinence are usually grouped into four categories: CNS, GI, respiratory, and autonomic nervous system. CNS signs of neonatal abstinence are usually the most obvious clinically and include irritability, tremulousness, hypertonia, and excessive crying. Opiate-exposed infants often show a voracious appetite and an exaggerated sucking drive, but coordination between sucking and swallowing is frequently abnormal (Kron et al. 1976). This incoordination poses a risk of poor nutrient intake, excessive weight loss, and suboptimal weight gain (Weinberger et al. 1986), as well as the potentially more serious complications of regurgitation and pulmonary aspiration. Abstinence-

associated seizures are seen in about 1 percent of heroin-exposed infants and about 5 to 7 percent of methadone-exposed infants (Herzlinger et al. 1977). GI symptoms of abstinence include vomiting and diarrhea. Respiratory symptoms include tachypnea, hyperpnea, respiratory alkalosis, cyanosis, and apnea. Autonomic nervous system signs of abstinence include sneezing, yawning, tearing, sweating, and hyperpyrexia.

Neonates exposed to maternal doses of phenobarbital of at least 90 mg/day for 12 weeks prior to delivery may also exhibit symptoms of abstinence. Barbiturate-dependent infants have symptoms similar to those of opiate abstinence such as hyperactivity, tremors, crying, vomiting, and diarrhea, usually beginning 4 to 8 days after birth (Desmond et al. 1972).

TREATMENT

The appropriate treatment of drug-exposed infants rests on sound principles of diagnosis and assessment. Since individual signs and symptoms of the neonatal abstinence syndrome tend to be nonspecific, other diagnoses such as sepsis, electrolyte imbalance, hypoglycemia, CNS hemorrhage, and ischemia must always be considered as part of the infant assessment. This consideration is especially relevant since maternal drug abuse frequently occurs in a clinical and social environment that poses multiple medical risks to the infant.

It is also important to gather objective information about the mother's drug use to provide optimal treatment for the infant. Data gathering should include a comprehensive interview with the mother, reports from drug treatment facilities and social service agencies, and more objective measures such as urine toxicology assays for drugs and their metabolites. Recognizing the limitations of urine testing, it is now known that drug exposure may be detected over a wider gestational period by assay of infant meconium samples or infant and maternal hair samples (Callahan et al. 1992; Ostrea et al. 1992).

Since the occurrence, time of onset, and ultimate severity of the neonatal abstinence syndrome is not totally predictable, the use of a semiobjective abstinence score is strongly recommended. This scoring system should. be used to monitor the onset, progression, spontaneous regression, and response to treatment of the neonatal abstinence syndrome.

Date: Daily Weight:

System	Signs and Symptoms	Score	AM	PM	Comments
	Excessive High Pitched (other) Cry *Continuous High Pitched (other) Cry*	*2* *3*			
	Sleeps <1 hour after feeding *Sleeps <2 hours after feeding* *Sleeps <3 hours after feeding*	*3* *2* *1*			
	Hyperactive Moro reflex *Markedly Hyperactive Moro reflex*	*2* *3*			
	Mild Tremors Disturbed *Moderate-Severe Tremors Disturbed*	*1* *2*			
	Mild Tremors Undisturbed *Moderate-Severe Tremors Undisturbed*	*3* *4*			
	Increased Muscle Tone	*2*			
	Excoriation (specific areas)	*1*			
	Myoclonic Jerks	*3*			
	Generalized Convulsions	*5*			
	Sweating	*1*			
	Fever <101 (99-100.8F/37.2-38.2C) *Fever >101 (38.4C and higher)*	*1* *2*			
	Frequent Yawning (>3-4 times/ interval)	*1*			
	Mottling	*1*			
	Nasal Stuffiness	*1*			
	Sneezing (>3-4 times/ interval)	*1*			
	Nasal Flaring	*2*			
	Respiratory Rate >60/min. *Respiratory Rate >60/min. with retractions*	*1* *2*			
	Excessive Sucking	*1*			
	Poor Feeding	*2*			
	Regurgitation *Projectile Vomiting*	*2* *3*			
	Loose Stools *Watery Stools*	*2* *3*			

TOTAL SCORE

INITIALS OF SCORER

FIGURE 1. *Neonatal abstinence score sheet.*

SOURCE: From Finnegan, L.P. Neonatal abstinence syndrome: assessment and pharmacology. In Rubatelli, F.F., and Granati, L., eds. *Neonatal Therapy: An Update.* New York: Excerpta Medica, 1986.

The most comprehensive abstinence scoring system is that proposed by Finnegan (Finnegan and Kaltenbach 1992) (figure 1). This scoring system rates 21 symptoms commonly seen in the neonatal abstinence syndrome. Each is assigned an individual score based on its postulated relationship with the outcome variables of morbidity and mortality. Infants are scored 2 hours after birth and every 4 hours thereafter. Infants

may be scored every 2 hours if the total severity score exceeds 8, but scoring every 4 hours may be resumed if the severity score decreases. All symptoms exhibited during the entire 2-hour or 4-hour interval should be included. In addition to the quantitative scoring, relevant clinical observations should be noted in the "comments" column on the scoring sheet. Using the Finnegan scale, specific pharmacologic treatment to control opiate abstinence symptoms is usually initiated when the total severity score exceeds 8 for three consecutive scoring periods or when the average of three consecutive scores is 8 or higher.

While the infant is undergoing assessment with the aid of this scoring scale to determine whether specific treatment will be necessary, general treatment measures should be instituted. Environmental modification, such as swaddling in a prone or side-lying position on soft bedding material in a quiet, dimly lit room, has been generally recommended despite the lack of firm evidence of its efficacy in controlling the severity of neonatal abstinence symptoms (Ostrea et al. 1976). Such measures also place additional burdens on medical and nursing staff to monitor vital signs, prevent hyperthermia, note excoriations, and detect seizures. In addition, placing infants in the prone position for sleep, especially on soft bedding material, has recently been implicated in higher rates of sudden infant death syndrome (SIDS) in infants (Ponsonby et al. 1993). This is especially relevant in opiate-exposed infants, since their risk of SIDS is approximately three- to fourfold that of infants who were not drug exposed (Kandall et al. 1993).

Gentle handling based on individual infant cues and control of external stimulation appear to benefit the opiate-exposed infant. One study has suggested that opiate-exposed infants benefit from being placed on nonoscillating waterbeds (Oro and Dixon 1988). Infants treated with medication and waterbeds as adjunctive therapy had lower severity scores on day 5 and a better pattern of weight gain than infants conventionally treated with pharmacotherapy alone.

Supportive treatment measures also include provision of adequate fluids and calories based on the infant's individual needs. Abnormal postnatal weight changes should be anticipated due to the infant's hypermetabolic state, excessive fluid loss, and suboptimal intake. One study (Weinberger et al. 1986) showed that infants with mild abstinence symptoms lost an average of 4 percent of their birth weight, reached a nadir on day 3, and regained their birth weight by the end of the first week. Newborns who developed more severe abstinence symptoms lost more weight and

required a longer time to regain their birth weight. These data support both the need for prompt initiation of specific pharmacologic treatment of neonatal abstinence symptoms and the importance of nutritional support of those infants.

Breastfeeding should be offered, and may even be encouraged in those infants born to mothers who are well maintained on methadone, not abusing other substances, and HIV negative. Breastfeeding enhances the mother-infant bond, an important consideration when mothers and babies are separated because of prolonged hospitalization. Although methadone does pass to the infant in breast milk, no study has documented the impact of breastfeeding on the course of neonatal abstinence symptoms.

PHARMACOTHERAPY

Naloxone is often used in the delivery room to reverse the depressant effects on the newborn infant of medications such as meperidine, which may be used to provide analgesia for the parturient. Naloxone is usually contraindicated in opiate-exposed infants since its use may precipitate acute abstinence symptoms. Naloxone is not specifically contraindicated following intrauterine exposure to cocaine, but caretakers must remember that cocaine use may be accompanied by narcotic use; in this circumstance, naloxone may precipitate acute opiate abstinence symptoms in the infant.

In the neonatal period, specific pharmacotherapy to control opiate abstinence symptoms should be provided when the severity score (discussed earlier) reaches a predetermined level. Therapy is aimed at clinical stabilization of those narcotic-exposed infants who require specific treatment, followed by gradual reduction of the medication with close and objective assessment. Failure to treat the effects of neonatal abstinence may result in significant morbidity, and mortality may result from excessive fluid loss, respiratory distress, seizures, vomiting and aspiration, or hyperpyrexia. Pharmacotherapeutic control of the neonatal opiate abstinence syndrome can be accomplished with either a substitute opiate such as paregoric (camphorated tincture of opium) or a nonspecific CNS depressant such as phenobarbital. The advantages of paregoric include its oral administration, its lack of significant adverse effects, its wide margin of safety because of the low dosage needed to control abstinence symptoms, and its short half-life. Phenobarbital also controls the major signs of abstinence quite adequately and provides much

broader coverage in those cases of exposure to both opiates and depressants. Phenobarbital appears to be the logical choice to treat neonatal dependence on barbiturates. Phenobarbital, however, has the potential disadvantages of producing depression of neonatal respiration and sucking, especially when the medication is used at higher dosage ranges (see below).

Comparison of phenobarbital and paregoric suggest the superiority of the latter in the treatment of neonatal opiate abstinence symptoms. Finnegan and Ehrlich (1990), in a study of 176 infants, found that paregoric was better able than phenobarbital to control signs of opiate abstinence, although the treatment period with paregoric was slightly longer (24 days versus 20 days). In that study, paregoric was also more successful in the control of abstinence symptoms when only one therapeutic agent was used.

In another comparative study, Kandall and colleagues (1983) found that paregoric and phenobarbital, administered randomly to 153 passively addicted infants, initially controlled signs of abstinence equally well. Of the 12 infants who developed abstinence-associated seizures, however, 7 had been treated with phenobarbital (n = 62), while none of the infants treated with paregoric (n = 49) developed seizures. The authors note that since a low-dosage phenobarbital regimen was used, a protective blood level of the drug may not have been achieved in light of phenobarbital's ability to induce microsomal enzymes and speed the disposition of methadone from tissue stores in the neonate.

Since sucking disorders are frequently seen in the neonatal opiate abstinence syndrome and since sucking represents an important function of neurobehavioral integration in the neonate, Kron and colleagues (1976) compared the effect of treatment regimens on this behavior. Opiate-exposed infants treated with paregoric tended to suck more vigorously and with more normal periodicity than those infants treated either with phenobarbital or with no specific therapy.

Additional evidence for the superiority of paregoric therapy was provided by Kaltenbach and Finnegan (1986). In that study of infant outcome following intrauterine drug exposure, the authors found that treatment with paregoric was far more successful in controlling neonatal abstinence symptoms than was either phenobarbital or diazepam.

Following some initial enthusiasm over the use of diazepam, it is now recognized that diazepam may cause respiratory and CNS depression in the neonate. In addition, diazepam has been shown to provide poor prophylaxis and treatment for abstinence-associated seizures (Herzlinger et al. 1977). The use of chlorpromazine to treat the neonatal opiate abstinence syndrome is limited by the drug's potential hepatotoxicity and its adverse effect on the extrapyramidal tracts of the CNS. Other depressant agents such as morphine, methadone, and laudanum have been used to treat neonatal abstinence symptoms, but insufficient data exist to assess their efficacy and limitations.

Paregoric

A consensus panel convened in 1992 by the Center for Substance Abuse Treatment (CSAT) has promulgated useful guidelines for the treatment of opioid-exposed infants (U.S. Department of Health and Human Services 1993). The panel recommended paregoric as the treatment of choice (figure 2). Paregoric treatment is usually begun at a dosage of 0.2 milliliters (ml) every 3 hours by mouth. If the severity of abstinence symptoms does not decrease, the stabilizing dosage is raised by 0.05 ml with each succeeding dose to a maximum dosage of 0.4 ml that is administered until the severity score decreases to less than 8. Once the infant is stabilized, the stabilizing dosage is maintained for 3 to 5 days. Following stabilization, paregoric may be slowly decreased by 0.05 ml per kilogram (kg) every other day, as dictated by the severity score. While the dosage is being reduced, the dosing interval (every 3 hours) should remain the same. Paregoric may be discontinued once the infant is stable on 0.05 ml every 3 hours. Following detoxification, the infant should be assessed with the aid of the severity scale for 1 to 2 days in the hospital to observe for rebound symptomatology.

A slightly different treatment regimen has been suggested by Finnegan and Kaltenbach (1992). In that regimen, paregoric is administered every 4 hours with the dosage based on the severity score and the infant's weight. Infants with abstinence scores of 8 to 10 are treated with a total dose of 0.8 ml/kg/day; those with scores of 11 to 13 receive 1.2 ml/kg/day; those with scores of 14 to 16 receive 1.6 ml/kg/day; those with scores of 17 or above receive 2.0 ml/kg/day. Once the infant is stabilized, paregoric may be slowly reduced by 10 percent of the total daily dosage every 24 hours, as dictated by the severity score. Paregoric therapy may be discontinued once the infant is stable on a dosage of

- Paregoric (camphorated tincture of opium, 0.4 mg/ml morphine): Begin with 0.2 ml every 3 hours PO. If abstinence uncontrolled, increase by 0.05 ml each dose to a maximum of 0.4 ml every 3 hours. After stabilization for 5 days, reduce the dose gradually by 0.05 ml/dose every other day, using severity score. Observe off medications 1-2 days.

- Phenobarbital: Loading dose 5 mg/kg IV, IM, or PO. Maintain at 3-5 mg/kg/day PO, divided every 8 hours. May increase dose by 1 mg/kg/day to maximum of 10 mg/kg/day. Once stable, reduce by 1 mg/kg/day every other day, using severity score. Observe off medications 1-2 days.

FIGURE 2. *Pharmacologic treatment of opiate abstinence.*

0.5 ml/kg/day. Following discontinuance of treatment, the infant should be observed in the hospital for 2 days. With either of the two regimens, close observation of the infant and use of a severity scoring system to monitor the need for and effect of treatment is of paramount importance.

The anticipated length of treatment of the neonatal opiate abstinence syndrome with paregoric cannot be predicted with certainty. Kandall and colleagues (1977) found a mean treatment time of 10 days for the effects of heroin abstinence, 20 days for the effects of abstinence from heroin and methadone, and 29 days for the effects of abstinence from methadone alone. Although dose equivalencies obviously cannot be calculated for heroin and methadone, the pharmacokinetics of methadone, including tissue storage, suggest that these comparative treatment data can be generalized. In another confirmatory study, Finnegan and Ehrlich (1990) found a mean treatment time of opiate abstinence symptoms with paregoric to be 24 days.

Phenobarbital

The CSAT Consensus Panel found phenobarbital to be a useful agent in treatment of the neonatal abstinence syndrome (U.S. Department of

Health and Human Services 1993). Phenobarbital treatment can usually be started at 5 mg/kg/day as a loading dose given either intramuscularly (IM) or intravenously (IV) to ensure effective absorption (figure 2). Using the same severity scale as described above, an oral maintenance dose is reached by increasing the dose by 1 mg/kg to a maximum of 10 mg/kg/day until the severity score indicates that the effects of abstinence are controlled. Because of its longer half-life compared to paregoric, phenobarbital is administered every 8 hours in this regimen. Following stabilization for about 5 days, the phenobarbital dosage may be lowered by 1 mg/kg/day every other day, with monitoring of the severity score. In this regimen, phenobarbital levels are monitored only when clinically indicated (e.g., poor control of abstinence symptoms or excessive sleepiness of the infant).

The phenobarbital treatment regimen proposed by Finnegan and Kaltenbach (1992) is somewhat more rigorous. This regimen relies heavily on frequent monitoring of plasma phenobarbital levels, with titration of the dosage to both the drug level and severity score. This regimen begins with a loading dosage of 20 mg/kg/day, followed by a maintenance dose range of 2 to 6 mg administered daily if the plasma phenobarbital level is therapeutic and the infant is clinically stable. If the plasma concentration needs to be raised, this is accomplished by increasing the frequency of administration to every 12 hours. When an optimal plasma level is obtained (approximately 20 micrograms (mcg)/ml) and the severity score is less than 8, the phenobarbital dosage is maintained for 72 hours. A maintenance dosage of 4 to 6 mg/kg/day is usually adequate to maintain clinical stability.

If the total score continues to exceed 8, Finnegan and Kaltenbach (1992) recommend increasing the dosage by administering 10 mg/kg of phenobarbital every 12 hours until control is achieved, the blood level reaches 70 mcg/ml, or the infant becomes clinically toxic. Following a clinically stable period of 72 hours, reduction of the serum phenobarbital level by about 15 percent per day can usually be accomplished by administering phenobarbital at a dosage of 2 mg/kg/day. Minor variations in this dosage are based on the clinical severity score and serum phenobarbital level. Phenobarbital is discontinued when the serum level falls below 10 mcg/ml and the severity score is less than 8. In the next 72 hours, if the infant remains stable, he or she may be discharged. The length of treatment of the neonatal opiate abstinence syndrome with phenobarbital is similar to that with paregoric. In one study using the

above regimen, Finnegan and Ehrlich (1990) found a mean treatment time of 20 days with phenobarbital compared with 24 days with paregoric.

The regimen detailed by Finnegan and Kaltenbach (1992) offers the advantage of extremely careful assessment and documentation of the infant's therapeutic response. It has the disadvantage, however, of requiring frequent clinical assessments by trained personnel as well as drawing of blood for drug levels, which is expensive, time-consuming, and painful to the infant.

Despite some methodologic variation, all of the therapeutic regimens are based on the following principles: complete assessment of the patterns of prenatal drug use will allow for the most appropriate treatment of neonatal abstinence symptoms; an abstinence scoring system should be used to guide the initiation, maintenance, and discontinuation of drug treatment; paregoric represents the most effective treatment when the neonate has had either sole or major exposure to opiates; phenobarbital is most effective when the infant has been exposed to nonopiates only; and other drugs such as diazepam and chlorpromazine are not appropriate for the treatment of the neonatal opiate abstinence syndrome. Other opiates, such as morphine and methadone, lack enough published data to fully assess their efficacy and safety.

ABSTINENCE-ASSOCIATED SEIZURES

As noted earlier, seizures occur in about 1 percent of heroin-exposed infants and about 5 percent of methadone-exposed infants (Herzlinger et al. 1977). The etiology of these seizures is not well understood. Abstinence-associated seizures occur unpredictably, tend to be myoclonic in type, generally occur between 1 and 2 weeks after birth, and are more common when either phenobarbital or no drug is used to treat early signs of opiate abstinence. Part of the reason why studies cite different incidences of these seizures may be the fact that these seizures can easily be missed if tht infants are swaddled in a dimly lit room.

If seizures occur, the infant should have a full sepsis workup, including lumbar puncture, to rule out systemic or CNS infection. A complete metabolic evaluation, including blood sugar, electrolytes, calcium, phosphorus, and magnesium levels should also be performed. CNS imaging, such as ultrasound, computerized axial tomography (CAT)

scan, or magnetic resonance imaging (MRI), should be obtained. An electroencephalogram (EEG) will be abnormal in about 50 percent of the infants, and serial EEGs may be useful as a guide to further assessment, treatment, and followup.

Abstinence-associated seizures should initially be treated with IV phenobarbital at a loading dose of 10 to 20 mg/kg. If the lower dose is used, a second dose of 10 mg/kg can be administered 10 minutes later if seizures persist. When seizures are controlled, a serum phenobarbital level should be obtained in 24 hours, just prior to starting maintenance therapy at 3 to 5 mg/kg/day divided into two doses. Paregoric therapy should also be started if the infant has not been previously treated.

Little data exist as to the continuing management of infants with abstinence-associated seizures. It appears reasonable to base the ongoing management of these infants on clinical and laboratory assessments. If other neuropathology is excluded, these seizures tend to be self-limited. If the first EEG is normal or the followup EEG is normal in the course of the infant's neonatal stay, medications may be tapered under close observation. Once paregoric has been given, phenobarbital may be slowly discontinued at the rate of 1 mg/kg every other day. Following discontinuation of phenobarbital, paregoric may be slowly discontinued as outlined above.

If the seizures are not easily controlled despite the administration of phenobarbital and paregoric in adequate doses, other anticonvulsant medications such as diphenylhydantoin may be required. In those cases, however, it is likely that another cause for the persistent seizures will be found. If the EEGs do not normalize in spite of good clinical control of seizures, the infant should be discharged from the hospital on maintenance anticonvulsant treatment, and further management decisions should be made jointly with a pediatric neurologist.

Serial observations of these infants, as well as followup studies at 1 year of age, suggest that these seizures carry an excellent prognosis in the short term. Doberczak et al. (1988a) found normalization of neurologic and electroencephalographic abnormalities in these infants during the first year of life. In addition, Bayley developmental test scores remained normal during that period of observation. In that study, 7 of the 14 infants were able to be discharged from the nursery without anticonvulsant medication.

COCAINE

Although the use of cocaine in the United States dates back to the 1870s the recent epidemic of smokeable cocaine ("crack") in the 1980s coupled with increased drug use by pregnant women and the epidemic of perinatal HIV and acquired immunodeficiency syndrome, brought a new level of concern to the impact of cocaine use during pregnancy.

As with opiates, life circumstances and behavior of the mother often place the fetus and newborn infant at increased risk for suboptimal perinatal outcome. Many obstetric complications stem from the potent vasoconstrictive properties of cocaine due to the drug's inhibition of neurotransmitter uptake in the synaptic cleft. Vasoconstriction in the uteroplacental circulation may lead to acute and chronic fetal hypoxia, IUGR, and congenital anomalies.

Similar to treatment for exposure to opiates, treatment of the cocaine-exposed neonate rests on an objective assessment of the impact of intrauterine drug exposure. But unlike opiate-exposed infants, cocaine-exposed infants do not undergo a physical abstinence or withdrawal. These infants do, however, show signs of neurotoxicity such as transient irritability and tremulousness (Chasnoff et al. 1985; Doberczak et al. 1988b). Following this period of CNS irritability, cocaine-exposed infants tend to experience a period of hyporeactivity, lethargy, and poor interaction with caretakers. In addition, specific neurobehavioral testing has led to a general agreement that these infants evidence lability of state, with wide swings from hyperalertness to reduced reactivity, decreased habituation, and visual tracking difficulties (Chasnoff et al. 1989; Eisen et al. 1991; Mayes et al. 1993).

Cocaine-exposed infants show a very wide spectrum of effects ranging from a lack of obvious symptoms, to neurobehavioral dysfunction (described above), to more dramatic complications such as seizures (Kramer et al. 1990) and cerebrovascular accidents (CVAs) (Chasnoff et al. 1986). These serious complications may be due either to an ischemic insult secondary to vasoconstriction or to hemorrhage from acute hypertension. EEG abnormalities have been reported in as many as 50 percent of cocaine-exposed infants in one study (Doberczak et al. 1988b), but this observation was not confirmed in another study (Legido et al. 1992).

In addition, echoencephalographic (ECHO) abnormalities have been reported in 35 percent of infants exposed to either cocaine or methamphetmaines (Dixon and Bejar 1989). These abnormalities include ischemic injury with cavitary lesions (8 percent), intraventricular hemorrhage (12 percent), subependymal hemorrhage (11 percent), subarachnoid hemorrhage (14 percent), and ventricular dilatation (10 percent). In another study of infants with birth weights under 1,500 grams, however, cocaine exposure did not increase the incidence of intraventricular hemorrhage or periventricular leukomalacia compared with controls (Dusick et al. 1993).

TREATMENT

Since cocaine-exposed infants differ quite significantly from opiate-exposed infants, use of the opiate abstinence assessment scale is inappropriate following cocaine exposure. The subtlety of cocaine-related signs and the nature of those neurological abnormalities suggest the need for an assessment such as the Brazelton Neonatal Behavioral Assessment Scale. An appropriate assessment should focus on areas such as habituation, responsivity, state, and motor assessment as well as a more general neurologic evaluation.

Although most cocaine-exposed infants show only modest signs of neurodysfunction that do not require the use of pharmacotherapeutic agents, some infants who are excessively irritable appear to benefit from a short course of treatment with phenobarbital. In such instances, phenobarbital treatment is rarely needed for more than a few days and, following control of the infant's irritability, therapy may be discontinued without tapering. Treatment with an opiate such as paregoric is inappropriate unless significant maternal opiate use compounds the cocaine exposure.

Seizures due to cocaine neurotoxicity should be treated acutely with a loading dose of 10 to 20 mg/kg of phenobarbital IV. If the lower dose of 10 mg/kg is used and seizures persist, that dose should be repeated in 10 to 15 minutes. While seizure control is being accomplished, diagnostic workup should be initiated; this workup usually includes determination of electrolytes and serum glucose levels, full sepsis workup including lumbar puncture, and CNS imaging by ultrasound and either CAT scan or MRI.

If seizures are controlled with phenobarbital, continued seizure management should be based on clinical assessment and results of the diagnostic workup. Phenobarbital levels should be drawn 24 hours after administration of the loading dose. If levels are in the therapeutic range, maintenance therapy, usually at a dose of 5 mg/kg/day, should be started. Refractory seizures, such as may occur following a CVA, may require the addition of other anticonvulsants (e.g., phenytoins) to the treatment regimen.

An important part of the therapeutic management of cocaine-exposed infants is an appropriate nursery environment. In contrast to opiate-exposed infants, whose irritability draws the attention of the nursery staff, cocaine-exposed infants tend towards hyporeactivity and decreased social responsiveness. This may result in these infants being left for periods of time without appropriate stimulation. Cocaine-exposed infants, therefore, should be provided with an individualized program of structured physical contact, including gentle handling with support of the head and body, soft social talking, and eye contact without overstimulation.

As with maternal opiate use, intervention programs for cocaine-exposed infants should include mothers and fathers of the infants as much as possible. Parents benefit significantly from inclusion in the assessment and treatment of their infants. This is especially true with the involvement of trained personnel who are skilled in both assessing the infant and working with the parents in a supportive and nonjudgmental manner.

Breastfeeding, which could foster mother-infant bonding, is contra-indicated if the mother is actively using cocaine. Cocaine may readily pass to the infant through breast milk and may produce a neonatal neurotoxic syndrome including hypertonia, tremors, apnea, and seizures (Chaney et al. 1988). In addition, breastfeeding is contraindicated when the mother is HIV positive due to transmissibility of the virus in breast milk.

AMPHETAMINES

Amphetamine stimulates the release and blocks the reuptake of neurotransmitters, similar to the action of cocaine. Methamphetamine is structurally similar to amphetamine but has relatively greater CNS effects and less prominent peripheral actions.

The impacts of cocaine and amphetamines on pregnancy appear to be similar. Two studies of amphetamine-exposed infants in Sweden by Eriksson and colleagues (1978, 1981) reported a high perinatal mortality rate, an increased incidence of low birth weight and congenital malformations, and neurologic abnormalities including drowsiness, poor feeding, and seizures. Neither of the reports commented on the need for specific treatment in the newborn period.

More recently, Oro and Dixon (1987) found a wide range of abnormalities including abnormal sleep patterns, tremors, poor feeding, hyperactive reflexes, abnormal cry, state disorganization, vomiting, sneezing, and tachypnea in a group of 46 infants following intrauterine exposure to cocaine and methamphetamines. Despite these findings, only 1 of 28 methamphetamine-exposed infants required specific treatment.

In a study cited previously, Dixon and Bejar (1989) found ECHO abnormalities in 35 percent of infants following intrauterine exposure to cocaine and methamphetamines. Despite these impressive findings, neurobehavioral assessment of the infants did not correlate well with ECHO abnormalities, perhaps because damage in the frontal lobes and basal ganglia may produce clinical abnormalities only later in infancy.

FUTURE RESEARCH

Although much has been learned recently about the clinical management of infants following intrauterine exposure to narcotics and stimulants, questions remain that might be addressed in the future.

1. Can the severity of the neonatal opiate abstinence syndrome as well as the need for specific treatment of the newborn infant be reduced through modification of the maternal methadone dosage during pregnancy? Controversy still exists over the relationship of maternal drug dosages to severity of the effects of neonatal abstinence. In addition, it is still unclear whether careful discontinuation or even lowering of the maternal dosage can be undertaken safely, given the complexities of drug pharmacokinetics during pregnancy and the tendency of women to abuse street drugs and thus increase health-related risks such as HIV acquisition when maintenance therapy is reduced.

2. What is the impact, both individually and combined, of exposure to other neurotoxins such as HIV, syphilis, alcohol, and lead that frequently complicate drug use? What are the implications of these interactions on treatment regimens in the newborn period?

3. Can efficacy of treatment with agents such as paregoric and phenobarbital be measured with more precision than at present? Can more objective assessments such as sucking response (Kron et al. 1976) or cry analysis (Corwin et al. 1992) provide useful data as to the most appropriate therapy for drug-exposed infants?

4. Can new delivery systems, such as transdermal patches, be developed to treat drug-exposed infants? If the infant is vomiting and has diarrhea, oral medications may be inappropriate; if the infant is hyperirritable, IM medications may worsen the effects of the abstinence. What are the transdermal kinetics of medications in the newborn period?

5. What is the most effective way to prevent or control abstinence-associated seizures? What is the mechanism of these seizures?

6. What is the impact of breastfeeding on the treatment of neonatal abstinence symptoms? Can drug assays of breast milk in conjunction with careful clinical assessment be useful in treating these infants?

7. What is the role of intervention in the management of drug-exposed infants? Which of these therapies really ameliorates neonatal signs and symptoms of abstinence or neurotoxicity? How carefully do these therapies have to be tailored to the individual infant? Are there general interventions that should form an integral part of the therapeutic approach to drug-exposed infants?

8. Would complementary therapies such as acupressure, massage, and hydrotherapy prove useful as specific or adjunctive therapy for drug-exposed infants? How would such therapies be objectively evaluated?

REFERENCES

Callahan, C.M.; Grant, T.M.; Phipps, P.; Clark, G.; Novack, A.H.; Streissguth, A.P.; and Raisys, V.A. Measurement of gestational cocaine exposure: Sensitivity of infants' hair, meconium, and urine. *J Pediatr* 120:763-768, 1992.

Chaney, N.E.; Franke, J.; and Wadlington, W.B. Cocaine convulsions in a breast-feeding baby. *J Pediutr* 112:134-135, 1988.

Chasnoff, I.J.; Bums, W.J.; Schnoll, S.H.; and Bums, K. Cocaine use in pregnancy. *N Engl J Med* 313:666-669, 1985.

Chasnoff, I.J.; Bussey, M.E.; Savich, R.; and Stack, C.M. Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 108:456-459, 1986.

Chasnoff, I.J.; Griffith, D.R.; MacGregor, S.; Dirkes, K.; and Bums, K.A. Temporal patterns of cocaine use in pregnancy. *JAMA* 261:1741-1744, 1989.

Chasnoff, I.J. Drug use and women: Establishing a standard of *care. Ann N Y Acad Sci* 562:208-210, 1989.

Corwin, M.J.; Lester, B.M.; Sepkoski, C.; McLaughlin, S.; Kayne, H.; and Golub, H.L. Effects of in utero cocaine exposure on newborn acoustical cry characteristics. *Pediatrics 89:* 1199-1203, 1992.

Desmond, M.M.; Schwanecke, R.P.; Wilson, G.S.; Yasunaga, S.; and Burgdorff, I. Maternal barbiturate utilization and neonatal withdrawal symptomatology. *J Pediatr* 80:190-197, 1972.

Dicker, M., and Leighton, E. Trends in diagnosed drug problems among newborns: United States, 1979-1987. *Drug Alcohol Depend* 28:151-165, 1991.

Dixon, S.D., and Bejar, R. Echoencephalographic findings in neonates associated with maternal cocaine and methamphetamine use: Incidence and clinical correlates. *J Pediatr* 115:770-778, 1989.

Doberczak, T.M.; Shanzer, S.; Cutler, R.; Senie, R.; Loucopoulos, J.; and Kandall, S.R. One-year follow-up of infants with abstinence-associated seizures. *Arch Neurol* 45:649-653, 1988a.

Doberczak, T.M.; Shanzer, S.; Senie, R.T.; and Kandall, S.R. Neonatal neurologic and electroencephalographic effects of intrauterine cocaine exposure. *J Pediatr* 113:354-358, 1988b.

Doberczak, T.M.; Kandall, S.R.; and Friedmann, P. Relationships between maternal methadone dosage, maternal-neonatal methadone levels, and neonatal withdrawal. *Obstet Gynecol* 81:936-940, 1993.

Dusick, A.M.; Covert, R.F.; Schreiber, M.D.; Yee, G.T.; Browne, S.P.; Moore, C.M.; and Tebbett, I.R. Risk of intracranial hemorrhage and other adverse outcomes after cocaine exposure in a cohort of 323 very low birth weight infants. *J Pediatr* 122:438-445, 1993.

Eisen, L.N.; Field, T.M.; Bandstra, E.S.; Roberts, J.P.; Morrow, C.; Larson, S.K.; and Steele, B.M. Perinatal cocaine effects on neonatal stress behavior and performance on the Brazelton scale. *Pediatrics* 88:477-480, 1991.

Eriksson, M.; Larsson, G.; Winbladh, B.; and Zetterstrom, R. The influence of amphetamine addiction on pregnancy and the newborn infant. *Acta Paediatr Scand* 67:95-99, 1978.

Eriksson, M.; Larsson, G.; and Zetterstrom, R. Amphetamine addiction and pregnancy. *Acta Obstet Gynecol Stand* 60:253-259, 1981.

Finnegan, L.P., and Ehrlich, S.M. Maternal drug abuse during pregnancy: Evaluation and pharmacotherapy for neonatal abstinence. *Mod Methods Pharmacol Test Eva1 Drugs Abuse* 6:255-263, 1990.

Finnegan, L.P., and Kaltenbach, K. Neonatal abstinence syndrome. In: Hoekelman, R.A.; Friedman, S.B.; Nelson, N.; and Seidel, H.M., eds. *Primary Pediatric Care.* 2d ed. St. Louis: C.V. Mosby, 1992. pp. 1367-1378.

Herzlinger, R.A.; Kandall, S.R.; and Vaughan, H.G. Neonatal seizures associated with narcotic withdrawal. *J Pediatr* 91:638-641, 1977.

Kaltenbach, K., and Finnegan, L.P. Neonatal abstinence syndrome, pharmacotherapy and developmental outcome. *Neurobehav Toxicol Teratol* 8:353-355, 1986.

Kandall, S.R., and Gartner, L.M. Late presentation of drug withdrawal symptoms in newborns. *Am J Dis Child* 127:58-61, 1974.

Kandall, S.R.; Albin, S.; Gartner, L.M.; Lee, K.S.; Eidelman, A.; and Lowinson, J. The narcotic-dependent mother: Fetal and neonatal consequences. *Early Hum Dev* 1/2:159-169, 1977.

Kandall, S.R. ; Doberczak, T.M.; Mauer, K.R.; Strashun, R.H.; and Korts, D.C. Opiate v CNS depressant therapy in neonatal drug abstinence syndrome. *Am J Dis Child* 137:378-382, 1983.

Kandall, S.R.; Gaines, J.; Habel, L.; Davidson, G.; and Jessop, D. Relationship of maternal substance abuse to subsequent sudden infant death syndrome in offspring. *J Pediatr* 123:120-126, 1993.

Kramer, L.D.; Locke, G.E.; Ogunyemi, A.; and Nelson, L. Neonatal cocaine-related seizures. *J Child Neural* 5:60-64, 1990.

Kron, R.E.; Litt, M.; Phoenix, M.D.; and Finnegan, L.P. Neonatal narcotic abstinence: Effects of pharmacotherapeutic agents and maternal drug usage on nutritive sucking behavior. *J Pediatr 88:637-*641. 1976.

Legido, A.; Clancy, R.R.; Spitzer, A.R.; and Finnegan, L.P. Electroencephalographic and behavioral-state studies in infants of cocaine-addicted mothers. *Am J Dis Child* 146:748-752, 1992.

Mayes, L.C.; Granger, R.H.; Frank, M.A.; Schottenfeld, R.; and Bornstein, M.H. Neurobehavioral profiles of neonates exposed to cocaine prenatally. *Pediatrics* 91:778-783, 1993.

Oro, A.S., and Dixon, S.D. Perinatal cocaine and methamphetamine exposure: Maternal and neonatal correlates. *J Pediatr* 111:571-578, 1987.

Oro, A.S., and Dixon, SD. Waterbed care of narcotic-exposed neonates. *Am J Dis Child* 142:186-188, 1988.

Ostrea, E.M.; Chavez, C.J.; and Strauss, M.E. A study of factors that influence the severity of neonatal narcotic withdrawal. *J Pediatr* 88:642-645, 1976.

Ostrea, E.M.; Brady, M.; Gause, S.; Raymundo, A.L.; and Stevens, M. Drug screening of newborns by meconium analysis: A large-scale, prospective, epidemiologic study. *Pediatrics* 89:107-113, 1992.

Ponsonby, A.L.; Dwyer, T.; Gibbons, L.E.; Cochrane, J.; and Wang, Y.G. Factors potentiating the risk of sudden infant death syndrome associated with the prone position. *N Engl J Med* 329:377-382, 1993.

Rosen, T.S., and Pippenger, C.E. Pharmacologic observations on the neonatal withdrawal syndrome. *J Pediatr* 88:1044-1048, 1976.

U.S. Department of Health and Human Services. Improving treatment for drug-exposed infants: The recommendations of a consensus panel. In: U.S. Department of Health and Human Services, ed. *Treatment Improvement Protocol (TIP).* Center for Substance Abuse Treatment. DHHS Pub. No. (SMA)93-2011. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1993.

Weinberger, S.M.; Kandall, S.R.; Doberczak, T.M.; Thornton, J.C.; and Bernstein, J. Early weight-change patterns in neonatal abstinence. *Am J Dis Child* 140:829-832, 1986.

AUTHOR

Stephen R. Kandall, M.D.
Chief, Division of Neonatology
Beth Israel Medical Center
First Avenue at 16th Street
New York, NY 10003

Opioid Receptor Approaches for the Development of Medications for Pregnant Women

Hazel H. Szeto

INTRODUCTION

Opiates are widely used and abused by pregnant women across the country. Acutely, opiates are used in late pregnancy for the relief of labor pain. Chronically, methadone is used in the treatment of opiate addicts throughout pregnancy. Both acute and chronic use of opiates are known to result in a variety of adverse effects on pregnancy outcome. Thus, there is clearly a need for the development of a better opioid for pregnant women with fewer adverse effects on the fetus and neonate.

Opiates may adversely affect the fetus *directly* via placental transfer or *indirectly* by altering maternal-placental physiology. All available opiates are readily distributed to the fetus and can be shown to affect fetal cardiovascular, respiratory, neurobehavioral, metabolic, and neuroendocrine functions. Opiates may also alter maternal glucose regulation, decrease arterial pressure and uterine blood flow, and depress respiratory function. These actions may compromise the delivery of oxygen and substrates to the fetus. One approach toward the development of a better opioid may be to design molecules that would have more restricted placental transfer by virtue of their physiochemical properties. This would reduce the *direct* actions of opioids on the fetus. However, this pharmacokinetic approach does not address the problem of *indirect* drug actions on the mother.

In this chapter, the author introduces another approach that may be added to the opioid development program: the use of receptor selectivity. Biochemical, functional, and more recently, cloning data support the existence of at least three different classes of opioid receptors: mu (μ), delta (δ), and kappa (k). While they all mediate analgesia, they are associated with very different response profiles. Thus, it may be possible to minimize the adverse effect profile by developing compounds that show high selectivity for a particular receptor subtype.

This chapter briefly reviews some of the known adverse effects of acute and chronic prenatal opiate exposure on pregnancy outcome and the potential mechanisms by which opiates may affect fetal development. This is followed by a summary of the attempts that have been made to minimize the extent of fetal exposure to opioid drugs. Finally, the author presents experimental evidence to support the use of receptor selectivity in the development of a better opioid for use during pregnancy.

EFFECTS OF PRENATAL EXPOSURE TO OPIATES ON THE FETUS AND NEWBORN

Acute Exposure During Labor and Delivery

The use of opiates during labor is associated with both immediate and long-term effects on the fetus and neonate. Early effects that can be detected in the fetus include a transient drop in transcutaneous oxygen tension (Baxi et al. 1988) and a change in fetal heart rate pattern and baseline variability (Baxi et al. 1988; Epstein et al. 1982; Petrie 1988; Viscomi et al. 1990). Fetal heart rate variability is the most commonly used indicator of fetal well-being, and the loss of heart rate variability is indicative of a compromised fetus (Yeh et al. 1973). Opiates have been reported to decrease fetal heart rate variability, essentially depriving the obstetrician of an objective measure of fetal viability. This loss of fetal heart rate variability appears to be an opioid effect, as it can be reversed by the administration of naloxone to the mother (Epstein et al. 1982).

Neonatal respiratory depression is widely reported following maternal administration of opiates, and naloxone reversal is often required in these newborns (Shnider and Moya 1964). Administration of meperidine and other opiates also have been reported to cause changes in neonatal electroencephalogram (EEG) and neurobehavior (Brackbill et al. 1974; Hodgkinson and Farkhanda 1982; Hodgkinson et al. 1978, 1979). While most of the other effects are of short duration, occurring immediately after birth, the effects on fetal EEG and neurobehavior may persist for several days.

Chronic Exposure to Opiates Throughout Pregnancy

Chronic exposure to opiates has been linked to shorter gestation and lower birth weights (Finnegan 1976; Kandall et al. 1976; Wilson et al. 1981). Although methadone-maintained infants are larger than heroin-

exposed infants, they still have lower birth weights than unexposed infants (Finnegan 1976; Kandall et al. 1976; Wilson et al. 1981). Currently, the reduced birth weight and head circumference in these children are thought to be the result of intrauterine growth retardation rather than premature birth. A small number of studies also suggest that postnatal growth is also reduced in these children (Hans 1989; Strauss et al. 1976; Ting et al. 1974).

Within 1 to 3 days after birth, most infants born to opiate-addicted mothers show clear signs of the effects of abstinence (Desmond and Wilson 1975). In addition to the typical withdrawal signs, these children show alterations in suckling rate (Kron et al. 1976) and sleep patterns (Dinges et al. 1980; Schulman 1969). These assessments all point to increased central nervous system (CNS) irritability. These symptoms diminish quickly over the first month of life, but a question that remains is whether more subtle developmental problems can be observed after the neonatal period.

MECHANISMS BY WHICH OPIATES MAY AFFECT FETAL DEVELOPMENT

Direct Drug Actions on the Fetus

Some of the adverse effects on the fetus and neonate clearly may result from the distribution of opiates across the placenta to the fetus. Meperidine, morphine, and fentanyl have all been detected in cord blood, neonatal plasma, and neonatal urine after acute administration to the mother during labor (for review, see Reynolds 1987). Studies in pregnant sheep and primates have also revealed rapid distribution of these drugs to the fetus (Golub et al. 1986; Szeto et al. 1978, 1981). Thus, opiates may cause direct drug actions on the fetus.

Specific opioid binding sites are present before birth in humans and in many animal species (Clendeninn et al. 1976; Coyle and Pert 1976; Dunlap et al. 1986; Magnan et al. 1988; Zhang and Pastemak 1981). The pharmacology of opiates in the fetus has been studied by direct administration of these drugs to the fetal lamb. Low doses of methadone or morphine have been found to result in behavioral excitation in the fetus, with tachycardia, EEG activation, and respiratory stimulation (Szeto 1983; Szeto et al. 1988; Umans and Szeto 1983; Zhu and Szeto 1989). Higher doses caused behavioral sedation, EEG slowing, and

respiratory depression (Szeto et al. 1988; Umans and Szeto 1983; Zhu and Szeto 1989). These effects have been shown to be reversible by naloxone, suggesting that they are mediated by specific opioid receptors. Morphine has also been reported to increase plasma glucose (Szeto et al. 1994) and prolactin (McMillen and Deayton 1989) levels in the fetus. These data show that opiates exert significant actions on cardiovascular, respiratory, neurobehavioral, metabolic, and neuroendocrine functions in the fetus; these direct drug actions can explain many of the adverse effects that have been observed in the human fetus.

Indirect Drug Actions on Maternal Physiology

The adverse effects observed in the fetus and neonate may be secondary to opiate-induced alterations in maternal physiology. Opiates may adversely affect the fetus by compromising the delivery of oxygen and substrates to the fetus. The respiratory depressant actions of opiates in humans and animals are well known and may decrease fetal oxygen availability. In addition, opioid-induced maternal hypotension may result in a reduction in uterine blood flow. Any reduction in uteroplacental perfusion coupled with respiratory depression may significantly reduce the delivery of oxygen and substrates to the fetus. Fetal hypoxia and hypoglycemia are known to alter fetal cardiorespiratory and neurobehavioral function. Acute hypoxia has been shown to cause fetal bradycardia and decrease rapid eye movement (REM) sleep and fetal breathing activity (Boddy et al. 1974; Koos et al. 1987). Fetal hypoglycemia has also been shown to significantly alter fetal EEG and decrease breathing activity (Richardson et al. 1982). Opiate use during pregnancy may also indirectly affect fetal neurobehavior and cardiorespiratory function as a result of maternal hypotension and respiratory depression.

The mechanism behind the reduction in fetal heart rate variability by opiates is not understood. It is known, however, that heart rate variability is under autonomic control and is enhanced during REM sleep and periods of fetal breathing (Dawes et al. 1972). The reduction in fetal heart rate variability after maternal opiate administration may be the result of a reduction in autonomic tone or changes in fetal sleep state and breathing activity.

ATTEMPTS AT MINIMIZING THE EXTENT OF FETAL DRUG EXPOSURE

Current attempts at minimizing adverse effects in the fetus have centered on decreasing the extent of fetal drug exposure, thus reducing the magnitude of the direct effects of opiates on the fetus. Two different approaches have been tried.

Different Routes of Drug Administration

The use of intrathecal and epidural routes of drug administration during labor and delivery have only been somewhat successful in reducing the effects of opiates on the fetus. Epidural opiates alone have proved to be inadequate for labor pain, and effective doses have been reported to result in fetal plasma levels that are comparable to those attained with systemic administration (Nybell-Lindahl et al. 1981). Furthermore, the adverse effects in the fetus and neonate were also similar to those after intramuscular (IM) administration.

Altering the Physiochemical Properties of the Drug

The placenta is a lipid membrane, and passive diffusion is the most important mode of transport for most drug molecules, as they tend to be sufficiently small and lipid soluble. The factors that influence the rate and extent of drug transfer from mother to fetus have been reviewed extensively by a number of investigators and include molecular weight, lipid solubility, plasma protein binding, placental surface area, and placental blood flow (Mihaly and Morgan 1984; Mirkin and Singh 1976; Reynolds and Knott 1989). Pharmacokinetic studies in pregnant sheep have revealed significant differences in the extent of fetal exposure to different drugs (for review, see Szeto 1992).

Among the opiate drugs, the ratio of fetal to maternal concentrations was 0.13: 1 for morphine and 0.40: 1 for methadone and meperidine (Szeto et al. 1978, 1982). Thus, the extent of fetal exposure to methadone is 3 times greater than to morphine. Pharmacokinetic analyses suggested that the difference was due to a higher placental transfer for methadone, which may be explained by its greater lipid solubility compared to morphine (Szeto et al. 1982). These data show that the extent of fetal drug exposure can be modified by altering the physiochemical properties of the drug. Subsequent studies showed that the magnitude of effects on the fetus was directly related to the extent of fetal drug exposure and the

fetal response to maternally administered methadone was 3 times greater than that to morphine (Umans and Szeto 1983).

Another very interesting example of manipulating the physiochemical properties of the drug in order to minimize placental transfer was the development of metkephamid, an analog of met-enkephalin, as an obstetric analgesic (Frederickson 1986; Frederickson et al. 1981, 1983). Being a pentapeptide, its distribution across the placenta was thought to be minimal. Indeed, limited studies showed that the fetal-to-maternal ratio was less than 1:200 in sheep compared with 1:2 for meperidine. In the rat, the fetal-to-maternal ratio was 1:60 for metkephamid compared with 1: 1.8 for meperidine (Frederickson 1986). Thus it seemed that opioid peptides may have an advantage over alkaloids as obstetric analgesics. Although there were concerns regarding the ability of peptides to cross the blood-brain barrier, results from clinical studies suggested that IM metkephamid was as effective as meperidine in the relief of postoperative pain (Bloomfield et al. 1983; Calimlim et al. 1982). Nonetheless, the delivery of adequate amounts of drug into the CNS without substantial distribution of the drug across the placenta may be difficult to accomplish.

Furthermore, simply minimizing the extent of placental transfer does not address the problem of *indirect* drug actions on the mother. In fact, the development of metkephamid was curtailed after it was found to significantly decrease maternal blood pressure (J.R. Woods, personal communication, June 1993). This was unexpected, as hypotension was not reported when metkephamid was given to male subjects or postpartum female subjects (Bloomfield et al. 1983; Calimlim et al. 1982). This finding highlights the importance of considering the *indirect* actions of drugs on the fetus in any drug development program.

RECEPTOR SELECTIVITY AS AN ALTERNATIVE APPROACH TO MINIMIZE THE IMPACT OF OPIATES ON THE FETUS

The use of receptor selectivity is proposed as a means of minimizing the impact of opiates on the fetus. The diverse actions of opiates have been postulated to be mediated by multiple classes of opioid receptors. Based on the response profiles to different opiate drugs in the chronic spinal dog model, Martin and coworkers (1976) first proposed that there were at least three types of opiate receptors, which they named μ (for morphine), κ (for ketocyclazocine) and sigma (σ) (for SKF-10,047). The discovery

TABLE 1. *Postulated functions for opioid receptor subtypes.*

Function	μ	δ	κ
Analgesia	✓	✓	✓
Respiration	depression	↑ / no effect	
Cardiovascular	↓ BP, ↓ HR	no effect	↓ / no effect
Gastrointestinal	constipation		
Endocrine	↑ prolactin	↑ GH	↓ ADH
Behavioral Activity	decrease	increase	decrease
Metabolism	↑ glucose		
Other	pruritis; muscle rigidity		

of the enkephalins led to the proposal of another receptor type, 8, with preference for the enkephalins (Lord et al. 1977). Subsequent in vitro binding and autoradiographic studies provided further support for the existence of multiple subclasses of opioid receptors (Chang et al. 1979; Itzhak et al. 1982; James et al. 1982). Recently several laboratories reported on the cloning of the δ, μ, and κ receptors (Chen et al. 1993; Evans et al. 1992; Kieffer et al. 1992; Yasuda et al. 1993).

Extensive pharmacologic studies using selective agonists and antagonists suggest different functional roles for the various subtypes of opioid receptors (table 1). Although μ, δ, and κ agonists all appear to result in analgesia, they are associated with very different pharmacologic profiles. For instance, μ agonists have been reported to cause pruritis, constipation, muscle rigidity, respiratory depression, and hypotension with bradycardia (Paul and Pastemak 1988; Portolano et al. 1991; Stevens Negus et al. 1993; Thomas et al. 1992; Yeadon and Kitchen 1989). On the other hand, δ agonists have been shown to stimulate respiration (Cheng et al. 1992, 1993; Kramer et al. 1992), and they appear to have little or no effect on cardiovascular control (Kiritsy-Roy et al. 1989). Kappa agonists cause sedation and decrease body temperature, and they either depress or have no effect on cardiorespiratory function (Castillo et al. 1986; Howell et al. 1990; Spencer et al. 1988).

Although no information exists on the action of μ and δ agonists on cardiovascular, respiratory, metabolic, and neuroendocrine control during pregnancy, the data from nonpregnant animals and humans suggest that δ agonists may have fewer adverse effects than μ agonists on the mother and fetus. First, μ agonists depress respiration, whereas δ agonists actually cause a small stimulation in breathing. Second, δ agonists appear to have much less effect on cardiovascular function in the nonpregnant adult and may therefore have less effect on uteroplacental perfusion. Third, some evidence suggests that pruritis is only observed with μ agonists and not δ or κ agonists. Fourth, there is some evidence to suggest that chronic use of δ agonists may not result in physical dependence. Finally, and perhaps the most interestingly, the ontogeny of the δ receptor seems to lag behind that of the μ and κ receptor.

ONTOGENY OF THE DIFFERENT SUBCLASSES OF OPIOID RECEPTORS

The ontogeny of opioid binding sites has been studied in a number of animal species. Specific binding sites can be detected by midgestation in rodents, reaching ~40 percent of adult level at birth, and continuing to increase through the 3rd week after birth (Clendeninn et al. 1976; Coyle and Pert 1976; Zhang and Pastemak 1981). In contrast, binding levels in the guinea pig and sheep reach mature levels by the time of birth (Clendeninn et al. 1976; Dunlap et al. 1986). Studies using more selective ligands have revealed differential development of μ, δ, and κ binding sites, with development of δ sites lagging behind μ and κ sites in all species studied (Dunlap et al. 1986; Magnan and Tiberi 1989; Petrillo et al. 1987; Spain et al. 1985). Delta sites are not present at midgestation in the human brain (Magnan and Tiberi 1989) and can only be detected by postnatal day 10 in the rat (McDowell and Kitchen 1986). In contrast, δ binding was detected by midgestation in sheep and undergoes a linear increase between midgestation and 90 percent of term (Dunlap et al. 1986). On the other hand, there was little change in μ binding throughout the 3rd trimester.

Although detailed ontogeny of the δ binding site in the human is not known, it is likely that it falls somewhere between the developmental profile in the rather immature rodent and the more precocious sheep. Thus there may be few, if any, functional δ receptors in the human fetus, even in the latter part of gestation. In this case, even if substantial

amounts of δ agonists should be distributed across the placenta to the fetus, the pharmacologic effects on the fetus may be insignificant.

PHARMACOLOGY OF OPIOID RECEPTOR SUBTYPES IN THE OVINE FETUS

The pharmacology of the different subtypes of opioid receptors has been studied in the more precocious fetal lamb with the use of selective agonists and antagonists. The results showed that selective δ agonists do not depress fetal breathing or alter fetal heart rate, while μ agonists cause significant tachycardia and respiratory depression (Cheng et al. 1992, 1993; Szeto et al. 1990, 1994). Recent studies also showed that δ agonists had no effect on fetal plasma glucose regulation, while μ agonists caused a significant increase in plasma glucose levels (Szeto et al. 1994). Dynorphin, a κ agonist, caused hypertension and bradycardia (Dunlap and Valego 1989). However, the effects of κ agonists on neurobehavioral, respiratory, or metabolic control in the fetus have not been investigated. There is also data showing that the μ agonist FK33,824 increased plasma adrenocorticotropic hormone in the fetal lamb (Brooks and Challis 1988) while dynorphin caused a significant increase in plasma arginine vasopressin levels (Dunlap and Valego 1989). There is no evidence that δ agonists have any significant neuroendocrine effects in the fetus. Together, these studies show that δ agonists have minimal adverse effects on the fetus and may be superior to selective μ or κ agonists at this stage of development.

SUMMARY

It is proposed that receptor selectivity may be used as a rational approach in the design and development of new opioid agents for use in pregnant women. While minimizing placental drug transfer will only reduce the direct effects of opioid drugs on the fetus, the use of selective opioid drugs may, in addition, reduce the indirect effects of opioids secondary to alterations in maternal and placental physiology. By taking advantage of the differential ontogeny of the different receptor subtypes, it may even be able to prevent significant drug effects on the fetus despite considerable placental transfer. The combined use of maternal-fetal pharmacokinetics and receptor selectivity may lead to the development of superior opioid drugs with minimal adverse effects on the mother and fetus. Finally, the approaches proposed here may be suitable for the

development of other agents that may be useful in the treatment of pregnant addicts and their infants.

ACKNOWLEDGMENTS

This chapter was prepared with support from National Institute on Drug Abuse grant DA-02475. Dr. Szeto is the recipient of a Research Scientist Development Award from the National Institute on Drug Abuse (DA-00100).

REFERENCES

Baxi, L.V.; Petrie, R.H.; and James, L.S. Human fetal oxygenation (tcPO2), heart rate variability and uterine activity following maternal administration of meperidine. *J Perinat Med* 16:23-30, 1988.

Bloomfield, S.S.; Barden, T.P.; and Mitchell, J. Metkephamid and meperidine analgesia after episiotomy. *Clin Pharmacol Ther* 34:240-247, 1983.

Boddy, K.; Dawes, G.S.; Fisher, R.; Pinter, S.; and Robinson, J.S. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxia and hypercapnia in sheep. *J Physiol* 243:599-618, 1974.

Brackbill, Y.; Kane, J.; Manniello, R.L.; and Abramson, D. Obstetric meperidine usage and assessment of neonatal status. *Anesthesiology* 40:116-120, 1974.

Brooks, A.N., and Challis, J.R.G. Exogenous opioid regulation of the hypothalamic-pituitary-adrenal axis in fetal sheep. *J Endocrinol* 119:389-395, 1988.

Calimlim, J.F.; Wandell, W.M.; Sriwatanakul, K.; Lasagna, L.; and Cox, C. Analgesic efficacy of parenteral metkephamid acetate in treatment of post-operative pain. *Lancet* 1:1374-1375, 1982.

Castillo, R.; Kissin, I.; and Bradley, E.L. Selective kappa opioid agonist for spinal analgesia without the risk of respiratory depression. *Anesth Analg* 350:354, 1986.

Chang, K.J.; Cooper, B.R.; Hazum, E.; and Cuatrecasas, P. Multiple opiate receptors: Different regional distribution in the brain and differential binding of opiates and opiate peptides. *Mol Pharmacol* 16:91-104, 1979.

Chen, Y.; Mestek, A.; Liu, J.; Hurley, J.A.; and Yu, L. Molecular cloning and functional expression of a μ-opioid receptor from rat brain. *Mol Pharmacol* 44:8-12, 1993.

Cheng, P.Y.; Wu, D.L.; Decena, J.A.; Cheng, Y.; McCabe, S.; and Szeto, H.H. Central opioid modulation of breathing dynamics in the fetal lamb: Effects of [D-Pen^2,D-Pen^5]-enkephalin and partial antagonism by naltrindole. *J Pharmacol Exp Ther* 262:1004-1010, 1992.

Cheng, P.Y.; Wu, D.; Decena, J.; Soong, Y.; McCabe, S.; and Szeto, H.H. Opioid-induced stimulation of fetal respiratory activity by [D-Ala^2]deltorphin I. *Eur J Pharmacol* 230:85-88, 1993.

Clendeninn, N.J.; Petraitis, M.; and Simon, E.J. Ontological development of opiate receptors in rodent brain. *Brain Res* 118: 157-160, 1976.

Coyle, J.T., and Pert, C.B. Ontogenetic development of [^{3}H]naloxone binding in rat brain. *Neuropharmacology* 15:555-560, 1976.

Dawes, G.S.; Fox, H.E.; Leduc, M.B.; Liggins, G.C.; and Richards, R.T. Respiratory movements and rapid eye movement sleep in the fetal lamb. *J Physiol* 220:119-143, 1972.

Desmond, M.M., and Wilson, G.S. Neonatal abstinence syndrome: Recognition and diagnosis. *Addict Dis* 2:113-121, 1975.

Dinges, D.F.; Davis, M.M.; and Glass, P. Fetal exposure to narcotics: Neonatal sleep as a measure of nervous system disturbance. *Science* 209:619-621, 1980.

Dunlap, C.E.; Christ, G.J.; and Rose, J.C. Characterization of opioid receptor binding in adult and fetal sheep brain regions. *Brain Res Dev* 24:279-285, 1986.

Dunlap, C.E., and Valego, N.K. Cardiovascular effects of dynorphin A-(1- 13) and arginine vasopressin in fetal lambs. *Am J Physiol* 256:R1318-R1324, 1989.

Epstein, H.; Waxman, H.; Gleicher, N.; and Laversen, N.H. Meperidine induced sinusoidal fetal heart rate pattern and reversal by naloxone. Supplement, *Obstet Gynecol* 59:22S, 1982.

Evans, C. J.; Keith, D.E., Jr.; Morrison, H.; Magendzo, K.; and Edwards, R.H. Cloning of a delta opioid receptor by functional expression. *Science* 258:1952-1955, 1992.

Finnegan, L.P. Clinical effects of pharmacologic agents on pregnancy, the fetus, and the neonate. *Ann N Y Acad Sci* 281:74-89, 1976.

Frederickson, R.C.A. Progress in the potential use of enkephalin analogs. In: Rapaka, R.S., and Hawks, R.L., ed. *Opioid Peptides: Molecular Pharmacology, Biosynthesis, and Analysis.* National Institute on Drug Abuse Research Monograph No. 70. DHHS Pub. No. (ADM)86-1455. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1986. pp. 367-384.

Frederickson, R.C.; Parli, C.J.; De Vane, G.W.; and Hynes, M.D. Preclinical pharmacology of metkephamid (LY127623), a Met-enkephalin analogue. In: Harris, L., ed. *Problems of Drug Dependence* 1982. National Institute on Drug Abuse Research Monograph No. 43. DHHS Pub No. (ADM)83-1264. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1983. pp. 150-156.

Frederickson, R.C.A.; Smithwick, E.L.; Shuman, R.; and Bemis, K.G. Metkephamid, a systemically active analog of methionine-enkephalin with potent opioid delta-receptor activity. *Science* 211:603-604, 1981.

Golub, M.S.; Eisele, J.H.; and Anderson, J.H. Maternal-fetal distribution of morphine and alfentanil in near-term sheep and rhesus monkeys. *Dev Pharmacol Ther 9: 12-22,* 1986.

Hans, S.L. Developmental consequences of prenatal exposure to methadone. *Ann N Y Acad Sci* 562:195-207, 1989.

Hodgkinson, R.; Bhatt, M.; Kim, S.S.; Grewol, G.; and Marx, G.F. Neonatal neurobehavior in the first 48 hours of life: Effect of the administration of meperidine with and without naloxone in the mother. *Pediatrics* 62:294-298, 1978.

Hodgkinson, R., and Farkhanda, J.H. The duration of effect of maternally administered meperidine on neonatal neurobehaviour. *Anesthesiology* 56:51-52, 1982.

Hodgkinson, R.; Huff, R.W.; Hayashi, R.H.; and Husain, F.J. Double blind comparison of maternal analgesia and neonatal neurobehaviour following intravenous butorphanol and pethidine. *J Intern Res* 7:224-230, 1979.

Howell, L.L.; Bergman, J.; and Morse, W.H. Effects of levorphanol and several kappa-selective opioids on respiration and behavior in rhesus monkeys. *J Pharmacol Exp Ther* 254:786-791, 1990.

Itzhak, Y.; Bonnet, K.A.; Groth, J.; Hiller, J.M.; and Simon, E.J. Multiple opiate binding sites in human brain regions: Evidence for kappa and sigma sites. *Life Sci* 31:1363-1366, 1982.

James, I.F.; Chavkin, C.; and Goldstein, A. Preparation of brain membranes containing a single type of opioid receptor highly selective for dynorphin. *Proc Natl Acad Sci U S A* 79:7570-7574, 1982.

Kandall, S.R.; Albin, S.; Lowinson, J.; Berle, B.; Eidelman, A.I.; and Gartner, L.M. Differential effects of maternal heroin and methadone use on birth weight. *Pediatrics* 58:681-685, 1976.

Kieffer, B.L.; Befort, K.; Gaveriaux-Ruff, C.; and Hirth, C.G. The δ-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. *Proc Natl Acad Sci U S A* 89:12048-12052, 1992.

Kiritsy-Roy, J.A.; Matson, L.; and Van Loon, G.R. Sympathoadrenal, cardiovascular and blood gas responses to highly selective mu and delta opioid peptides. *J Pharmacol Exp Ther* 251:1096-1103, 1989.

Koos, B.J.; Sameshima, H.; and Power, G.G. Fetal breathing, sleep state, and cardiovascular responses to graded hypoxia in sheep. *J Appl Physiol* 62:1033-1039, 1987.

Kramer, T.H.; Ayres, E.A.; and Burks, T.F. "Contrasting Respiratory Effects of Delta and Mu Selective Opioid Analgesics in Conscious Rats." Paper presented at the meeting of the International Narcotics Research Conference, Keystone, CO, July 1992.

Kron, R.E.; Litt, M.; Phoenix, M.D.; and Finnegan, L.P. Neonatal narcotic abstinence: Effects of pharmacotherapeutic agents and maternal drug dosage on nutritive sucking behavior. *J Pediatr* 88:637-641, 1976.

Lord, J.A.; Waterfield, A.A.; Hughes, J.; and Kosterlitz, H. W. Endogenous opioid peptides: Multiple agonists and receptors. *Nature* 267:495-499, 1977.

Magnan, J.; Lemay, J.; and Tibet-i, M. Binding of the non-selective opioid [^{3}H]etorphine in the human fetal central nervous system. *Brain Res Dev Brain Res* 38:300-303, 1988.

Magnan, J., and Tiberi, M. Evidence for the presence of μ- and k- but not δ-opioid sites in the human fetal brain. *Brain Res Dev Brain Res* 45:275-281, 1989.

Martin, W.R.; Eades, C.G.; Thompson, J.A.; Huppler, R.E.; and Gilbert, P.E. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther* 197:517-532, 1976.

McDowell, J., and Kitchen, I. Ontogenesis of δ-opioid receptors in rat brain using [^{3}H][D-Pen^{2},D-Pen^{5}]enkephalin as a binding ligand. *Eur J Pharmacol* 128:287-289, 1986.

McMillen, I.C., and Deayton, J.M. Effect of morphine and naloxone on plasma prolactin concentrations in the fetal sheep and pregnant ewe during late gestation. *Neuroendocrinology* 49:286-290, 1989.

Mihaly, G.W., and Morgan, D.J. Placental drug transfer: Effects of gestational age and species. *Pharmacol Ther* 23:253-266, 1984.

Mirkin, B.L., and Singh, S. Placental transfer of pharmacologically active molecules. In: Mirkin, B.L., ed. *Perinatal Pharmacology and Therapeutics*. New York: Academic Press, 1976. pp. 1-70.

Nybell-Lindahl, G.; Carlsson, C.; Ingemarsson, I.; Westgren, M.; and Paalzow, L. Maternal and fetal concentrations of morphine after epidural administration during labour. *Am J Obstet Gynecol* 139:20-21, 1981.

Paul, D., and Pastemak, G.W. Differential blockade by naloxonazine of two μ opiate actions: Analgesia and inhibition of gastrointestinal transit. *Eur J Pharmacol* 149:403-404, 1988.

Petrie, R.H. Influence of meperidine on fetal movements and heart rate beat-to-beat variability in the active phase of labor. *Am J Perinatol* 5:306, 1988.

Petrillo, P.; Tavani, A.; Verotta, D.; Robson, L.E.; and Kosterlitz, H.W. Differential postnatal development of mu-, delta- and kappa-opioid binding sites in rat brain. *Brain Res* 428:53-58, 1987.

Portolano, F.; Filippelli, A.; Marrazzo, R.; Susanna, V.; Russo, S.; Stella, L.; Losasso, C.; Budetta, S.N.; Molinaro, L.; and Angrisani, M. Cariovascular and respiratory effects of dermophin in rats. *Res Commun Chem Pathol Pharmacol* 71:131-152, 1991.

Reynolds, F. Placental transfer of opioids. *Clin Anaesth* 1:859-881, 1987.

Reynolds, F., and Knott, C. Pharmacokinetics in pregnancy and placental drug transfer. *Oxf Rev Reprod Biol* 11:389-449, 1989.

Richardson, B.; Hohimer, A.R.; Mueggler, P.; and Bissonnette, J. Effects of glucose concentration on fetal breathing movements and electrocortical activity in fetal lambs. *Am J Obstet Gynecol* 142:678-683, 1982.

Schulman, C.A. Alterations in the sleep cycle in heroin-addicted and "suspect" newborns. *Neuropediatrics* 1:89-100, 1969.

Shnider, S.M., and Moya, F. Effects of meperidine on the newborn infant. *Am J Obstet Gynecol* 89:1009-1015, 1964.

Spain, J.W.; Roth, B.L.; and Coscia, C.J. Differential ontogeny of multiple opioid receptors *(μ,* δ, and k). *J Neurosci* 5:584-588, 1985.

Spencer, R.L.; Hruby, V.J.; and Burks, T.F. Body temperature response profiles for selective mu, delta and kappa opioid agonists in restrained and unrestrained rats. *J Pharmacol Exp Ther* 246:92-101, 1988.

Stevens Negus, S.; Pastemak, G.W.; Koob, G.F.; and Weinger, M.B. Antagonist effects of ß-funaltrexamine and naloxonazine on alfentanil-induced antinociception and muscle rigidity in the rat. *J Pharmacol Exp Ther* 264:739-745, 1993.

Strauss, M.E.; Starr, R.H.; Ostrea, E.M.; Chavez, C.J.; and Stryker, J.C. Behavioral concomitants of prenatal addiction to narcotics. *J Pediatr* 89:842-846, 1976.

Szeto, H.H. Effects of narcotic drugs on fetal behavioral activity: Acute methadone exposure. *Am J Obstet Gynecol* 146:211-217, 1983.

Szeto, H.H. Pharmacokinetic studies in experimental animals. In: Reynolds, F., ed. *Effects on the Baby of Maternal Analgesia and Anaesthesia*. London: W.B. Saunders Co. Ltd., 1992.

Szeto, H.H.; Cheng, P.Y.; Soong, Y.; and Wu, D.L. Are opioid-induced changes in fetal breathing related to changes in glucose metabolism? *Regul Pept* 51:5267-5268, 1994.

Szeto, H.H.; Clapp, J.F.; Larrow, R.W.; Hewitt, J.; Inturrisi, C.E.; and Mann, L.I. Disposition of methadone in the ovine maternal-fetal unit. *Life Sci* 28:2111-2117, 1981.

Szeto, H.H.; Mann, L.I.; Bhakthavathsalan, A.; Liu, M.; and Inturrisi, C.E. Meperidine pharmacokinetics in the maternal-fetal unit. *J Pharmacol Exp Ther* 206:448-459, 1978.

Szeto, H.H.; Umans, J.G.; and McFarland, J.W. A comparison of morphine and methadone disposition in the maternal-fetal unit. *Am J Obstet Gynecol* 143:700-706, 1982.

Szeto, H.H.; Zhu, Y.S.; and Cai, L.Q. Central opioid modulation of fetal cardiovascular function: Role of μ- and δ-receptors. *Am J Physiol* 258:R1453-R1458, 1990.

Szeto, H.H.; Zhu, Y.S.; Umans, J.G.; Dwyer, G.; Clare, S.; and Amione, J. Dual action of morphine on fetal breathing movements. *J Pharmacol Exp Ther* 245:537-542, 1988.

Thomas, D.A.; Williams, G.M.; Iwata, K.; Kenshalo, D.R.; and Dubner, R. Effects of central administration of opioids on facial scratching in monkeys, *Brain Res* 585:315-317, 1992.

Ting, R.; Keller, A.; Berman, P.; and Finnegan, L.P. Follow-up studies of infants born to methadone-addicted mothers. *Pediatr Res* 8:346, 1974.

Umans, J.G., and Szeto, H.H. Effects of opiates on fetal behavioral activity in utero. *Life Sci* 33:639-642, 1983.

Viscomi, C.M.; Hood, D.D.; Melone, P.J.; and Eisenach, J.C. Fetal heart rate variability after epidural fentanyl during labor. *Anesth Analg* 71:679-683, 1990.

Wilson, G.S.; Desmond, M.M.; and Wait, R.B. Follow-up of methadone-treated and untreated narcotic-dependent women and their infants: Health, developmental, and social implications. *J Pediatr* 98:716-722, 1981.

Yasuda, K.; Raynor, K.; Kong, H.; Breder, CD.; Takeda, J.; Reisine, T.; and Bell, G.I. Cloning and functional comparison of kappa and δ opioid receptors from mouse brain. *Proc Natl Acad Sci U S A* 90:6736-6740, 1993.

Yeadon, M., and Kitchen, I. Opioids and respiration. *Prog Neurobiol* 33:1-16, 1989.

Yeh, S.Y.; Forsythe, A.; and Hon, E.H. Quantitation of fetal heart rate beat to beat interval differences. *Obstet Gynecol* 41:355-363, 1973.

Zhang, A.Z., and Pastemak, G.W. Ontogeny of opioid pharmacology and receptors: High and low affinity site differences. *Eur J Pharmacol* 73:29-40, 1981.

Zhu, Y.S., and Szeto, H.H. Morphine-induced tachycardia in fetal lambs: A bell-shaped dose-response curve. *J Pharmacol Exp Ther* 249:78-82, 1989.

AUTHOR

Hazel H. Szeto, M.D., Ph.D.
Professor of Pharmacology
Department of Pharmacology
Cornell University Medical College
1300 York Avenue
New York, NY 10021

Pharmacokinetic and Pharmacodynamic Considerations for the Design and Screening of Potential Medications

C. Lindsay DeVane

INTRODUCTION

One objective of pharmacotherapy of the pregnant addict is to decrease or eliminate drug abuse while minimally exposing the fetus to therapy with potentially harmful medications or their metabolites. Complete absence of fetal drug exposure is a practically unattainable goal, as essentially all administered drugs with lipid solubility sufficient to enter the central nervous system (CNS) are transferred across the placenta to the fetus. Pharmacokinetic principles can be used to screen drugs that are suitable candidates for addiction treatment while at the same time are minimally transferred across the placenta. However, depending on the specific addiction being treated, it may not be desirable to avoid all fetal drug exposure. The fetus that has been chronically exposed to a drug of abuse may also benefit from pharmacotherapy of the pregnant addict or may require therapy for drug withdrawal after birth.

This chapter reviews some of the characteristics of maternal-fetal pharmacokinetics, factors influencing fetal drug exposure, and methods of predicting placental transfer of drugs. An appreciation of factors that influence fetal drug exposure should be helpful in guiding drug development for treatment of the pregnant addict.

PHARMACOKINETICS AND DYNAMICS OF DRUGS IN THE MATERNAL-FETAL UNIT

The maternal-placental-fetal unit is represented in figure 1. Drug input (administration) may occur by oral, intravenous (IV), intramuscular (IM), or another route of administration. Following oral administration, a drug may first be subject to presystemic elimination, primarily in the maternal

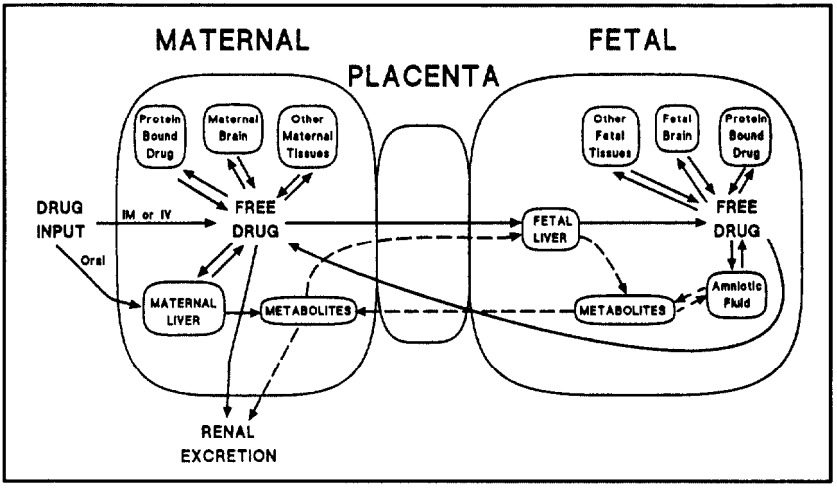


FIGURE 1. *Schematic representation of drug disposition in the maternal-placental-fetal unit. Redrawn from Mirkin 1975.*

liver. A drug circulates in maternal plasma as a free drug and as a drug bound to proteins, principally albumin, alpha- 1 -acid glycoprotein, or lipoproteins. A drug is available in plasma to distribute to other maternal tissues including the brain, the primary target for treating drug addiction. Drugs are eliminated by renal excretion in an unchanged form or are metabolized in the liver, frequently to more polar metabolites that are sometimes pharmacologically active.

Distribution

Both drugs and metabolites may pass the placenta and can exert effects on the fetus. The rate of placental drug transfer depends partly on a drug's molecular size, lipid solubility, and its degree of ionization (Mirkin 1975). Eventually, an equilibrium should occur between maternal and fetal plasma drug concentrations, especially in the case of a free, nonprotein-bound drug. Experimental evidence is available in support of this theory. Thomas and colleagues (1976) measured maternal venous and umbilical venous plasma concentrations of bupivacaine at delivery following epidural administration to 31 women in labor. The umbilical venous plasma concentration of the drug was lower than the maternal venous plasma concentration, and binding to fetal plasma proteins was less than to maternal total plasma protein. There was no significant difference between the unbound drug concentration in umbilical venous plasma and maternal venous plasma.

Data on lorazepam (Kanto et al. 1980) and other drugs also support the observation that plasma-protein binding of drugs may be less on the fetal side than maternal side, yet unbound drug concentrations may be similar. These results are consistent with the distribution of many drugs across the placenta governed by simple diffusion of the unbound molecule. Figure 2 shows a theoretical example of drug distribution between maternal and fetal plasma. The lower percentage of binding on the fetal side results in a greater percentage of free-drug concentration, equivalent to that on the maternal side, even though the total concentration (bound plus free) is less in the fetal compartment. Some factors that could contribute to this situation include differences in pH between maternal and fetal plasma, differences in concentrations of particular drug-binding proteins, differences in concentrations of endogenous ligands competing for the same binding sites on proteins, and saturation of drug protein binding. Hill and Abramson (1988) have reviewed many of these factors. Thus, measurement of plasma-protein binding of potential compounds for drug development for the pregnant addict is important in assessing the degree of fetal exposure.

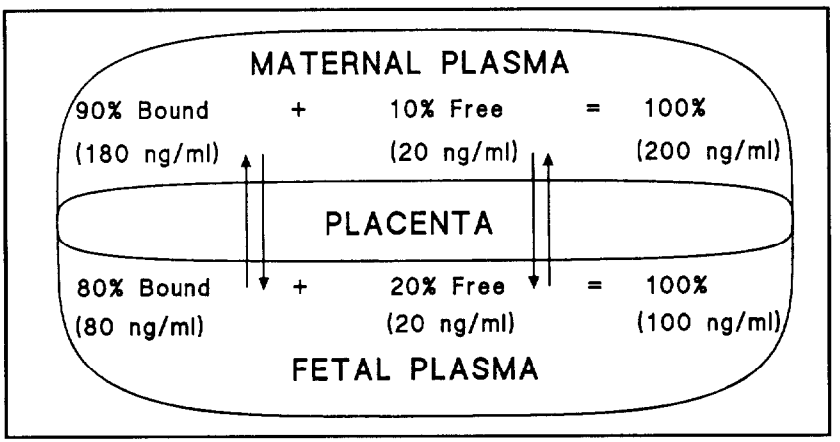


FIGURE 2. *A theoretical example of drug distribution across the placenta. Total drug concentration on the fetal side is lower than on the maternal side (fetal to maternal drug concentration ratio equal to 0.50), although free drug concentration is similar due to a lesser percentage of plasma-protein binding on the fetal side.*

In contrast to the results described above, Szeto and colleagues (1982) found the steady-state concentrations of unbound methadone in fetal and maternal plasma to differ widely in the ovine maternal-fetal unit. The steady-state unbound methadone concentration in the fetal plasma is approximately one-third of that in the maternal plasma. The explanation probably lies in the ability of the fetal lamb to clear methadone. The degree to which the fetus may participate in drug elimination reduces the overall fetal plasma concentration of the drug as compared with the maternal plasma concentration.

Elimination

In addition to maternal organs, other sources of drug elimination include the placenta and fetal liver. The current understanding of drug metabolism in the human placenta and fetus is very limited. Human placental tissues were found to be capable of metabolizing drugs via each of the major drug metabolic reactions, although at a very slow rate (Juchau 1985). However, the significance of this placental metabolism to the extent of fetal drug exposure and fetal effects remains to be investigated.

Fetal metabolism has been found in studies using fetal liver tissue preparations and animal models. In the pregnant ewe model, the fetus was able to metabolize drugs such as methadone (Szeto et al. 1982) and acetaminophen (Wang et. al. 1985); this metabolism resulted in significantly lower drug levels in the fetal plasma than in the maternal plasma. Since the metabolic rate of the fetus generally is a fraction of that of the mother on a body weight basis, the fetal metabolic rate is negligible when compared to the maternal metabolic rate. Therefore, fetal metabolism contributes insignificantly to the overall clearance of a drug during pregnancy, although it may play a role in reducing the overall fetal exposure to the drug.

Drugs or metabolites that pass the placenta are carried by the umbilical vein into the fetal circulation. Drugs may be subject to fetal hepatic metabolism, or may be diverted from the fetal liver by the ductus venosus directly to the inferior vena cava and to the right side of the fetal heart and eventually to other tissues and organs. When eliminated by the fetal kidney, drugs or metabolites may accumulate in the amniotic fluid and be swallowed by the fetus to create an amniotic-enterohepatic recirculation. Alternatively, drugs or metabolites may return to the maternal circulation through the umbilical artery via the placenta. Although rarely possible

except when using animal models, an estimate of the ability of the fetus to clear a potential medication will lend support to the safety of a candidate compound.

Pharmacokinetics-Single Dose

The time course of drugs in the maternal and fetal plasma after acute drug administration is theoretically proposed, and frequently observed in animal models, to follow several typical patterns. These have been discussed in detail by Levy (1981), Szeto (1982), and others. After single dose administration, drug concentration in the fetus at some time following equilibration will either be similar in magnitude, higher in fetal than maternal plasma, or lower than in the mother. The pharmacokinetic characteristics of drugs that exhibit each of these patterns may differ substantially. As a hypothetical example, consider a drug that equilibrates freely between maternal and fetal plasma. This is the situation that may occur when lipophilic soluble drugs freely diffuse across the placenta and distribute rapidly in the fetus. One could expect that this drug is not preferentially bound to either maternal or fetal plasma proteins. If the fetus itself is not eliminating a significant amount of the drug, then an early equilibrium may occur and the ratio of fetal to maternal concentration is essentially unity. Ethanol is an example of a drug showing this type of distribution pattern in monkeys (Hill et al. 1983).

A second drug may exhibit a disposition pattern that can be characterized by higher fetal than maternal concentrations. Following maternal administration, there may be a delay in the time it takes for fetal drug concentration to equal maternal concentration, but eventually fetal concentration is higher for the majority of time during drug disposition. This pattern could be exhibited by a drug with higher plasma-protein binding in the fetal than in the maternal compartment, or by extensive drug distribution to fetal tissues with relatively slow transfer back to the mother as compared with maternal elimination. Drugs that have shown higher fetal than maternal concentrations include atropine (Onnen et al. 1979), diazepam (Nau et al. 1984), and valproic acid (Nau et al. 1981).

For still another drug, fetal concentration may be lower than maternal concentration for most or the entire time course of drug disposition. An explanation for this situation could be more extensive maternal than fetal protein binding or efficient drug metabolism by the fetus. The majority

of therapeutically used drugs appear to show this pattern (Hill and Abramson 1988).

In studies using the pregnant ewe as a model for drug disposition (Burchfield et al. 1991; DeVane et al. 1991), the author observed that individual animals studied in identical experiments of administering single IV doses of cocaine could show either of the above patterns of maternal and fetal drug concentration profiles. A similar result was found with atropine; umbilical vein concentration was found to be higher than maternal plasma concentration in some, but not all, neonates and mothers studied (Onnen et al. 1979). In figure 3, fetal cocaine concentration can be seen to be higher than maternal concentration after 10 minutes in animal A and lower than maternal concentration in animal B for the entire time course observed. This is an example of intersubject variability, from which different conclusions might be reached about cocaine disposition if experimental data from only one animal were available. Reasons for these differences could include rapid changes in maternal or fetal drug-binding proteins that occur near term, the effects of differences in pH, or competing ligands. Drug development for the pregnant addict should ideally include sufficient experimental data to adequately characterize intersubject variability in fetal exposure. What is not discernible from the data in figure 2 is the degree of intra-animal (i.e., intrasubject) variation

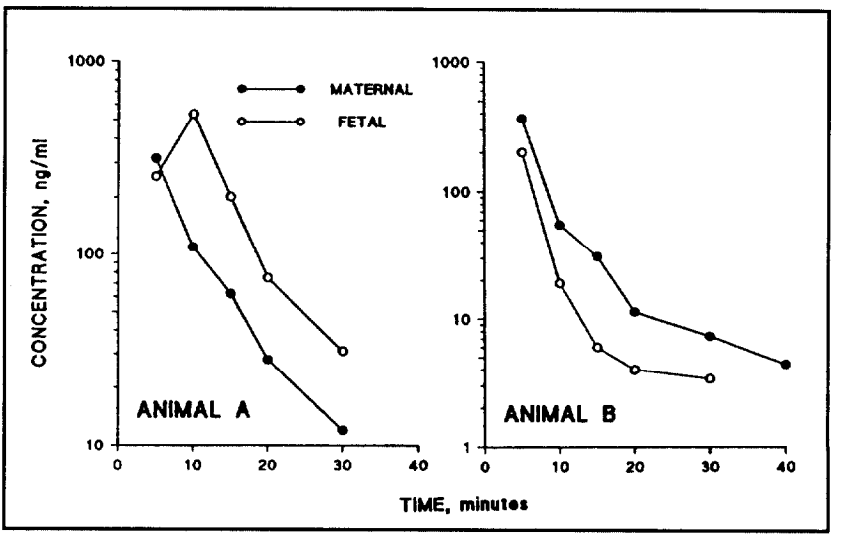


FIGURE 3. *Maternal and fetal cocaine concentrations in two sheep following a 2 mg/kg intravenous maternal dose. Data from DeVane et al. 1991.*

in drug concentration that would exist if this experiment had been performed at different times during gestation.

Pharmacodynamics

Similar to the variability in pharmacokinetics, intrasubject variation in pharmacodynamic effects may also occur in the maternal-fetal unit. To what extent does the same maternal or fetal drug concentration produce different degrees of pharmacologic effects at different times during pregnancy? Some data exist to emphasize the importance of this issue. Middaugh and colleagues (1983) found that pregnant mice injected with phenobarbital had lower concentrations of the drug in plasma compared with nonpregnant controls, but equivalent concentrations in the brain. In spite of similar brain concentrations, the pregnant mice showed an exaggerated behavioral response to phenobarbital compared with the nonpregnant animals. These data suggest that both the pharmacokinetics and pharmacodynamics of phenobarbital are altered in pregnancy. Krauer and colleagues (1980) and Mihaly and Morgan (1984) have summarized some of the many physiological changes that occur during pregnancy that may influence drug disposition and drug pharmacodynamics.

Pharmacokinetic variability is much easier to quantify than pharmacodynamic variability. Pharmacokinetic studies in animals have value in allowing exploration of several characteristics of maternal-fetal drug disposition that may increase researchers' insight into drug use in pregnant women. For example, when increasing drug doses are administered, peak fetal concentration also increases as does overall fetal drug exposure. In a linear system, the exposure of the fetus should be independent of the route of maternal drug administration (oral versus IM versus IV) when bioavailability is complete. Therefore, in developing drugs for the pregnant addict, the assessment of linearity is important for evaluating the potential for fetal exposure and pharmacodynamic effects. If the drug dose exceeds the metabolic capability of the mother, then increasing doses will lead to disproportionate increases in drug exposure in both the mother and fetus. A consideration in drug development is that changing the route of administration for the pregnant addict will not likely result in a lower fetal drug exposure, but the rate of drug exposure to the fetus may be affected.

Pharmacokinetic principles have been useful in preventing fetal drug effects when drugs are administered shortly before delivery. An example

is an accurately timed administration of an anesthetic that is slowly distributed to the fetus and allows childbirth before significant amounts of fetal drug accumulation can occur to produce sedation or respiratory depression in the neonate. This approach is advantageous only in the acute dose situation. With chronic pharmacotherapy, as would likely be required in treating drug addiction, there is no real possibility of excluding the fetus from exposure to the maternally administered drug. The current drugs used in the treatment of opiate addiction, including methadone and levo-alpha-acetylmethadol (LAAM), appear to pass the placenta easily (Lichtblau et al. 1982).

MODELS FOR SCREENING TRANSPLACENTAL PROPERTIES OF COMPOUNDS

Physicochemical properties influence the passage of drugs across the placenta. Most drugs with molecular weights below 500 readily pass the placenta. With higher weights in the range of 500 to 1,000, passage may be slowed but not appreciably limited. Proteins and drugs with molecular weights above 1,000 become more restricted (Mirkin 1975).

Lipid solubility is a major determinant of drug distribution to body tissues. In a previous summary of the author's work using a variety of drugs active in the CNS, the ratio of area under the concentration (AUC) versus time curve for whole fetal tissues in rats compared to the AUC in maternal plasma was shown to correlate with lipid solubility as measured by oil-water partition coefficient (DeVane 1991). Lipid solubility may also be measured by retention times on reversed-phase liquid chromatography columns (Abemethy and Greenblatt 1984).

The in vitro perfused placental preparation, using guinea pig or human tissue, may be used to estimate the participation of the placenta in drug clearance, whether metabolites are formed, and the ease with which drugs may pass the placenta. In drug development, the in vitro perfused human placenta has the advantage of being able to screen for drugs that exhibit a large first-pass metabolism by the placenta. Although there are enzyme systems in the placenta capable of metabolizing drugs, a first-pass metabolism by the placenta does not appear to be a mechanism to extensively protect the fetus from drug exposure.

METHODS FOR EXTRAPOLATING ANIMAL PHARMACOKINETIC DATA TO HUMANS

Allometric analvsis is a powerful tool of comparative physiology that was pioneered by Adolph before 1949 (Adolph 1949). The basic allometric equation is of the form $Y = a M^b$ (equation 1), which relates some physiological variable Y to body mass *M* raised to a fractional power b. A constant, a, is incorporated in the equation. In the logarithmic form, the equation is written $\log Y = \log a + b \log M$ (equation 2) where *b* is the slope of a straight-line plot and *a* is the Y-intercept. Allometric equations are derived by taking the antilog of empirically observed relationships in the form of equation 2 (Dedrick 1973; Mordenti 1986).

Despite large differences in mass among animals, most mammals have similar anatomy, physiology, and biochemistry. Adolph (1949) compiled 33 equations that related quantitative physiological properties in various animals to body weight. Examples include ventilation rate, clearance of creatinine, heartbeat duration, and nitrogen output. Since renal blood flow is approximately 25 percent of cardiac output regardless of mammalian species, it could be expected that allometric relationships might exist among different animals in the ability to eliminate drugs. Boxenbaum (1984) demonstrated that the intrinsic clearance of antipyrine could be scaled across species with the exception of man. When maximum lifespan potential (MLP) was incorporated into the comparison, which can be scaled among species using body weight and brain weight, the addition of human data improved the correlation.

Various pharmacokinetic parameters have been successfully scaled among different species with a variety of drugs. The application of interspecies scaling has not been widespread in the field of drug abuse. Owens and colleagues (1987) found that phencyclidine (PCP) pharmacokinetic parameters (systemic clearance, volume of distribution and half-life) correlated well with body weight ($r = 0.799$ to 0.966) across six animal species, including man, using linear regression and an allometric equation. An example of the goodness of fit of data from this study is presented in figure 4.

Considerable advantages lie in being able to scale across species. These include the ability to produce more meaningful data from animal experiments and to interpolate drug doses between animals and humans. Interspecies scaling is an attractive approach to predicting drug disposition, defining pharmacokinetic equivalence in different species,

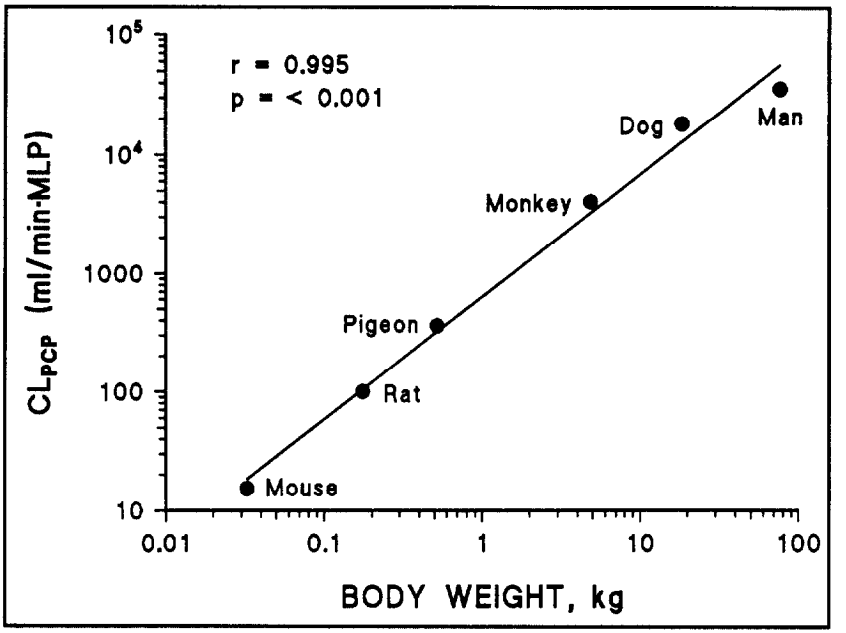


FIGURE 4. *Allometric relationship between body weight and phencyclidine clearance (CL_{PCP}). CL_{PCP} is multiplied by the maximum lifespan potential (MLP) for each species. Data are taken from Owens et al. 1987. The steady-state unbound methadone concentration in the fetal plasma is approximately one-third of that in the maternal plasma.*

and designing dosage regimens, but does not yet appear to have been adapted for measures of fetal drug exposure in animals.

FURTHER CONSIDERATIONS FOR TREATING THE PREGNANT ADDICT

Dramatic physiological changes occur during pregnancy. This suggests an instability exists in pharmacokinetic parameters and pharmacodynamic response. Thus, treatment of the pregnant addict must rely on principles of good clinical observation and care in addition to pharmacokinetic and dynamic studies conducted in animals to predict potential benefits and adverse effects.

Drugs that are more highly hepatically cleared will likely show greater intersubject and intrasubject variability in the degree of fetal exposure than drugs that are renally cleared. Unfortunately for drug development for the pregnant addict, drugs that are renally cleared may also be less lipid soluble and hence of less value in treating drug addiction when the CNS is the target.

The value of conducting concentration-controlled clinical trials in drug development programs for treating the pregnant addict can be increased. Unfortunately, the pharmacodynamic variability of CNS active drugs frequently exceeds their pharmacokinetic variability, so that the value of conducting controlled trials with targeted concentrations may be limited. Nevertheless, it may be important to monitor plasma drug concentration to assess any relationship to side effects or toxicity and to assess the degree of intersubject variability. Animal models remain useful in screening for physiological and behavioral teratogenic effects during the drug development process.

Drug selection for the pregnant addict relies heavily on a value judgment concerning an absence of adverse effects in the neonate or infant, as there is no way of avoiding some minimal fetal exposure to drugs that require penetration to the mother's CNS. Nevertheless, the goal is to use enough of the drug to be therapeutic without being toxic. Therefore, for adequate dosage regimen design, knowledge of some fundamental pharmacokinetic parameters is critical. These include clearance and the elimination rate constant from which the drug's half-life can be determined. Interspecies scaling using allometric principles to predict pharmacokinetics in pregnant animals may be an attractive alternative to human studies, but should complement studies conducted in nonpregnant women.

CONCLUSION

The current understanding of drug metabolism in the human placenta and fetus is very limited. Human placental tissues were found to be able to metabolize drugs via each of the major drug metabolic reactions, although at a very slow rate (Juchau 1985). However, the significance of the placental metabolism to the fetal drug exposure remains to be investigated. Fetal metabolism has been demonstrated in fetal liver tissue preparations and in utero in animal models. In the pregnant ewe model, the fetus was found to be capable of metabolizing drugs such as

methadone and acetaminophen; this resulted in an overall reduced fetal exposure to the drugs. The metabolic rate in the fetus in general is a fraction of the maternal rate on a body weight basis, and therefore is inconsequential to the overall total body metabolism (including the maternal and the fetal clearance) of a drug in pregnancy. However, the degree to which the fetus participates in drug elimination will reduce the overall exposure of the unchanged drug but may result in accumulation of the metabolites.

REFERENCES

Abemethy, D.R., and Greenblatt, D.J. In vitro indices of drug distribution in obesity. *Clin Pharmacol Ther* 35:225, 1984.

Adolph, E.A. Quantitative relations in the physiological constitutions of mammals. *Science* 109:579-585, 1949.

Boxenbaum, H. Interspecies pharmacokinetic scaling and the evolutionary-comparative paradigm. *Drug Metab Rev* 15:1071-1121, 1984.

Burchfield, D.J.; Lucas, V.W.; Abrams, R.M.; Miller, R.L.; and DeVane, C.L. Disposition and pharmacodynamics of methamphetamine in pregnant sheep. *JAMA* 265:1969-1975, 1991.

Dedrick, R.L. Animal scale-up. *J Pharmacokinet Biopharm* 1:435-461, 1973.

DeVane, C.L. Pharmacokinetic correlates of fetal drug exposure. In: Kilbey, M.M., and Asghar, K., eds. *Methodological Issues in Controlled Studies on Effects of Prenatal Exposure to Drug Abuse.* National Institute on Drug Abuse Research Monograph No. 114. DHHS Pub. No. (ADM)91-1837. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1991. pp. 118-136.

DeVane, C.L.; Burchfield, D.J.; Abrams, R.M.; Miller, R.L.; and Braun, S.B. Disposition of cocaine in pregnant sheep. Part I. Pharmacokinetics. *Dev Pharmacol Ther* 16:123-129,199l.

Hill, D.E.; Slikker, W., Jr.; Goad, P.T.; Bailey, J.R.; Siszak, T.J.; and Hendricks, A.G. Maternal, fetal, and neonatal elimination of ethanol in nonhuman primates. *Dev Pharmacol Ther* 6:259-268, 1983.

Hill, M.D., and Abramson, F.P. The significance of plasma protein binding on the fetal/maternal distribution of drugs at steady-state. *Clin Pharmacokinet* 14:156-170, 1988.

Juchau, M.R. Biotransformation of drugs and foreign chemicals in the human fetal-placental unit. In: Chiang, C.N., and Lee, C., eds. *Prenatal Drug Exposure: Kinetics and Dynamics.* National Institute on Drug Abuse Research Monograph No. 60. DHHS Pub. No. (ADM)85-1413. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1985. pp. 17-24.

Kanto, J.; Aaltonen, L.; Liukko, P.; and Maenpaa, K. Transfer of lorazepam and its conjugate across the human placenta. *Acta Pharmacol Toxicol* 47:130-134, 1980.

Krauer, B.; Krauer, F.; and Hytten, F.E. Drug disposition and pharmacokinetics in the maternal-placental-fetal unit. *Pharm Ther* 10:301-328, 1980.

Levy, G. Pharmacokinetics of fetal and neonatal exposure to drugs. Supplement 5. *Obstet Gynecol* 58:9-16, 1981.

Lichtblau, L.; Finkle, B.S.; and Sparber, S.B. Cumulation of active metabolites of levo-alpha-acetylmethadol in the rat fetus and neonate. *Life Sci* 30:307-312, 1982.

Middaugh, L.D.; Zemp, J.W.; and Boggan, W.O. Pregnancy increases reactivity of mice to phenobarbital. *Science* 220:534-536, 1983.

Mihaly, G.W., and Morgan, D.J. Placental drug transfer: Effects of gestational age and species. *Pharm Ther* 23:253-266, 1984.

Mirkin, B.L. Perinatal pharmacology: Placental transfer, fetal localization, and neonatal disposition of drugs. *Anesthesiology* 43:156-170, 1975.

Mordenti, J. Man versus beast: Pharmacokinetic scaling in mammals. *J Pharm Sci* 75:1028-1040, 1986.

Nau, H.; Luck, W.; and Kuhnz, W. Decreased serum protein binding of diazepam and its major metabolite in the neonate during the first postnatal week relate to increased free fatty acid levels. *Br J Clin Pharmacol* 17:92-98, 1984.

Nau, H.; Rating, D.; Koch, S.; Hauser, I.; and Helge, H. Valproic acid and its metabolites: Placental transfer, neonatal pharmacokinetics, transfer via mother's milk and clinical status in neonates of epileptic mothers. *J Pharm Exp Ther* 219:768-777, 1981.

Onnen, I.; Barrier, G.; d'Athis, P.H.; Sureau, C.; and Olive, G. Placental transfer of atropine at the end of pregnancy. *Eur J Clin Pharmacol* 15:443-446, 1979.

Owens, S.M.; Hardwick, W.C.; and Blackall, D. Phencyclidine pharmacokinetic scaling among species. *J Pharm Exp Ther* 242:96-101, 1987.

Szeto, H.H. Pharmacokinetics in the ovine maternal-fetal unit. *Annu Rev Pharmacol Toxicol* 22:221-243, 1982.

Szeto, H.H.; Umans, J.G.; and Rubinow, S.I. The contribution of transplacental clearances and fetal clearance to drug disposition in the ovine maternal-fetal unit. *Drug Metab Dispos* 10:382-386, 1982.

Thomas, J.; Long, G.; Moore, G.; and Morgan, D. Plasma protein binding and placental transfer of bupivacaine. *Clin Pharmacol Ther* 19:416-434, 1976.

Wang, L.H.; Rudolph, A.M.; and Benet, L.Z. Pharmacokinetics of drugs and metabolites in the maternal-placental-fetal unit: General principles. In: Chiang, C.N., and Lee, C., eds. *Prenatal Drug Exposure: Kinetics and Dynamics.* National Institute on Drug Abuse Research Monograph No. 60. DHHS Pub. No. (ADM)85-1413. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1985. pp. 25-38.

AUTHOR

C. Lindsay DeVane, Pharm. D.
Department of Psychiatry
Medical University of South Carolina
171 Ashley Street
Charleston, SC 29425

The Application of the Principles of Toxicology and Teratology in Evaluating the Risks of New Drugs for Treatment of Drug Addiction in Women of Reproductive Age

Robert L. Brent

INTRODUCTION

A great deal has been learned about the causes of human birth defects during the past few decades. Yet a substantial percentage of human birth defects do not have a definitive etiology (Brent 1985). It is important to recognize that environmental causes are responsible for about 10 percent of human birth defects including maternal disease states, maternal infection, mechanical factors or problems of constraint, the etiology of birth defects, and exogenous chemicals, drugs, and physical agents. Yet the etiology of birth defects is an area of active epidemiological and laboratory investigation. Prescription drugs, illicit drugs, and environmental chemicals in all likelihood account for a very small proportion of human malformations, but illicit drug use is associated with a high incidence of reproductive problems. Environmentally induced birth defects can be prevented; therefore, the identification of drugs and chemicals with a significant teratogenic risk is worthy of pursuit.

The scientific basis for understanding the risk of congenital malformations from exposure to environmental agents relates to several concepts based on toxicological and embryological dogma. The first principle is that teratogens have a typical toxicological dose-response relationship along with a no-effect dose. Both the severity and frequency of the effects are expected to increase as the dose is increased, but there is a dose below which no increased teratogenic effects are observed. Secondly, the stage of gestation is critical to the effects that are expected; all stages of embryogenesis and fetogenesis are vulnerable to environmental toxicants. Thirdly, the response of the embryo and fetus is quite characteristic for each teratogenic agent, although there is clearly

some similarity and overlap with regard to the effect of certain teratogens. It is very clear that known teratogens have a specificity and a confined limit to their ability to injure the developing embryo or fetus.

Genetic causes are an important etiology of reproductive failure and account for 20 to 25 percent of human birth defects. However, the largest proportion of birth defects have no definitive etiology. Some of these malformations may be due to intrinsic, nonpreventable, spontaneous errors of development.

It is important to recognize that the most reliable estimate of the risk of environmental teratogens is derived from human epidemiological studies and that laboratory toxicology studies may clarify some aspects of the epidemiological studies. Methods of evaluating alleged teratogenicity are presented in this chapter. Since many drugs developed to treat drug addiction may be new drugs, results of epidemiological studies may not be available. Therefore, appropriate animal studies may be necessary to screen these new drugs for their reproductive toxicity using modem pharmacokinetic tools. This chapter presents the pitfalls of in vivo and in vitro studies, and includes methods to improve the quality of animal studies for determining reproductive risks.

BASIC PRINCIPLES

Etiologies of Congenital Malformations

There have been dramatic changes in man's explanations of the causes of human birth defects. In ancient times, the causes of birth defects were dominated by superstition, ignorance, and prejudice. The stigma associated with birth defects has primitive beginnings and persists today. In the minds of many, even the most sophisticated, a birth defect may be perceived as a punishment. At the beginning of this century the predominant cause of birth defects was believed to be genetic, and the remaining birth defects were unsolved clinical problems. The etiology of congenital malformations can be divided into three categories: unknown, genetic, and environmental factors (table 1).

The etiology of the majority of human malformations, approximately 65 to 75 percent, is unknown (Brent 1976, 1985; Heinonen et al. 1977; Wilson 1973). However, a significant proportion of congenital malformations of unknown etiology is likely to be polygenic, that is, due

TABLE 1. *Etiology of human congenital malformations observed during the first year of life.* *

SUSPECTED CAUSE	PERCENTAGE OF TOTAL
Unknown	65-75
Polygenic	
Multifactorial (gene-environment interactions)	
Spontaneous errors of development	
Synergistic interactions of teratogens	
Genetic	10-25
Autosomal and sex-linked genetic disease	
New mutations	
Cytogenetic (chromosomal abnormalities)	
Environmental	10
Maternal conditions: Alcoholism; diabetes; endocrinopathies; phenylketonuria; smoking and nicotine; starvation; nutritional	4
Infectious agents: Rubella, toxoplasmosis, syphilis, herpes, cytomegalic inclusion disease, varicella, Venezuelan equine encephalitis, parvovirus B 19	3
Mechanical problems (deformations): Amniotic band constrictions; umbilical cord constraint; disparity in uterine size and uterine contents	1-2
Chemicals, prescription drugs, high dose ionizing radiation, hyperthermia	< 1

*Adapted from Brent (1976, 1985) and Brent and Holmes (1988).

to two or more genetic loci (Carter 1976; MacLaughlin 1977) or at least having an important genetic component. Malformations with an increased recurrent risk such as cleft lip and palate, anencephaly, spina bifida, certain congenital heart diseases, pyloric stenosis, hypospadias, inguinal hernia, talipes equinovarus, and congenital dislocation of the hip can fit the categories of multifactorial disease and polygenic inherited disease (Carter 1976; Fraser 1976).

The multifactorial/threshold hypothesis (Fraser 1976) involves the modulation of a continuum of genetic characteristics by intrinsic and extrinsic (environmental) factors. Although the modulating factors are not known, they probably include placental blood flow, placental transport, site of implantation, maternal disease states, infections, drugs, chemicals, and spontaneous errors of development.

Spontaneous errors of development may account for some of the malformations that occur without apparent abnormalities of the genome or environmental influence. The author postulates that there is a low probability for error during embryonic development based on the fact that embryonic development is a complicated process that may go awry, similar to the concept of spontaneous mutations (Brent 1964; Fraser 1976). It has been estimated that up to 50 percent of all fertilized human ova are lost within the first 3 weeks of development (Hertig 1967). The World Health Organization (1970) estimated that 15 percent of all clinically recognizable pregnancies end in a spontaneous abortion, while 50 to 60 percent of the spontaneously aborted fetuses have chromosomal abnormalities (Boue et al. 1975; Simpson 1980) (tables 2 and 3). This estimate means that, conservatively, 1,173 clinically recognized pregnancies will result in approximately 173 miscarriages, and 30 to 60 infants will have congenital anomalies in the remaining 1,000 live births. The true incidence of pregnancy loss is much higher, but undocumented pregnancies are not included in this risk estimate.

The 3 to 6 percent incidence of malformed offspring represents the background risk for human maldevelopment. It is obvious that the human species has significant developmental risks at the beginning of each pregnancy (table 2). It is important to recognize the high proportion of the population that is affected by reproductive problems before undertaking any epidemiological study dealing with reproduction. While little is known about the mechanisms that result in the in utero death of defective embryos (Warkany 1978), it is perhaps more important to

TABLE 2. *Reproductive risks in human populations.*

Reproductive Risk	Frequency
Immunologically and clinically diagnosed spontaneous abortions per 10^6 conceptions	350,000
Clinically recognized spontaneous abortion per 10^6 pregnancies	150,000
Genetic diseases per 10^6 births	110,000
Multifactorial or polygenic (genetic-environmental interactions)	90,000
Dominantly inherited disease	10,000
Autosomal and sex-linked genetic disease	1,200
Cytogenetic (chromosomal abnormalities)	5,000
New mutations	3,000
Major congenital malformations per 10^6 births (many are genetic in etiology)	30,000
Prematurity per 10^6 births	40,000
Fetal growth retardation per 10^6 births	30,000
Stillbirths per 10^6 pregnancies (>20 wks)	20,900
Infertility	15% of couples

Environmental Risk Parameters or Modifiers

A basic tenet of environmentally produced malformations is that teratogens or teratogenic milieu have certain characteristics in common and follow certain basic principles. These principles determine the

TABLE 3. *Estimated outcome of 100 pregnancies versus time from conception.*

Time from Conception	Percent Survival To Term*	Percent Death During Interval*	Last Time For Induction of Selected Malformations*
Preimplantation			
0-6 days	25	54.55	
Postimplantation			
7-13 days	55	24.66	
14-20 days	73	8.18	
3-5 weeks	79.5	7.56	22-23 days Cyclopia; sirenomelia, microtia 26 day Anencephaly 28 day Meningomyelocele 34 day Transposition of great vessels
6-9 wk	90	6.52	36 day Cleft lip 6 wk Diaphragmatic hernia, rectal atresia, ventricular septal defect, syndactyly 9 wk Cleft palate
10-13 wk	92	4.42	10 wk Omphalocele
14-17 wk	96.26	1.33	12 wk Hypospadias
18-21 wk	97.56	0.85	
22-25 wk	98.39	0.31	
26-29 wk	98.69	0.30	
30-33 wk	98.98	0.30	
34-37 wk	99.26	0.34	
38+ wk	99.32	0.68	38+ wk CNS cell depletion

SOURCE: * Data from Kline and Stein 1985.

NOTE: An estimated 50 to 70 percent of all human conceptions are lost in the first 30 weeks of gestation (Hertig 1967) and 78 percent are lost before term (Robert and Lowe 1975).

KEY: + Modified from Schardein 1985.

quantitative and qualitative aspects of environmentally produced malformations.

Embryonic Stage. The induction of malformations by environmental agents usually results in a spectrum of malformations that varies somewhat because of variations in stage of exposure and dose. The gestational period when an exposure occurs determines what structures are most susceptible to the deleterious effects of the drug or chemical and to what extent the embryo can repair the damage. Furthermore, the period of sensitivity may be narrow or broad, depending on the environmental agent and the malformation in question. Limb defects and other malformations produced by thalidomide have a very short period of susceptibility (table 4), while microcephaly produced by radiation has a long period of susceptibility.

Dose or Magnitude of the Exposure. The quantitative correlation of the severity and frequency of the embryopathic effects with the dose of a drug, chemical, or other agent is referred to as the dose-response

TABLE 4. *Human developmental stages sensitive to thalidomide teratogenesis.*

Developmental Stage (days)	Congenital Malformations
21-26	Thumb aplasia
22-24	Microtia
23-34	Hip dislocation
24-29	Amelia, upper limbs
24-33	Phocomelia, upper limbs
25-31	Preaxial aplasia, upper limb
27-32	Amelia, lower limb
28-33	Preaxial aplasia, lower limb
28-33	Phocomelia, lower limb Femoral hypoplasia Girdle hypoplasia

SOURCE: Adapted from Brent and Holmes 1988.

relationship. This is extremely important when comparing effects among different species, because usage of milligram/kilogram (mg/kg) doses are, at most, rough approximations. Dose equivalence among species can only be accomplished by performing pharmacokinetic studies, metabolic studies, and dose-response investigations in humans and the species being studied.

Threshold Dose. The threshold dose is the exposure below which the incidence of death, malformation, growth retardation, or functional deficit is not statistically greater than that of controls. The threshold level of exposure is usually from less than one to three orders of magnitude below the teratogenic or embryopathic dose for drugs and chemicals that kill or malform half of the embryos. Therefore, an exogenous teratogenic agent has a demonstrable no-effect dose as compared to mutagens or carcinogens, which have a stochastic dose response curve. Threshold phenomena are compared to stochastic phenomena in table 5. The

TABLE 5. *Relationship of the risk and nature of diseases produced by environmental agents and the exposure.*

Relationship	Pathology	Site	Diseases	Risk	Definition
Stochastic phenomena	Damage to a single cell may result in disease	DNA	Cancer, mutation	Some risk exists at all dosages; at low exposures the risk is below the spontaneous risk	The incidence of disease increases but the severity and nature of the disease remain the same
Threshold phenomena	Multicellular injury	Great variation in etiology, affecting many cell and organ processes	Malformation, growth retardation, chemical toxicity, etc.	Completely disappears below threshold dose	Both the severity and incidence of disease increase with dose

SOURCE: From Brent 1986.

severity and incidence of malformations produced by every exogenous teratogenic agent that has been appropriately tested have exhibited threshold phenomena during organogenesis (Wilson 1973).

Pharmacokinetics and Metabolism of the Agent. The physiologic alterations in pregnancy and the bioconversion of compounds can significantly influence the teratogenic effects of drugs and chemicals by affecting absorption, body distribution, active form(s), and excretion of the compound.

Placental Transport. The exchange between the embryo and the maternal organism is controlled by the placenta, which includes the chorioplacenta, the yolk sac placenta, and the paraplacental chorion. The placenta varies in structure and function among species and for each stage of gestation. As an example, the rodent yolk sac placenta continues to function as an organ of transport for a much greater part of gestation than in the human. Thus species differences in placental function and structure may affect the ability to apply teratogenic data developed in one species directly to other species, including the human (Brent 1976). As pharmacokinetic techniques and the actual measurement of metabolic products in the embryo become more sophisticated, the appropriateness of using animal data to predict human effects may improve.

While it has been alleged that the placental barrier was protective, and therefore harmful substances did not reach the embryo, it is now clear that there is no placental barrier per se. Yet the package inserts on many drugs state that "this drug crosses the placental barrier" (Brent 1982). The uninitiated may infer from this statement that this characteristic of a drug is both unusual and hazardous. The fact is that most drugs and chemicals cross the placenta. It would be a rare substance that could cross the placental barrier in one species, yet be unable to reach the fetus in another. No such chemical exists, except for selected proteins and many macromolecules whose actions are species-specific.

Species Differences. The genetic constitution of an organism is an important factor in a species' susceptibility to a drug or chemical. More than 30 disorders of increased sensitivity to drug toxicity or effects have been reported in humans due to an inherited trait (McKusick 1988). The effect of a drug or chemical depends on both the maternal and fetal genotypes, and may result in differences in cell sensitivity, placental transport, absorption, metabolism (activation, inactivation, active metabolites), receptor binding, and distribution. Differences in any of

these areas may account for some variations in teratogenic effects among species and in individual subjects.

Evaluation of Drugs and Chemicals for Potential Teratogenicity in the Human

While human epidemiological studies and clinical teratology observations are the foundation of teratogen discovery, chemicals and drugs can be evaluated for fetotoxic potential using in vivo animal studies and in vitro systems. It should be recognized that these nonhuman testing procedures are only one component in the process of evaluating the potential teratogenic risk of drugs and chemicals in humans. When possible, the evaluation of drug and chemical teratogenicity should include data obtained from human epidemiological studies, secular trend data in humans, animal developmental toxicity studies, the dose-response relationship to the teratogen and the relationship to the human pharmacokinetic equivalent dose in the animal studies, and considerations of biological plausibility (table 6) (Brent 1978, 1983, 1986; Shepard 1986). This method is of greatest value when used to evaluate chemicals and drugs that have been in use for some time, and (to a lesser extent) to evaluate new drugs that have a similar mechanism of action, structure, pharmacology, and purpose relative to other agents that have been extensively studied.

TABLE 6. *Proof of teratogenesis in the human.*

1)	Controlled epidemiologic studies consistently demonstrate an increased incidence of a particular spectrum of congenital malformation in exposed human populations.
2)	Secular trends demonstrate a relationship between the incidence of a particular malformation and changing exposures in human populations.
3)	An animal model mimics the human malformations at clinically comparable exposures.
4)	The teratogenic effects increase with dose.
5)	The mechanisms of teratogenesis are understood and/or the results are biologically plausible.

SOURCE: Brent 1986.

TABLE 7. *Human teratogens identified since the thalidomide tragedy by human epidemiological studies, alert physicians or scientists, and/or animal studies.*

Teratogenic agents	Year	Human studies	In vivo or in vitro animal studies
Anticonvulsants			
(Chronic administration)			
Hydantoins	1963	++	
Trimethadione	1970	++	
Valproic acid	1982	++	+
Vitamin analogs			
Hypervitamin A	1953		+
Isotretinoin Etretinate	1983	++	++
PCBs	1968	++	
Coumarin	1968	++	
Alcohol	1967	++	
Lithium	1970	++	
Diethylstilbestrol	1971	++	
Penicillamine	1971	++	
ACE inhibitors	1982	++	
Chorionic villus sampling	1991	++	+ / -

KEY: ++ Indicates that it was the major factor in the discovery of a human teratogenic effect.
+/- Findings controversial.
+ Indicates that it contributed to the suspicion that there was a teratogenic effect.

Few human teratogens have been initially discovered from animal experiments (table 7). Animal experiments are very helpful in supporting consistent findings discovered in human epidemiological studies or to study mechanisms of teratogenesis and the pharmacokinetics of reproductive toxins.

Some investigators and regulatory agencies divide drugs and chemicals into teratogenic and nonteratogenic compounds. In reality, teratogenic potential can only be evaluated if one considers the agent, the dose, the species, and the stage of gestation at the time of administration. For

example, vitamin A and aspirin are not teratogenic during the sensitive organogenetic period if used in their appropriate dose, although they are teratogenic at higher exposures. Working definitions are suggested.

- *Human Teratogen:* An agent or milieu that has been demonstrated to produce permanent alterations in the human embryo or fetus following intrauterine exposures that usually occur or are attainable.

- *Potential Human Terutogen:* An agent or milieu that has not been demonstrated to produce permanent alterations in the embryo or fetus following intrauterine exposures that usually occur or are attainable, but can affect the embryo or fetus if the exposure is substantially greater than the usual human exposure.

- *Nonhuman Teratogen:* An agent or milieu that has no embryotoxic or fetotoxic potential because it is nontoxic at any dose, or because it is so toxic to the mother that it kills the mother before or at the same dose that it begins to affect the embryo.

Potential human teratogens constitute the largest group, because it includes all drugs and chemicals that can produce embryotoxic and fetotoxic effects at some exposure. Since these exposures do not occur or are not attained in humans, they usually represent no risk or minimal risks to the human embryo.

PRINCIPLES OF CLINICAL TERATOLOGY

Clinicians and scientists' misconceptions have lead to some confusion regarding the potential effects of proven teratogens. Erroneous dogma include the following concepts:

- If an agent can produce one type of malformation, it can produce any malformation.

- An agent presents a risk at any dose once it is proven to be teratogenic.

Both of these concepts are wrong. The contributions of clinical teratologists and dysmorphologists clearly indicate that proven teratogens do not have the ability to produce every birth defect. More importantly, the concept of the syndrome in clinical medicine is probably more

appropriate in clinical teratology than any other area of clinical medicine. Many teratogens can be identified on the basis of the malformations that are produced. It is also true that there is substantial overlap in malformation syndromes. The syndromes may not always be separable, and environmentally produced birth defects may be confused with genetically determined malformations. As an example, a patient with bilateral radial aplasia and a ventricular defect may have Holt-Oram syndrome or thalidomide teratogenesis. It may or may not be possible to make a definitive diagnosis, even with a history of thalidomide ingestion during pregnancy.

The specificity of some environmental teratogens can sometimes point to the mechanism or site of action. For instance, the predominant central nervous system (CNS) effects of methyl mercury are understood when one realizes the propensity for organic mercury to be stored in lipid.

Similar symptoms or signs appear in many teratogenic syndromes and are therefore not very discriminating, such as growth retardation or mental retardation. On the other hand, rare or specific neurologic effects such as deafness, retinitis, or the pattern of cerebral calcifications may point to a specific teratogen.

Epidemiologists sometimes use poor judgment when collating and classifying malformations. As an example, limb reduction defects (LRD) are frequently studied with regard to their association with environmental teratogens. In many of the studies, limb defects that are clearly related to problems of organogenesis are classified with congenital amputations. Yet it is very unlikely that any agent being studied is responsible for both types of malformations. It is clear that epidemiological studies could be markedly improved if there were more input from clinical teratologists in planning and performing the studies.

HUMAN TERATOGENS

There are over 40 environmental agents or groups of agents that result in reproductive toxicity, teratogenicity, or both (table 8). In the past few years, new teratogens that produce vascular disruptive phenomena have been reported, such as chorionic villus sampling, misoprostol, and most recently cigarette smoking. All of these agents are low risk teratogens

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations.*

Environmental influence	Reported effects or associations	Comments
Alcohol	Fetal alcohol syndrome: intrauterine growth retardation (IUGR), maxillary hypoplasia, reduction in width of palpebral fissures. characteristic but not diagnostic facial features microcephaly, mental retardation.	Direct cytotoxic effects of ethanol and indirect effects of alcoholism. Consumption of 6 oz. of alcohol or more per day constitutes a high risk; likely that detrimental effects can occur at lower exposures. Threshold teratogenic dose is likely; varies in individuals due to multiple factors.
Aminopterin, Methotrexate	Microcephalus, hydrocephalus, cleft palate, meningomyelocele, IUGR, abnormal cranial ossification, reduction in derivatives of first branchial arch mental retardation, postnatal growth retardation.	Anticancer, antimetabolic agents; folic acid antagonists that inhibit dihydrofolate reductase, resulting in cell death.
Androgens	Masculinization of female embryo: clitotomegaly with or without fusion of labia minora Nongenital malformations not a reported risk.	Effects are dose dependent; stimulates growth and differentiation of sex steroid receptor-containing tissue.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Angiotensin converting enzyme (ACE) inhibitors	Fetal and neonatal death, oligohydramnios, pulmonary hypoplasia, neonatal anuria, IUGR, and skull hypoplasia.	Antihypertensive agents; adverse fetal effects are related to severe fetal hypotension over a long period of time during the second or third trimester. Risk appears to be low. If a woman becomes pregnant, therapy can be changed during the first trimester without increased risk of teratogenesis. This group of drugs does not interfere with organogenesis.
Caffeine	Teratogenic in rodent species with doses of 150 mg/kg. There is no convincing data that moderate or usual exposures present a measurable teratogenic risk. Some epidemiological studies indicate small differences in growth and pregnancy loss in the caffeine-exposed groups; many other studies are negative. Co-use of alcohol and tobacco makes analysis extremely difficult.	Exposure to 300 mg caffeine per day or less presents no reproductive risks. Behavioral effects reported but appear to be transient or temporary, although more research is needed. No evidence that a fetal caffeine syndrome exists for any malformation or group of malformations.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Carbamazepine	Minor craniofacial defects (upslanting palpebral fissures, epicanthal folds, short nose with long philtrum), fingernail hypoplasia, and developmental delay.	Anticonvulsant; little known concerning mechanism. Risk unknown but likely to be significant for minor defects.
Cocaine	Preterm delivery; fetal loss; IUGR; microcephaly; neurobehavioral abnormalities; vascular disruptive phenomena resulting in limb amputation, cerebral infarctions and certain types of visceral and urinary tract malformations. Poor nutrition accompanies drug abuse, and multiple drug use is common. Because of the mechanism of cocaine teratogenicity, a well-defined cocaine syndrome is not likely.	Cocaine causes a complex pattern of cardiovascular effects due to its local anesthetic and sympathomimetic activities in the mother. Fetopathology likely due to decreased uterine blood flow and fetal vascular effects. Significant risk of deleterious effects on fetal outcome. Low risk of major disruptive effects, but can occur in the latter portion of the first trimester as well as the second and third trimester.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Chorionic villus sampling (CVS)	Low but increased risk of orofacial malformations and limb reduction defects of the congenital amputation type as seen in vascular disruption malformations.	Reports from several clinics; many large clinical programs using CVS do not report an increase in LRD in the offspring. Undetermined whether technical skill in CVS, ascertainment bias, or clustering accounts for these findings.
Coumarin	Nasal hypoplasia, stippling of secondary epiphysis; IUGR, anomalies of eyes, hands, neck, variable CNS anatomical defects such as absent corpus callosum. hydrocephalus, or asymmetrical brain hypoplasia.	Anticoagulant; bleeding is an unlikely explanation for effects produced in the first trimester. Risk 10 to 25 percent during 8th to 14th week of gestation. CNS anatomical defects may occur anytime during second and third trimester and may be related to bleeding.
Cyclophosphamide	Growth retardation, ectrodactyly, syndactyly, cardiovascular anomalies, and other minor anomalies.	Anticancer, alkylating agent; requires cytochrome P450 monooxydase activation; interacts with DNA, resulting in cell death. Magnitude of risk unknown.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Diethylstilbestrol (DES)	Clear cell adenocarcinoma of the vagina occurs between 1:1,000 and 1: 10,000 in girls exposed in utero. Vaginal adenosis much more frequent. Anomalies of the uterus and cervix may play a role in decreased fertility and increased prematurity although the majority of DES babies can conceive and deliver normal babies. Case reports of masculinization of the female fetus after high doses. The dose that increases risk of genitourinary abnormalities in the male is controversial.	Synthetic estrogen; stimulates estrogen receptor-containing tissue, may cause misplaced genital tissue which has a greater propensity to develop cancer. Vaginal adenosis from exposures before 9th week of pregnancy, 75 percent risk; risk of adenocarcinoma is low (1 in 10,000).
Diphenylhydantoin	Hydantoin syndrome: microcephaly, mental retardation, cleft lip/palate, hypoplastic nails and distal phalanges; characteristic, but not diagnostic facial features.	Anticonvulsant; direct effect on cell membranes, folate, and vitamin K metabolism. Metabolic intermediate (epoxide) suggested as the teratogenic agent. Wide variation in reported risk. Associations documented only with chronic exposure.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Electromagnetic fields (EMF)	Although there are reports that video display terminals (VDT) and power lines are associated with abortion and congenital malformations in the offspring of exposed mothers, the majority of studies do not support this association.	Pregnant animals exposed to EMF do not exhibit consistent or reproducible reproductive effects. Human exposures to VDTs and power lines are quite low and are unlikely to have reproductive effects. Questions about biologic effects from frequencies and wave forms of magnetic fields have not been adequately studied.
Infectious agents		Cytotoxic effects and inflammatory responses from fetal infections interfere with organogenesis and/or histogenesis. Characteristic syndromes related to the specific tissue localizaton and pathologic characteristics of the infectious agent and the duration of infectious process in embryo and fetus.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Infectious agents (cont.)		
Rubella	>80 percent incidence of embryonic infection with exposure in first 12 weeks, 54 percent at 13 to 14 weeks, 25 percent at end of second trimester, and 100 percent at term. Defects include mental retardation, deafness, cardiovascular malformations, cataracts, glaucoma, microphthalmia.	
Cytomegalovirus	IUGR. Risk of brain damage is 50 percent after infection early in pregnancy. Characteristic parenchymal calcification.	
Herpes simplex	Generalized organ infections, microcephaly, hepatitis, eye defects, vesicular rash. Maternal infection can be transmitted in utero or perinatally.	
Parvovims B 19	Infection can result in erythema infectiosum in children; in the fetus can result in hydrops fetalis and fetal death. Congenital anomalies likely to be very rare.	

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Infectious agents (cont.)		
Syphilis	Defects in 50 percent of offspring after early exposure to primary or secondary syphilis and 10 percent after late exposures. Defects include maculopapular rash, hepatosplenomegaly. deformed nails, osteochondritis at joints of extremities, congenital neurosyphilis, abnormal epiphyses, chorioretinitis.	
Toxoplasmosis	Hydrocephaly, microphthalmia, chorioretinitis. Risk is predominantly associated with maternal infection during pregnancy.	
Varicella-zoster	Skin and muscle defects, IUGR, LRD. No measurable increase in risk of classical early teratogenic effects. Actual risk of maternal varicella during pregnancy is quite low. Great risk of severe neonatal varicella if maternal infection occurs in last week of pregnancy.	

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Infectious agents (cont.)		
Venezuelan equine encephalitis	Hydroanencephaly, microphthalmia, CNS destructive lesions, and luxation of hip.	
Lead (serum levels of 10-25 µgm %)	While there is no indication that serum lead levels of this magnitude can result in congenital malformations in exposed embryos and fetuses, there are indications that the developing CNS in the fetus and child may be susceptible to lead effects resulting in decreased IQ and behavioral effects.	There is clear evidence that lead levels that result in anemia and encephalopathy (serum levels > 50-70 µgms %) can have serious effects on CNS development. Human studies indicate small deficiencies in IQ in patients with 20-25 µgm % serum level; there could be other explanations for these IQ differences. Pathological findings have not been described in the brain at these levels.
Lithium carbonate	Animal studies have demonstrated a clear teratogenic risk, effect in humans is uncertain. Early reports indicated an increased incidence of Ebstein's anomaly and other heart and great vessel defects, but as more studies are reported the magnitude of this association has diminished.	Antidepressant; mechanism undefined. Risk is low.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Maternal conditions		
Diabetes	Caudal dysplasia or caudal regression syndrome, congenital heart disease, anencephaly.	Insulin therapy protects the fetus. Fetal growth retardation may result from vascular lesions in long standing diabetics which can produce placental dysfunction, and from hyperglycemia as well as undetermined metabolic alterations.
Maternal endocrinopathy	If condition is compatible with pregnancy, effects are similar to those following administration of high doses of the hormone.	Receptor-mediated exposures to high levels of hormone (hypercorticosteroidism, hyperthyroidism, hyperinsulinism, hyperandrogens, etc.).
Nutritional deprivation	CNS anomalies, IUGR, and increased morbidity. In many instances of teratogenesis, abnormal nutrition may be the final common mechanism for teratogenesis.	The high mitotic rate of the fetus in general and the CNS in particular is very sensitive to severe alterations in nutrient supply.
Phenylketonuria	Mental retardation, microcephaly, IUGR, embryonic and fetal loss.	High levels of phenylalanine interfere with embryonic cell metabolism.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Mechanical problems	Birth defects such as club feet, limb reduction defects, aplasia cutis, cranial asymmetry, external ear malformations, midline closure defects, and muscle aplasia.	Physical constraint can result in distortion and a reduction in blood supply and is more frequent in pregnancies with multiple concepti, abnormal uteri, amniotic abnormalities, certain placental abnormalities, and oligohydramnios.
Methylmercury	Minamata disease: cerebral palsy, microcephaly, mental retardation, blindness, cerebellar hypoplasia.	Organic mercurials have a propensity to accumulate in lipid tissue, causing cell death due to inhibition of cellular enzymes, especially sulfhydryl enzymes. Since most cases are the result of accidental environmental exposure, estimation of risk is usually retrospective.
Misoprostol	A synthetic prostaglandin analog that is used illegally by millions of women for the purpose of abortion. A low but significant increase in vascular disruptive phenomenon such as LRD. Mobius syndrome has been reported.	Classical animal teratology studies would not be helpful in discovering these effects because vascular disruptive effects occur after early organogenesis and are low risk phenomena.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Oxazolidine-2,4-diones (Trimethadione, paramethadione)	Fetal trimethadione syndrome: V-shaped eyebrows, low-set ears with anteriorly folded helix, high-arched palate, irregular teeth, CNS anomalies, severe developmental delay.	Anticonvulsants; affects cell membrane permeability. Actual mechanism of action undetermined. Wide variation in reported risk. Characteristic facial features documented only with chronic exposure.
Penicillamine	Cutis laxa, hyperflexibility of joints.	Copper chelating agent; produces copper deficiency inhibiting collagen synthesis and maturation. Condition appears to be reversible and the risk is low.
Polychlorinated biphenyls (PCBs)	Cola-colored children; pigmentation of gums, nails, and groin; hypoplastic deformed nails; IUGR, abnormal skull calcification.	Environmental contaminants; PCBs and commonly occurring contaminants are cytotoxic. Body residues in women with large exposures can affect subsequent offspring for up to 4 years after exposure.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Progestins	Masculinization of female embryo exposed to high doses of some testosterone derived progestins. Dose of progestins in modem oral contraceptives presents no masculinization or feminization risks. All progestins present no risk for nongenital malformations.	Stimulates or interferes with sex steroid receptor-containing tissue.
Radioactive isotopes	Tissue- and organ-specific damage dependent on the radioisotope element and distribution; i.e., ^{131}I. If administered to pregnant mother can cause fetal thyroid hypoplasia after the 8th week of development.	Higher doses of radioisotopes can produce cell death and mitotic delay. Effect is dependent on dose, distribution, metabolism, and specificity of localization.
Radiation (external irradiation)	Microcephaly, mental retardation, eye anomalies, IUGR, visceral malformations depend on dose and stage of exposure.	Therapeutic radiation produces cell death and mitotic delay. No measurable risk with exposures of 5 rad (0.05 Gy) or less of x rays at any stage of pregnancy.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Retinoids, systemic administration (Etrentinate, isotretinoin)	Increased risk of CNS, cardioaortic, ear, and clefting defects. Microtia, anotia, thymic aplasia, and other branchial arch and aortic arch abnormalities.	Used in treatment of chronic dermatoses; retinoids can cause direct cytotoxicity and alter programmed cell death; affect many cell types, but neural crest cell derivatives are particularly sensitive.
Retinoids, topical (Tretinoin)	Case reports of malformed offspring of mothers who used topical tretinoin for treatment of acne or skin aging. All studies reported do not suggest that topical tretinoin presents a reproductive risk. The epidemiological studies, animal studies, and absorption studies in humans do not suggest a teratogenic risk.	Systemically administered retinoids clearly have varying teratogenic potential. Topical administration of tretinoin in animals in therapeutic doses are not teratogenic; massive exposures can produce maternal toxicity and reproductive effects. More importantly, topical administration in humans results in nonmeasurable blood levels.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Smoking and nicotine	Placental pathology and IUGR. Increased postnatal morbidity and mortality. Some studies report increases in anatomical malformations; most studies do not report an association, At present, no syndrome is associated with maternal smoking, except for the recent report of vascular disruptive phenomena.	Maternal or placental complications can result in fetal death. While tobacco smoke contains many components, nicotine can result in vascular spasm and vasculitis which can result in a higher incidence of placental pathology. Poor placental perfusion could account for the decreased fetal size. It is of interest that this growth retardation is recuperable postnatally.
Sonography (ultrasound)	No confirmed detrimental effects resulting from medical sonography.	Levels and types of medical sonography used in the past have no measurable risks. Apparently, if the embryonic temperature never exceeds 39°C. there is no measurable risk.
Tetracycline	Bone staining and tooth staining can occur with therapeutic doses. Persistent high doses can cause hypoplastic tooth enamel. No other congenital malformations are associated.	Antibiotic; effects seen only if exposure is late in the first or during second or third trimester, since tetracyclines have to interact with calcified tissue.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Thalidomide	LRDs (preaxial preferential effects, phocomelia), facial hemangioma, esophageal or duodenal atresia, anomalies of external ears, kidneys, and heart. The thalidomide syndrome, while characteristic and recognizable, can be mimicked by some genetic diseases.	Sedative-hypnotic agent; multiple theories have been proposed. While it is likely that one or more of the theories have elements of the truth, the etiology of thalidomide teratogenesis has not been definitively determined.
Thyroid: Iodine deficiency, iodides, radioiodine, antithyroid drugs (Propylthiouracil)	Hypothyroidism or goiter; neurologic and aural damage is variable.	Fetopathic effect of endemic iodine deficiency occurs early in development. Fetopathic effect of iodides, antithyroid drugs, and radioiodine involves metabolic block, decreased thyroid hormone synthesis and gland development. Maternal intake of 12mg of iodide per day or more increases the risk of fetal goiter.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Valproic acid	Primarily facial dysmorphology and neural tube defects. Some facial characteristics associated with this drug; they are not diagnostic. Small head size and developmental delay have been reported with high doses.	Anticonvulsant; little is known about the teratogenic action of valproic acid. The risk for spina bifida is about 1 percent, but the risk for facial dysmorphology may be greater.
Vitamin A	Same malformations reported with the retinoids also reported with very high doses of vitamin A. Exposures below 10,000 I.U. present no risk to the fetus.	Retinoic acid is cytotoxic; it may interact with DNA to delay differentiation and/or inhibit protein synthesis.
Vitamin D	Large doses given as vitamin D prophylaxis are possibly involved in the etiology of supravalvular aortic stenosis, elfin faces, and mental retardation.	Mechanism likely to involve a disruption of cell calcium regulation. Genetic susceptibility and excessive doses are probably responsible.

TABLE 8. *Environmental influences on human teratogenesis: Effects, associations, and allegations (continued).*

Environmental influence	Reported effects or associations	Comments
Streptomycin	Hearing deficiency.	Although only rarely reported, streptomycin and a group of ototoxic drugs can interfere with hearing. Relatively low risk, associated with long duration maternal therapy during pregnancy.
Bendectin (doxylamine succinate pyridoxine)	Not teratogenic as used in doses to treat nausea and vomiting of pregnancy.	This drug is included because it was involved in so much litigation as an alleged teratogen. It is a drug with no measurable risk.

and therefore were difficult to discover. Vascular disruption is of interest because it is a likely cause of a significant proportion of LRD, believed to be one of the mechanisms of cocaine teratogenicity, another low-risk teratogen.

Table 8 lists human teratogens and reproductive toxins, their known effects, and when possible, their mechanism of action.

Because this chapter is directed toward investigators interested in the effects of illicit drugs and abused drugs and chemicals, the remainder of the discussion deals with these agents. Certain other reproductive toxins are discussed because they are teratogenic or toxic late in gestation, or because they clarify the mechanisms of some teratogenic illicit drugs or chemicals.

Major Illicit Drugs of Abuse

There does not appear to be a significant increase in teratogenic risk associated with the abuse of narcotics, marijuana, benzodiazepines, barbiturates, or amphetamines. However, increased fetal wastage, intrauterine growth retardation (IUGR), and complications of pregnancy are associated with the abuse of some of these drugs. The most difficult parameters to evaluate are the postnatal neurobehavioral effects such as developmental delay, minimal changes in intelligence quotient (I.Q.), and occurrence of impulsivity, hyperactivity, and other reported neuro-behavioral effects that may be transient or permanent. The question that is very difficult to answer is whether these changes, if present, are increased in the exposed groups; if increased, are they due to the intrauterine drug exposure or to other factors such as differences in maternal postnatal rearing practices?

The contribution of substance abuse (narcotics, cocaine, marijuana, benzodiazepines, barbiturates, amphetamines, toluene) to the incidence of congenital malformations is difficult to assess because street drugs are of variable potency and purity, abusers neglect health care and nutrition, the frequency of multiple drug use is high, and there is a high incidence of infections and venereal disease among drug abusers (Finnegan 1984). While there does not appear to be a definite teratogenic effect for most of these drugs, cocaine is an important exception. Along with increased perinatal morbidity, the available evidence indicates that cocaine does produce various types of vascular disruption and therefore has teratogenic potential.

Cocaine (benzoylmethylecgonine) is prepared from the leaves of the plants *Erythronylon coca* and, to a lesser extent, *Truxillo coca*. Cocaine in powder form is a water-soluble salt, cocaine hydrochloride, that may be adulterated by sugars, stimulants, or local anesthetics (Johanson and Fischman 1989). Cocaine has a half-life of about 40 to 60 minutes after intravenous (IV) or intranasal administration (Javaid et al. 1983). Crack or freebase cocaine is the highly purified alkaloidal form (Johanson and Fischman 1989) that, when smoked, produces a rapid increase in blood concentration and has a half-life similar to IV administration (Fischman 1988; Johanson and Fischman 1989; Scott and Purohit 1989). Cocaine is metabolized primarily by plasma and liver cholinesterase to water-soluble metabolites (benzoylecgonine and ecgonine methyl ester) that are excreted in the urine (Vitti and Boni 1985). Fetuses and pregnant women have low plasma cholinesterase activity, and are therefore likely to be more sensitive to the effects of cocaine than nonpregnant adults (Johanson and Fischman 1989).

Since cocaine is lipid soluble, 8.7 percent protein bound, has a low molecular weight, and is a weak base, it is not surprising that it crosses the placenta via diffusion. Cocaine users often abuse more than one substance, suffer from malnutrition, and neglect prenatal medical care (Kreek 1988; MacGregor et al. 1987, 1989). Cocaine use during pregnancy has been associated with abruptio placenta, preterm labor and delivery, fetal loss, decreased birth weight, microcephaly, limb defects, urinary tract malformations, and neurobehavioral abnormalities (Chasnoff et al. 1985, 1987, 1989a,b; Hadeed and Siegel 1989; MacGregor et al. 1987; Ryan et al. 1987).

The initial maternal effects of cocaine include hypertension, tachycardia, mydriasis, and hyperpyrexia. Temperatures rise as high as 45°C during acute intoxication. These sympathomimetic effects of cocaine are mediated by the inhibition of presynaptic catecholamine reuptake. Freebase cocaine may cause more vasoconstriction than intranasally administered cocaine. Placental vasoconstriction (Sherman and Gautieri 1972) and increased uterine contractility (Lederman et al. 1978) have been reported in pregnant women using cocaine. Cocaine has been shown to decrease uterine blood flow in animal studies (Moore et al. 1986; Woods et al. 1987) and to produce congenital malformations following administration during midgestation in the rat (Webster and Brown-Woodman 1990). A reduction in uterine blood flow due to the vasoconstrictive action of cocaine may cause hypoxia and infarction in

the brain, limbs, face, or visceral organs of the developing fetus (Chasnoff et al. 1988; Graham et al. 1980; Heier et al. 1991).

There is a substantial body of evidence indicating the vascular pathogenesis of major malformations that could be induced, not only during organogenesis, but also during later stages of development with high doses of cocaine in experimental animals (Franklin and Brent 1960a,b; Webster and Brown-Woodman 1990) and in humans (Bouwes-Bavinck and Weaver 1986; Carey et al. 1982; Graham 1986). Furthermore, because cocaine readily crosses the placenta and produces a cardiovascular response in the fetus similar to that during maternal administration (Chasnoff et al. 1989a, *b;* Woods et al. 1987), local vasoactive effects may exaggerate the deleterious effects caused by reduced uterine blood flow (Chavez et al. 1989). Localized hemorrhagic and cavitary lesions, as well as a generalized cerebral injury, have been reported in newborns of chronic cocaine abusers (Chasnoff et al. 1989a; Heier et al. 1991).

Although vasoconstrictive action on uterine and fetal blood vessels could explain the observed malformations associated with exposure to cocaine (Chasnoff et *al.* 1985, 1987, 1989a,b; Chavez et al. 1989; Franklin and Brent 1960b), cocaine does not cause a morphologically specified fetal cocaine syndrome analogous to fetal alcohol syndrome (FAS) (Brent 1990). Malformations with a vascular disruptive pathogenesis vary too widely between patients to constitute a recognized syndrome. Nevertheless, the reported fetal effects all appear to be various types of vascular disruptive phenomena: congenital limb amputations, cerebral infarctions, and certain types of visceral and urinary tract malformations. Experimental animal studies and human epidemiology indicate that the risk of major malformation from cocaine is low, but the malformations or embryopathic effects may be severe.

Toluene and Gasoline. Although occupational exposure to toluene has not been proven to cause congenital malformations, there are case reports of malformations resulting from toluene abuse. Three case reports of abuse throughout pregnancy described microcephaly, CNS defects, minor craniofacial and limb abnormalities, and variable growth retardation (Hersh et al. 1985). If there is an increased risk, it appears to be confined to toluene abusers, and of course the risk depends on the exposure. Two children with severe mental retardation and abnormal neurological findings following excessive prenatal gasoline exposure were reported by

Hunter and colleagues (1979). Gasoline was inhaled for recreational purposes during each of these pregnancies.

Addictive Drugs and Chemicals That Are Legal

Alcohol. Jones and Smith (1973) described FAS in children with IUGR, microcephaly, mental retardation, maxillary hypoplasia, flat philtrum, thin upper lip, and reduction in the width of palpebral fissures (cardiac abnormalities also were seen). Many children of alcoholic mothers had FAS, and all of the affected children evidenced developmental delay (Jones and Smith 1973, 1975; Jones et al. 1974).

A period of greatest susceptibility and a threshold dose have not yet been established. Although researchers are reluctant to claim that malformations are due to single exposures to alcohol in the human, binge drinking early in pregnancy has been suggested to be associated with neural tube defects (Graham 1985). Actually the neural tube defects, if real, are a minor risk when compared to the risk of decreased brain growth and differentiation that results from high alcohol consumption during the second and third trimester. Chronic consumption of 6 ounces of alcohol per day constitutes a high risk, while FAS is not likely when the mother has fewer than 2 drinks (equivalent to 2 ounces of alcohol) per day (Streissguth et al. 1980). Reduction of alcohol consumption at any time in pregnancy reduces the severity of FAS, but may not significantly reduce the risk of some degree of physical or behavioral impairment. The human FAS is likely to involve the direct effects of ethanol and the indirect effects of genetic susceptibility and poor nutrition. Although alcoholic mothers frequently smoke and consume other drugs, there is little doubt that alcohol ingestion alone can have a disastrous effect on the developing embryo or fetus. It is estimated that there are at least several hundred children born each year with full FAS and probably several thousand children with fetal alcohol effects.

Tobacco. Placental lesions and IUGR have been consistently reported in epidemiological studies involving pregnant women who smoke cigarettes. Increased postnatal morbidity and mortality have also been reported. While there have been some studies reporting increases in anatomical malformations, most studies do not report an association. At present, there is no syndrome associated with maternal smoking. Maternal or placental complications can result in fetal death. While tobacco smoke contains many components, nicotine can result in vascular spasm or vasculitis which cause a higher incidence of placental

pathology. The pharmacology of nicotine is consistent with the concept that smoking might have the potential for producing vascular disruptive phenomena, albeit in a very low incidence.

Caffeine. Caffeine in food and beverages is consumed in large quantities by most of the world's human population. Consumption in the United States is estimated to be 4.5 kg/person/year (Narod et al. 1991). Thus, if coffee or other foods containing caffeine had any measurable risk of interfering with embryonic development, the reproductive consequences could be very significant.

Caffeine is a methylated xanthine that acts as a CNS stimulant. It is contained in many beverages including coffee, tea, and colas, as well as chocolate. Caffeine constitutes 1 to 2 percent of roasted coffee beans, 3.5 percent of fresh tea leaves, and about 2 percent of mate leaves (Graham 1984a,b). Caffeine also constitutes a substantial portion of many over-the-counter (OTC) medications such as cold and allergy tablets, headache medicines, diuretics, and stimulants. The OTC medications contributed only a small proportion of the daily caffeine intake when compared with caffeine intake from beverages and food according to the Food and Drug Administration (FDA) (1980). The per capita consumption of caffeine from all sources is estimated to be about 200 mg/day, or about 3 to 7 mg/kg consumed per day (Barone and Roberts 1984). Consumption of caffeinated beverages during pregnancy is quite common (Hill et al. 1977), and is estimated to be approximately 144 mg of caffeine per day (Morris and Weinstein 1981).

The reproductive risks of caffeine have been reviewed and evaluated using data from human epidemiological studies, animal studies, and basic science principles (Schardein 1993). The evaluation indicates that caffeine consumption can result in congenital malformations in experimental animal models at a dose substantially above the dose received in ordinary human consumption. Although some human epidemiological studies have reported an association between caffeine ingestion and an increase in reproductive effects, the majority of human epidemiological studies do not indicate that there is an increased risk of spontaneous abortion or congenital malformations in the offspring of mothers who consume less than 300 mg of caffeine per day during pregnancy. Even the positive clinical studies do not indicate an increase in the kind of malformations that one would expect to observe, namely, vascular disruptive lesions. It appears that caffeine is another chemical that has the potential for injuring the embryo, but the usual range of

human exposures is below the threshold dose that would result in reproductive effects. Most reviewers and investigators concluded that there is a threshold below which caffeine does not exert a detrimental effect, and the usual human consumption falls in this nontoxic range.

Teratogenic Agents with Unique Characteristics

The following two summaries describe the teratogenic milieu that result in malformations that were not predicted by animal studies, either because of low risk or because the drug had its greatest deleterious effect at a time that is not usually associated with a teratogenic effect.

Chorionic Villus Sampiing (CVS) and the Occurrence of Limb Reduction Defects. Although there had been reports of limb reduction defects of the vascular-disruption type in fetuses and newborns whose mothers underwent CVS (Christiaens et al 1989, Planteydt et al. 1986), it was Firth and colleagues (1991) and Boyd and colleagues (1990) whose reports raised concern about the possible increased risk of some type of birth defects in infants who were exposed to CVS in utero. Although it appears clear that several clinical groups with modest populations of infants exposed to CVS have a definite but small increased frequency of LRD of the congenital amputation type, there are other large series that do not report an increase in the incidence of congenital malformations.

The spectrum of malformations that appears to be associated with CVS includes LRD and orofacial malformations, including cleft lip and hypoglossia. The pathophysiological explanation suggested is that the malformations are due to the hemorrhage associated with the sampling of the chorion, which is followed by insufficient perfusion of the limb, face, and tongue. These types of malformations have been reported to be associated with other procedures that produce vascular disruption (Brent 1990; Brent and Franklin 1960; Webster et al. 1987). It appears that the apparent risk of the procedure is greatest from the 50th to the 70th post-conception days. Yet very large series report that the procedure is very safe (Rhodes et al. 1989). Are the complications that have been reported due to variations in the CVS procedure or the experience of the operator? At this time the consensus is that there is a real but small risk associated with the procedure. Since CVS offers some advantages to certain patients, it will be important to determine whether a safer procedure can be designed.

Angiotensin Converting Enzyme (ACE) Inhibitors. The ACE inhibitors are discussed to emphasize the fact that a drug can have minimal or no effects during the period of early organogenesis, yet have severe developmental effects in the second and third trimesters. Warfarin has similar properties, except that there are two periods during fetal development when deleterious effects can be produced by war-farm: abnormalities of cartilage development may occur in the latter half of the first trimester, and brain hemorrhage may occur in the second and third trimester. The conventional animal teratology studies would miss the effects of the ACE inhibitors and warfarin.

ACE is a dipeptidyll-carboxypeptidase that catalyses the conversion of the biologically inactive decapeptide angiotensin I to the active octapeptide angiotensin II. Angiotensin II is one of the most potent vasoconstrictors known. Captopril and enalapril, competitive inhibitors of this enzyme, are used to treat resistant hypertension. Adverse effects on the fetus of a pregnant woman treated with captopril beginning in the 26th week of gestation were first reported in 1981 (Guignard et al. 1981). Oligohydramnios was detected 2 weeks later, and a Cesarean delivery was performed in the 29th week due to fetal distress. The child was anuric and hypotensive, and died on day 7. The kidneys and bladder were normally developed, but hemorrhagic foci were found in the renal cortex and medulla.

There have been several recent reports of oligohydramnios, neonatal amuria, mild to severe IUGR, renal tubular dysplasia, and fetal death resulting from maternal therapy with ACE inhibitors (Boutroy et al. 1984; Guignard and Gouyon 1988; Knott et al. 1989; Kreft-Jais et al. 1988; Mehta and Modi 1989; Rosa et al. 1989; Rothberg and Lorenz 1984; Schubiger et al. 1988; Scott and Purohit 1989; Smith 1989; Tchobroutsky et al. 1987). Animal studies have shown that ACE inhibitors cross the placenta and are fetotoxic, but not directly teratogenic (Batastini et al. 1988; Binder et al. 1989; Broughton et al. 1982; Ferris and Weir 1983; Keith et al. 1982). However, there are now four case reports of skull hypoplasia in the human fetus of mothers who had received ACE inhibitors (Barr 1990; Duminy 1981; Rothberg and Lorenz 1984; Schardein 1985).

The animal studies and the human case reports suggest that ACE inhibitors do not cause congenital malformations by interfering with organogenesis. The evidence suggests that fetal and neonatal mortality, oligohydramnios, neonatal anuria, renal tubular dysplasia, IUGR, and

skull hypoplasia are related to severe fetal hypotension occurring over a long period of time during the second and third trimester. Although the teratogenic risk appears to be low, the fetotoxic effects are severe. One can infer that adverse fetal effects will be applicable to all ACE inhibitors, since the fetal effects are plausibly explained by the direct therapeutic effectiveness of these drugs.

ACE inhibitors are effective and important therapeutic agents for the treatment of hypertension. There is no reason to change their use in women of reproductive age because the therapy can be changed during the first trimester if the woman becomes pregnant.

It is important to consider a second regimen for reducing blood pressure even though the ACE inhibitors may be the most effective and simplest regimen for controlling blood pressure. If a woman who is taking an ACE inhibitor learns that she is pregnant, there is no need to be concerned about an increased risk of adverse fetal effects. A rational, deliberative plan to switch over to the secondary regimen should be undertaken shortly after pregnancy has been diagnosed.

EVALUATION OF NEW DRUGS FOR CLINICAL USE IN THE TREATMENT OF DRUG ADDICTION FOR WHICH THERE ARE NO EPIDEMIOLOGICAL STUDIES AND NO HUMAN EXPERIENCE

The evaluation of new drugs, physical agents, and chemicals must depend more on in vivo and in vitro animal testing and the application of the principles of biologic plausibility, since there obviously is not human epidemiological data available. Even if the agent is closely related to a previously used compound, closely related compounds may have markedly different reproductive risks. It is well known that very minor changes in the thalidomide molecule can eliminate its teratogenic effect (Wuest 1968).

The purpose of the in vitro and in vivo testing is to determine whether a new environmental agent presents a measurable reproductive risk when a pregnant woman is exposed to this agent. The difficulty with the present in vitro testing system is that the results have not been reliable predictors of human teratogenicity (Brent 1964, 1988; Schardein 1988). While every drug that has been used for cancer chemotherapy in humans has been teratogenic in animal models, only a small fraction have resulted in

human teratogenesis. There are many drugs and chemicals that can produce malformations, embryonic death, or IUGR at doses far above the usual human exposure. These agents are therefore considered teratogens, but are not necessarily responsible for human teratogenesis. The definitions related to teratogenic potential are stated in a previous section of this chapter.

In reality, the largest group of drugs and environmental agents are the potential human teratogens because they include all drugs, chemicals, and physical agents that can produce embryotoxic and fetotoxic effects at some exposure. Since these levels of exposure are not attained in humans, they represent no risk or minimal risk to the human embryo.

The greatest problem facing regulatory agencies and teratologists is how to determine the margin of safety that should be required for exposures to potential reproductive toxicants (Brent 1987). This can be accomplished if it is recognized that the threshold concept of teratogenesis applies, and that even when drugs, chemicals, and environmental agents have toxic effects, there are also safe exposure for these agents. In most instances, exposure levels one to two orders of magnitude below the no-effect dose represent safe exposure for the embryo.

Animal data could be better interpreted if an evaluation of the ratio of the no-effect dose to the usual human dose were included. If one uses the more modem reproductive testing protocols for reproductive testing, one can better approximate safe exposure levels (Brent 1964, 1988; Slikker 1987) (table 9).

Although there have been extensive efforts to improve in vivo animal testing (Brent 1964, 1988; Butcher et al. 1979; Cahen 1964; Chemoff and Kavlock 1982; Collins 1978; D'Aguanno 1973; IRLG 1981, 1986; Jensh 1983; Kimmel et al. 1985; Nelson et al. 1985; Commission on Drug Safety 1963; Tuchmann-Duplessis 1964; Vorhees 1979; Wilson 1965, 1973), and to design in vitro test systems (Best and Morita 1982; Birge et al. 1983; Boumias-Vardiabasis et al. 1983; Braun et al. 1982; Brown and Fabro 1981; Cameron et al. 1985; Dumont and Epler 1984; Flint et al. 1984; Greenberg 1982; Hassell and Honigan 1982; Johnson 1980; Karnofsky and Basch 1960; Keller and Smith 1982; Kotzin and Baker 1972; Pratt and Willis 1985; Schuler et al. 1985; Sleet and Brendel 1985; Welsch and Stedman 1984; Wilk et al. 1980), there are still important limitations in the ability to apply these in vitro and in vivo testing models

TABLE 9. *A modern whole animal teratology-reproductive toxicity protocol should include the following parameters and goals.*

1. Determine the reproductive effects at stages of gestation that may have markedly different endpoints; namely, preimplantation, organogenesis, early fetal and late fetal stages.
2. The frequency of various reproductive effects may vary considerably from reproductive toxicant exposures at different gestational stages. Exposures at one stage may exaggerate, modify or eliminate effects at another stage: i.e.,
   a. teratogenesis
   b. embryolethality
   c. growth retardation
   d. postnatal physiological, biochemical, developmental and behavioral effects.
3. Determine the no-effect dose for the parameters mentioned in item 2 at various stages of gestation.
4. Determine the ratio of the no-effect dose to the human therapeutic dose, usual exposure dose, or maximal permissible exposure for the parameters mentioned in item 2.
5. Determine the quantitative relationship between the human and animal model pharmacokinetics, the relationship between dose and blood level, and the similarities and differences between the animal model and human in metabolism, placental transport and excretion.
6. Determine the ratio of the LD50 for the mother and the embryo at various embryonic and fetal stages.

directly to human risk assessment (Brent 1964, 1972, 1980, 1988; Fraser 1976; Schardein 1988). In spite of the extensive use of animal testing and in vitro tests, both these testing procedures have been minimally involved in identifying human teratogens since the thalidomide tragedy (table 7). Most human teratogens have been identified since 1960 by means of human epidemiological studies such as alert physicians reporting clusters, case control studies, or birth registries (table 7). In a few instances, animal studies have predicted human teratogenicity (table 7) or supported the association of teratogenicity in the human.

In a recent review of testing for reproductive effects, Schardein (1988) pointed out that whole-animal testing has not been modified or improved dramatically from the original two-litter and three-litter tests. He said,

"The segment II phase of the 1966 FDA Guidelines for Reproduction Studies . . . . remains after two decades of use, a valid testing procedure for identifying the potential for teratogenic induction and other developmental toxicity in laboratory animals. Its chief limitation resides in the extent to which such testing procedures are predictive of toxicity in the pregnant human, not in any inherent inadequacy of the testing procedure" (p. 24). In 1964, it was suggested that every whole animal mammalian testing protocol used to predict teratogenicity in humans should have certain essential features (Brent 1964) beyond those already suggested in 1963 by an international committee (Commission on Drug Safety 1963). Reproductive toxicity testing should include determination of the ratio of the maternal median lethal dose (LD50) to the fetal LD50, evaluation of embryonic death and growth retardation as well as teratogenicity, and determination of exposure during fetal stages because of the importance of critical cell loss of important organs (brain, gonads) during mid and late gestation (table 9).

These suggestions have been only partially included in routine whole-animal testing procedures for reproductive toxicity some 30 years after they were made (Brent 1964). Because of advances in science in general and teratology specifically, teratology and reproductive toxicity testing can be designed that is more meaningful and more predictive of human effects. A modem, whole-animal, teratology-reproductive toxicity protocol should include the principles, parameters, and goals listed in table 9.

While the cost of such an evaluation would be greater than for the 1966 FDA segment II reproductive studies, the ability to predict human reproductive risks and even more important, human reproductive safety, would be improved. A ratio between the no-effect level and the human therapeutic dose that is considered safe should be established. If this concept is not emphasized, reproductive toxicologists will have no incentive to determine the no-effect level and will not generate data to support the value of the ratio of the no-effect level to the therapeutic dose in establishing safe levels of usage or maximum permissible exposures. The fact that doxylamine succinate and pyridoxine (Bendectin), when administered to pregnant rats, had a no-effect dose hundreds of times greater than the human therapeutic dose, should be remembered when evaluating alleged human teratogenicity. Similarly, knowledge of pharmacokinetics, comparative metabolism, and blood levels would make undertaking an estimation of human risks much easier. Pharmacokinetic and metabolic data concerning Bendectin has been important in

interpreting animal results and has strengthened the conclusion that Bendectin is not a human teratogen (Holder et al. 1984, 1985; Korfmacher et al. 1985; Lay et al. 1986; Rushing et al. 1986; Slikker et al. 1986; Thompson et al. 1982, 1986). In fact, Kohlof and colleagues (1983) measured the blood level of Bendectin following a 25 mg human exposure and demonstrated that the in vitro test reported by Hassell and Hotigan (1982) had no relationship to human reproductive toxicity because the dose of Bendectin used in the in vitro test was so high.

In Vitro Tests

Each test system has some unique features that have been attractive to some investigators. With the proliferation of test systems, it is obvious that the cost of using a combination of these techniques could be more than the cost of a whole animal reproductive study.

More important than these unique features or possible reduced cost is an important principle: "The nature of these tests indicate that they can NEVER be more predictive of teratogenicity or embryotoxicity than *in vitro* systems" (Schardein 1988). Schardein (1988, p. 19) stated it quite eloquently: "The real dilemma in their use is eliminating procedures in animals and at the same time making tests more predictive; an incongruity to say the least."

In vitro tests offer experimental embryologists an opportunity to study various facets of their field. They can be used to study normal embryonic development and differentiation, mechanisms of teratogenesis and embryotoxicity, pharmacokinetics and the effect of isolated or combined metabolic products, and to screen for cytotoxicity and interference with differentiation.

It is also obvious that in vitro testing, using a single system, fails to delineate important reproductive toxicity effects including late CNS effects (brain histogenesis, behavior), unique unpredictable embryotoxic specificity (aspermatogenesis, cardiovascular hemodynamic changes, vascular disruption, yolk sac or chorioplacental effects), differentiating between recoupable and nonrecoupable growth retardation, transplacental carcinogenesis, lethal effects in the preimplantation period, and effects not previously reported.

The use of pregnant animals to study postnatal neurobehavioral effects is a very important area of investigation. While the testing of drugs in

pregnant primates may yield the best results for predicting human behavioral effects of drugs, the cost of such testing is prohibitive and does not guarantee the accuracy that one would like to attain. There has been some improvement in the behavioral testing of drugs in pregnant rats, and they have been used reasonably successfully to study postnatal neurobehavioral effects (Brent et al. 1986; Jensh and Brent 1986, 1987, 1988a,b, 1989; Jensh et al. 1982a,b, 1986, 1987). The formalization of neurobehavioral testing into a standard protocol should add measurably to researchers' ability to use the rodent model to study postnatal neurobehavioral effects of prenatal exposures (Jensh and Brent 1989).

It is important that when animal tests of the reproductive effects of drugs for the treatment of substance abuse are initiated, the tests should be specifically designed to use all the principles of teratology and the modem concepts of teratogen testing protocols. If the parameters outlined in table 9 were applied to in vivo animal testing procedures, it is very likely that researchers would be able to improve the risk of reproductive toxicity in humans, providing that the basic principles of teratology and developmental biology were applied.

REFERENCES

Barone, J.J., and Roberts, H. Human consumption of caffeine. In: Dews, P.B., ed. *Caffeine.* New York: Springer-Verlag, 1984. pp. 59-73.

Barr, M. Fetal effects of angiotensin converting enzyme inhibitor. *Teratology* 41:536, 1990.

Batastini, G.; Infoma, R.N.; Wimbert, K.L.V.; Youreneff, M.A.; Yau, E.T.; and Triana, V.M. Teratologic evaluation of CGS 16617, an angiotensin converting enzyme inhibiting agent. *Teratology* 37:445, 1988.

Best, J.B., and Morita, M. Planarians as a model system for in vitro teratogenesis studies. *Teratogenesis Carcinog Mutagen* 2:277-291, 1982.

Binder, N.D.; Faber, J.J.; and Anderson, D.F. The effect of captopril on blood pressure, uterine blood flow, and uterine oxygen consumption in the pregnant rabbit. *Clin Res* 37:176A, 1989.

Birge, W.J.; Black, J.A.; Westerman, A.G.; and Ramley, B.A. Fish and amphibian embryos - a model system for evaluating teratogenicity. *Fundam Appl Toxicol* 3:237-242, 1983.

Boue, J.; Boue, A.; and Lazar, P. Retrospective and prospective epidemiological studies of 1,500 karyotyped spontaneous abortions. *Teratology* 12:11-26, 1975.

Boumias-Vardiabasis, N.; Teplitz, R-L.; Chemoff, G.F.; and Seecof, R.L. Detection of teratogens in Drosophila embryonic cell culture test: Assay of 100 chemicals. *Teratology* 28:109-122, 1983.

Boutroy, M.J.; Vert, P.; Huralt de Ligny, B.; and Miton, A. Captopril administration in pregnancy impairs fetal angiotensin converting enzyme activity and neonatal adaption. *Luncet 935-936, 1984.*

Bouwes-Bavinck, J.N., and Weaver, D.D. Subclavin artery supply disruption sequence: Hypothesis of a vascular etiology for Poland, Klippel-Feil and Mobius anomalies. *Am J Med Genet* 23:903-918, 1986.

Boyd, P.A.; Keeling, J.W.; Selinger, M.; and MacKenzie, I.Z. Limb reduction and chorionic villus sampling. *Prenat Diagn* 10:437-441, 1990.

Braun, A.G.; Buckner, C.A.; Emerson, D.J.; and Michinson, B.B. Quantitative correspondence between the in vivo and in vitro activity of teratogenic agents. *Proc Natl Acad Sci U S A* 79:2056-2060, 1982.

Brent, R.L. Drug testing in animals for teratogenic effects: Thalidomide in the pregnant rat. *J Pediatr* 64:762-770, 1964.

Brent, R.L. Protecting the public from teratogenic and mutagenic hazards. *J Clin Pharmacol* 12:61-70, 1972.

Brent, R.L. Environmental factors: Miscellaneous. In: Brent, R.L., and Harris, M.I., eds. *Prevention of Embryonic, Fetal and Perinatal Disease.* DHEW Pub. No. (NIH)76-853. Bethesda, MD: Department of Health, Education and Welfare, 1976. pp. 211-218.

Brent, R.L. Method of evaluating alleged human teratogens. [Editorial] *Teratology* 17:83, 1978.

Brent, R.L. Radiation teratogenesis. *Teratology* 21:281-298, 1980.

Brent, R.L. Drugs and pregnancy: Are the insert warnings too dire? *Contemp Obstet Gynecol* 20:42-49, 1982.

Brent, R.L. The Bendectin saga: Another American tragedy. *Teratology* 27:283-286, 1983.

Brent, R.L. The magnitude of the problem of congenital malformations. In: Marios, M., ed. *Prevention of Physical and Mental Congenital Defects. Part A. The Scope of the Problem. New* York: Alan R. Liss, 1985. pp. 55-68.

Brent, R.L. Definition of a teratogen and the relationship of teratogenicity to carcinogenicity. [Editorial] *Teratology* 34:359-360, 1986.

Brent, R.L. Ionizing radiation. In: Queenan, J.T., and Hobbins, J.C., eds. *Protocols for High-Risk Pregnancies.* 2nd ed. Vol. 2. New York: Harwood Academic Publishers, 1987. pp. 121-154.

Brent, R.L. Predicting teratogenic and reproductive risks in humans from exposure to various environmental agents using in vitro techniques and in vivo animal studies. Supplement. *Cong Anom* 28:S41-S55, 1988.

Brent, R.L. Relationship between uterine vascular clamping, vascular disruption, and cocaine teratogenicity. [Editorial] *Teratology 4* 1:757-760,1990.

Brent, R.L., and Franklin, J.B. Uterine vascular clamping: New procedures for the study of congenital malformations. *Science* 132:89-91, 1960.

Brent, R.L., and Holmes, L.B. Clinical and basic science lessons from the thalidomide tragedy: What we learned about the causes of limb defects? *Teratology* 38:241-251, 1988.

Brent, R.L.; Beckman, D.A.; and Jensh, R.P. The relationship of animal experiments in predicting the effects of intrauterine effects in the human. In: Kriegel, H.; Schmahl, W.; Gerber, G.B.; and Stieve, F.E., eds. *Radiation Risks to the Developing Nervous System. New* York: Gustav Fisher, 1986. pp. 367-397.

Broughton Pipken, F.; Symonds, E.M.; and Turner, S.R. The effect of captopril (SQ 14,225) upon mother and fetus in the chronically cannulated ewe and in the pregnant rabbit. *J Physiol* 323:415-422, 1982.

Brown, N.A., and Fabro, S. Quantitation of rat embryonic development in vitro: A morphological scoring system. *Teratology* 24:65-78, 1981.

Butcher, R.E.; Hoar, R.M.; Nolen, G.A.; and Vorhees, C.V. Interlaboratory comparison of behavior testing. *J Assoc Off Anal Chem* 62:840-843, 1979.

Cahen, R.L. Evaluation of the teratogenicity of drugs. *J Clin Pharm Ther* 5:480-514, 1964.

Cameron, I.L.; Lawrence, W.C.; and Lum, J.B. Medaka eggs as a model system for screening potential teratogens. *Prog Clin Biol Res* 163C1:239-240, 1985.

Carey, J.C.; Eggert, L.; and Curry, W.R. Lower limb deficiency and the urethral obstruction sequence. *Birth Defects* 18(3B): 19-28, 1982.

Carter, C.O. Genetics of common single malformations. *Br Med Bull* 32:21-26, 1976.

Chasnoff, I.J.; Bums, W.J.; Scholl, S.H.; and Bums, K.A. Cocaine use in pregnancy. *N Engl J Med* 313:666-669, 1985.

Chasnoff, I.J.; Bums, K.A.; and Bums, W.J. Cocaine use in pregnancy: Perinatal morbidity and mortality. *Neurotoxicol Teratol* 9:291-293, 1987.

Chasnoff, I.J.; Chisum, G.M.; and Kaplan, W.E. Maternal cocaine use and genitourinary tract malformations. *Teratology* 37:201-204, 1988.

Chasnoff, I.; Lewis, D.E.; Griffith, D.R.; and Willey, S. Cocaine and pregnancy: Clinical and toxicological implications for the neonate. *J Clin Chem* 35:1276-1278, 1989a.

Chasnoff, I.J., and Griffith, D.R. Cocaine: clinical studies of pregnancy and the newborn. *Ann NY Acad Sci* 562:260-266, *19896.*

Chavez, G.F.; Mulinare, J.; and Cordero, J.F. Maternal cocaine use during early pregnancy as a risk factor for congenital urogenital anomalies. *JAMA* 262:795-798, 1989.

Chemoff, N., and Kavlock, R.J. An in vivo teratology screen utilizing pregnant mice. *J Toxicol Environ Health* 10:541-550, 1982.

Christiaens, G.C.M.L.; Van Baarlen, J.; Huber, J.; and Leschot, N.J. Fetal limb constriction. A possible complication of CVS. *Prenat Diagn* 9:67-71, 1989.

Collins, T.F.X. Reproduction and teratological guidelines: Review of deliberations by the National Toxicology Advisory Committee's Reproduction Panel. *J Environ Pathol Toxicol Oncol* 2:141-147, 1978.

Commission on Drug Safety. *Report of the Conference on Prenatal Effects of Drugs, Chicago.* Commission on Drug Safety Bulletin, June 1963.

D'Aguanno, W. Guidelines for reproduction studies for safety evaluation of drugs for human use. In: *FDA Introduction to Total Drug Quality.* DHEW Pub. No. (FDA) 74-3006, DHEW1/PHS/FDA. 1973.

Duminy, P.C. Fetal abnormality associated with the use of captopril during pregnancy. *S Afr Med J* 60:805, 1981.

Dumont, J.N., and Epler, R.G. Validation studies on the FETAX teratogenesis assay (frog embryos). Abstract. *Teratology* 29:27A, 1984.

Ferris, T.F., and Weir, E.K. Effect of captopril on uterine blood flow and prostaglandin E synthesis in the pregnant rabbit. *J Clin Invest* 71:809-815, 1983.

Finnegan, L.P. Drugs and other substances of abuse in pregnancy. In: Stem, L., ed. *Drug Use in Pregnancy.* Boston: ADIS Health Science Press, 1984. pp. 148-176.

Firth, H.V.; Boyd, P.A.; Chamberlain, P.; MacKenzie, I.Z.; Lindenbaum, R.H.; and Huson, S.M. Severe limb abnormalities after chorion villus sampling at 56-66 days' gestation. *Lancet* 337:762-763, 1991.

Fischman, M.W. Behavioral pharmacology of cocaine. *J Clin Psychiatry* 49(s): 7-10, 1988.

Flint, O.P.; Odrton, T.C.; and Ferguson, R.A. Differentiation of rat embryo cells in culture: Response following acute maternal exposure to teratogens and nonteratogens. *J Appl Toxicol* 4:109-116, 1984.

Food and Drug Administration. *Caffeine Content of Various Products.* FDA Talk Paper TX80-45. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1980.

Franklin, J.B., and Brent, R.L. The effect of uterine vascular clamping on the development of rat embryos three to fourteen days old. *J Morphol* 115:273-290, 1960a.

Franklin, J.B., and Brent, R.L. Interruption of uterine blood flow: A new technique for the production of congenital malformations. Comparison of the 8th, 9th, and 10th days of gestation. *Surg Forum* 11:415-416, 1960b.

Fraser, F.C. The multifactorial/threshold concept-uses and misuses. *Teratology* 14:267-280, 1976.

Graham, H.N. Tea: The plant and its manufacture, chemistry and consumption of the beverage. In: Spiller, G.A., ed. *Progress in Clinical and Biological Research* Vol. 159. *The Methyixanthine Beverages and Foods: Chemistry, Consumption and Health Effects. New* York: Alan R. Liss, 1984a. pp. 29-74.

Graham, H.N. Mate. In: Spiller, G.A., ed. *Progress in Clinical and Biological Research.* Vol. *158. The Methylxanthine Beverages and Foods: Chemistry, Consumption and Health Effects. New* York: Alan R. Liss, 19846. pp. 179-183.

Graham, J.M., Jr. The effects of alcohol consumption during pregnancy. In: Marois, M., ed. *Prevention of Physical and Mental Congenital Defects.* Part *C. Basic and Medical Science, Education, and Future Strategies. New* York: Alan R. Liss, 1985. pp. 335-339.

Graham, J.M., Jr. Causes of limb reduction defects: The contribution of fetal constraint and/or vascular disruption. *Clin Perinatol* 13(3):575-591, 1986.

Graham, J.M., Jr.; Miller, M.E.; Stephan, M.J.; and Smith, D.W. Limb reduction anomalies and early in utero limb compression. *J Pediatr* 96:1052-1056, 1980.

Greenberg, J.H. Detection of teratogens by differentiating embryonic cells in culture: Evaluation as a screening system. *Teratogenesis Carcinog Mutagen* 2:319-323, 1982.

Guignard, J.P., and Gouyon, J.B. Adverse effects of drugs on the immature kidney. *Perinatal Nephrol Biol Neonate* 53:243-252, 1988.

Guignard, J.P.; Burgener, F.; Calame, F.A. Persistent anuria in neonate: A side effect of captopril. *Intern J Pediatr Nephrol* 2:133, 1981.

Hadeed, A.J., and Siegel, S.R. Maternal cocaine use during pregnancy: Effect on the newborn infant. *Pediatrics* 84:205-210, 1989.

Hassell, J.R., and Horigan, E.A. Chondrogenesis: A model developmental system for measuring teratogenic potential of compounds. *Teratogenesis Carcinog Mutagen* 2:325-331, 1982.

Heier, L.A.; Carpanzano, C.R.; Mast, J.; Brill, P.W.; Winchester, P.; and Deck, M.D.F. Maternal cocaine abuse: The spectrum of radiologic abnormalities in the neonatal CNS. *AJNR* 12:951-956, 1991.

Heinonen, O.P.; Slone, D.; and Shapiro, *S. Birth Defects and Drugs in Pregnancy.* Littleton: John Wright-PSG, Inc., 1977.

Hersh, J.H.; Podruch, P.E.; Rogers, G.; and Weisskopf, B. Toluene embryopathy. *J Pediatr* 106:922-927, 1985.

Hertig, A.T. The overall problem in man. In: Benirschke, K., ed. *Comparative Aspects of Reproductive Failure.* Berlin: Springer-Verlag, 1967. pp. 11-41.

Hill, R.M.; Craig, J.P.; Chaney, M.D.; Tennyson, L.M.; and McCulley, L.B. Utilization of over-the-counter drugs during pregnancy. *Clin Obstet Gynecol* 20:381-394, 1977.

Holder, C.L.; Korfmacher, W.A.; Slikker, W., Jr.; Thompson, H.C., Jr.; and Gosnell, A.B. Mass spectral characterization of doxylasmine and its Rhesus monkey urinary metabolites. *Biomed M Spectra* 12:151-158, 1985.

Holder, C.L.; Thompson, H.C., Jr.; and Slikker, W., Jr. Trace level determination of doxylamine in nonhuman primate plasma and urine by GC/NPD and HPLC. *J Anal Toxicol* 8:46-50, 1984.

Hunter, A.G.W.; Thompson, D.; and Evans, J.A. Is there a fetal gasoline syndrome? *Teratology* 20:75-80, 1979.

IRLG. Recommended guideline for teratogenicity studies in the rat, mouse, hamster or rabbit. Testing Standards and Guidelines Work Group, Washington, DC: Department of Health, Education and Welfare, 1981.

IRLG. Workshop on reproductive toxicity risk assessment. *Environ Health Perspec 66:* 192-221, 1986.

Javaid, J.I.; Musa, M.N.; Fischman, M.W.; Schuster, C.R.; and Davis, J.M. Kinetics of cocaine in humans after intravenous and intranasal administration. *Biopharm Drug Dispos* 4:9-18, 1983.

Jensh, R.P. Behavioral testing procedures: A review. In: Johnson, E.M., and Kochhar, D.M., eds. *Teratogenesis and Reproductive Toxicology.* Berlin: Springer-Verlag, 1983. pp. 171-200.

Jensh, R.P., and Brent, R.L. Effects of 0.6-Gy postnatal neurophysiologic development in the Wistar rat. *Proc Soc Exp Biol Med* 181:611-619, 1986.

Jensh, R.P., and Brent, R.L. The effect of low-level prenatal x-irradiation on postnatal development in the Wistar rat. *Proc Soc Exp Biol Med* 184:256-263, 1987.

Jensh, R.P., and Brent, R.L. Effects of prenatal x-irradiation on the 14th-18th days of gestation on postnatal growth and development in the rat. *Teratology* 38:431-441, 1988a.

Jensh, R.P., and Brent, R.L. Effects of prenatal x-irradiation on postnatal testicular development and function in the Wistar rat: Development/ teratology/behavior radiation. *Teratology* 38:443-449, 1988b.

Jensh, R.P., and Brent, R.L. Development of a useful technique for analyzing behavioral teratologic data. *Teratology 39:* 17-3 19, 1989.

Jensh, R.P.; Brent, R.L.; and Vogel, W.H. Studies concerning the effects of low level prenatal x-irradiation on postnatal growth and adult behavior in the Wistar rat. *Int J Radiat Biol* 50:1069-1081, 1986.

Jensh, R.P.; Brent, R.L.; and Vogel, W.H. Studies of the effect of 0.4-Gy and 0.6-Gy prenatal x-irradiation on postnatal adult behavior in the Wistar rat. *Teratology* 35:53-61, 1987.

Jensh, R.P.; Vogel, W.H.; and Brent, R.L. Postnatal functional analysis of prenatal exposure of rats to 9 15 MHz microwave radiation. *J Am Coll Toxicol* 1:73-90, 1982a.

Jensh, R.P.; Weinberg, I.; and Brent, R.L.: Teratologic studies of prenatal exposure of rats to 915-MHZ microwave radiation. *Radiat Res* 92:160-171, 1982b.

Johanson, C.E., and Fischman, M.W. The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 41:3-52, 1989.

Johnson, E.M. A subvertebrate system for rapid determination of potential teratogenic hazards. *J Environ Pathol Toxicol Oncol* 24:153-156, 1980.

Jones, K.L., and Smith, D.W. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 2:99-101, 1973.

Jones, K.L., and Smith, D.W. The fetal alcohol syndrome. *Teratology* 12:1-10, 1975.

Jones, K.L.; Smith, D.W.; Streissguth, A.P.; and Myrianthopoulous, N.C. Outcome in offspring of chronic alcoholic women. *Lancet* 1: 1076-1078, 1974.

Kamofsky, D.A., and Basch, R.S. Effects of 5-fluorodeoxyuridine and related halogenated pyrimidines on the sanddollar embryo. *J Biophys Biochem Cytol* 7:61-71, 1960.

Keith, I.M.; Will, J.A.; and Weir, E.K. Captopril: Association with fetal death and pulmonary vascular changes in the rabbit. *Proc Soc Exp Biol Med* 170:378-383, 1982.

Keller, S.J., and Smith, M. Animal virus screens for potential teratogens: Poxvirus morphogenesis. *Teratogenesis Carcinog Mutagen* 2:361-374,1982.

Kimmel, C.A.; Buelke-Sam, J.; and Adams, J. Collaborative behavioral teratology study: Implications, current applications and future directions. *Neurobehav Toxicol Teratol* 7:669-673, 1985.

Kline, J., and Stein, Z. Very early pregnancy. In: Dixon, R.L., ed. *Target Organ Toxicology Series: Reproductive Toxicology. New* York: Raven Press, 1985. pp. 251-265.

Knott, P.D.; Thorpe, S.S.; and Lamont, C.A.R. Congenital renal dysgenesis possibly due to captopril. *Lancet* 1:451, 1989.

Kohlof, K.J.; Stump, D.; and Zizzamia, J.A. Analysis of doxylamine in plasma by high performance liquid chromatography. *J Pharm Sci* 72:961-962, 1983.

Korfmacher, W.A.; Holder, C.L.; Freeman, J.P.; and Mitchum, R.K. Chemical ionization mass spectrometry of doxylamine and related compounds. *Org Mass Spectra* 20:435-439, 1985.

Kotzin, B.L., and Baker, R.F. Selective inhibition of genetic transcription in sea urchin embryos. *J Cell Biol* 55:74-81, 1972.

Kreek, M.J. Multiple drug abuse patterns and medical consequences. In: Meltzer, H., ed. *Psychopharmacology: The Third Generation of Progress.* New York: Raven Press, 1988. pp. 1597-1604.

Kreft-Jais, C.; Plouin, P.F.; Tchobroutsky, C.; and Boutroy, M. Angiotensin-converting enzyme inhibitors during pregnancy: A survey of 22 patients given captopril and nine given enalapril. *Brit J Obstet Gynecol* 95:420-422, 1988.

Lay, J.O., Jr.; Korfmacher, W.A.; Miller, D.W.; Siitonen, P.; Holder, C.L.; and Gosnell, A.B. Desorption chemical ionization and fast atom bombardment mass spectrometric studies of the glucuronide metabolites of doxylamine. *Biomed Environ Mass Spectra* 13:627-632, 1986.

Lederman, R.P.; Lederman, E.; Work, B.A., Jr.; and McCann, D.S. The relationship of maternal anxiety, plasma catecholamines, and plasma cortisol to progress in labor. *Am J Obstet Gynecol* 132:495-500, 1978.

MacGregor, S.N.; Keith, L.G.; Chasnoff, I.J.; Rosner, M.A.; Chisum, G.M.; Shaw, P.; and Minogue, J.P. Cocaine use during pregnancy: Adverse perinatal outcome. *Am J Obstet Gynecol* 157:686-690, 1987.

MacGregor, S.N.; Keith, L.G.; Bachicha, J.A.; and Chasnoff, I.J. Cocaine abuse during pregnancy: correlation between prenatal care and perinatal outcome. *Obstet Gynecol* 74:882-885, 1989.

McKusick, V.A. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phentotypes.* 8th ed. Baltimore: Johns Hopkins University Press, 1988.

McLaughlin, J.A. Prenatal exposure to diethylstilbestrol in mice: Toxicological studies. *J Toxicol Environ Health* 2:527-537, 1977.

Mehta, N., and Modi, N. ACE inhibitors in pregnancy. *Lancet* 2:96-97, 1989.

Moore, T.R.; Sorg, J.; Miller, L.; Key, T.C.; and Resnik, R. Hemodynamic effects of intravenous cocaine on the pregnant ewe and fetus. *Am J Obstet Gynecol* 157:883-888, 1986.

Morris, M.B., and Weinstein, L. Caffeine and the fetus-is trouble brewing? *Am J Obstet Gynecol* 140:607-610, 1981.

Narod, S.A.; Sanjose, S.; and Victora, C. Coffee during pregnancy: A reproductive hazard? *Am J Obstet Gynecol* 164:1109-1114, 1991.

Nelson, C.J.; Felton, R.P.; Kimmel, C.A.; Buelke-Sam, J.; and Adams, J. Collaborative behavioral teratology study. Statistical approach. *Neurobehav Toxicol Terato* 7:587-590, 1985.

Planteydt, H.T.; van de Vorren, M.J.; and Verweij, H. Amniotic bands and malformation in child born after pregnancy screened by chorionic villus biopsy. *Lancet* 2:756-757, 1986.

Pratt, R.M., and Willis, W.D. In vitro screening assay for teratogens using growth inhibition of human embryonic cells. *Proc Nat Acad Sci U S A* 82:5791-5794, 1985.

Rhodes, G.G.; Jackson, L.G.; Schlesselman, S.E.; de la Cruz, F.F.; Desnick, R.J.; Golbus, G.M.S.; Ledbetter, D.H.; Lubs, H.A.; Mahoney, M.J.; Pergament, E.; Simpson, J.L.; Carpenter, R.J.; Elias, S.; Ginsberg, N.A.; Goldberg, J.D.; Hobbins, J.C.; Lynch, L.; Shiono, P.H.; Wapner, R.J.; and Zachary, J.M. The safety and efficacy of chorionic villus sampling for early prenatal diagnosis of cytogenetic abnormalities. N *Engl J Med* 320:609-617, 1989.

Robert, C.J., and Lowe, C.R. Where have all the conceptions gone? *Lancet* 1:498-499, 1975.

Rosa, F.W.; Bosco, L.A.; Graham Fossum, C.; Milstein, J.B.; Dreis, M.; and Creamer, J. Neonatal anuria with maternal angiotensin-converting enzyme inhibition. *Obstet Gynecol* 74:371-374, 1989.

Rothberg, A.D., and Lorenz, R. Can captopril cause fetal and neonatal renal failure? *Pediatr Pharm* 4:189-192, 1984.

Rushing, L.G.; Gosnell, A.B.; Holder, C.L.; Korfmacher, W.A.; and Slikker, W., Jr. Separation and detection of doxylamine and its Rhesus monkey urinary metabolites by high resolution gas chromatography utilizing nitrogen/phosphorus detection. *J High Resol Chroma Chroma Comm* 1986. pp. 435-440.

Ryan, L.; Ehrlich, S.; and Finnegan, L. Cocaine abuse in pregnancy: Effects on the fetus and newborn. *Neurotoxicol Teratol* 9:295-299, *1987.*

Schardein, J.L. *Chemically Induced Birth Defects.* New York: Marcel Dekker, 1985.

Schardein, J.L. *Chemically Induced Birth Defects.* 2d ed. New York: Marcel Dekker, 1993. p. 902.

Schardein, J.L. Teratological testing: Status and issues after two decades of evaluation. In: Ware, G.W., ed. *Reviews of Environmental Contamination and Toxicology.* New York: Springer-Verlag, 1988. pp. 1-78.

Schubiger, G.; Flury, G.; and Nussberger, J. Enalapril for pregnancy-induced hypertension: Acute renal failure in a neonate. *Ann Intern Med* 108:215-216, 1988.

Schuler, R.L.; Radike, M.A.; Hardin, B.D.; and Niemeier, R. W. Pattern of response of intact drosophila to known teratogens. *J Am Col Toxicol* 4:291-303, 1985.

Scott, A.A., and Purohit, D.M. Neonatal renal failure. A complication of maternal antihypertensive therapy. *Am J Obstet Gynecol* 1:1223-1224, 1989.

Shepard, T.H. *Catalogue of Teratogenic Agents.* 5th ed. Baltimore: Johns Hopkins University Press, 1986.

Sherman, W.T., and Gautieri, R.F. Effect of certain drugs on perfused human placenta. X. Norepinephrine release by bradykinin. *J Pharm Sci* 61:870-873, 1972.

Simpson, J.L. Genes, chromosomes and reproductive failure. *Fertil Steril* 33:107-116, 1980.

Sleet, R.B., and Brendel, K. Homogenous populations of Artemia nauplii and their potential use for in vitro testing in developmental toxicology. *Teratogenesis Carcinog Mutagen* 4:41-54, 1985.

Slikker, W., Jr. The role of metabolism in the testing of developmental toxicants. *Regul Toxicol Pharmacol* 7:390-413, 1987.

Slikker, W., Jr.; Holder, C.L.; Lipe, G. W.; Korfmacher, W.A.; Thompson, H.C. Jr.; and Bailey, J.R. Metabolism of 14C-labeled doxylamine succinate (Bendectin) in the Rhesus monkey (Macaca Mulatta). *J Anal Toxicol* 10:87-92, 1986.

Smith, A.M. Are ACE inhibitors safe in pregnancy? *Lancet* 2:750-751, 1989.

Streissguth, A.P.; Landesman-Dwyer, C.; Martin, J.C.; and Smith, D.W. Teratogenic effects of alcohol in humans and laboratory animals. *Science* 209:353-361, 1980.

Tchobroutsky, C.; Kreft-Jais, C.; and Plouin, P.F. Angiotensin converting enzyme inhibitors during pregnancy. *Clin Exp Hypertens* [B6]:71, 1987.

Thompson, H.C., Jr.; Gosnell, A.B.; Holder, C.L.; Siitonen, P.H.; Rowland, K.L.; and Cmarik, J.L. Metabolism of doxylamine succinate in Fischer 344 rats. Part I. Distribution and excretion. *J Anal Toxicol* 10:18-23, 1986.

Thompson, H.C., Jr.; Holder, C.L.; and Bowman, M.C. Trace analysis of doxylamine succinate in animal feed, human urine and wastewater by GC using a rubidium-sensitized nitrogen detector. *J Chromatogr Sci* 20:373-380, 1982.

Tuchmann-Duplessis, H., and Mercier-Parot, L. A propos des tests teratogenes. Malformations spontanees du lapin. *C R Soc Biol* 158:666-670, 1964.

Vitti, T.G., and Boni, R.L. Metabolism of cocaine. In: Bamett, G., and Chiang, *C.N.,* eds. *Pharmacokinetics and Pharmacodynamics of Psychoactive Drugs: A Research Monograph.* California: Biomedical Publications, 1985. pp. 427-440.

Vorhees, C.V.; Butcher, R.E.; Brunner, R.L.; and Sobtka, T.J. A developmental test battery for neurobehavioral toxicity in rats: A preliminary analysis using monosodium glutamate, calcium carrageenan and hydroxyurea. *Toxicol Appl Pharmacol* 50:267-282, 1979.

Vorhees, C.V. Behavioral teratogenicity testing as a method of screening for hazards to human health: A methodological approach. *Neurobehav Toxicol Teratol* 5:469-474, 1983.

Warkany, J. Aminopterin and methotrexate: Folic acid deficiency. *Teratology* 17:353-358, 1978.

Webster, W.S.; Lipson, A.H.; and Brown-Woodman, P.D.C. Uterine trauma and limb defects. *Teratology* 35:253-260, *1987.*

Webster, W.S., and Brown-Woodman, P.D.C. Cocaine as a cause of congenital malformations of vascular origin: Experimental evidence in the rat. *Teratology* 41:689-697, 1990.

Welsch, F., and Stedman, D.B. Inhibition of metabolic cooperation between Chinese hamster V79 cells by structurally diverse teratogens. *Teratogenesis Carcinog Mutagen* 4:285-302, 1984.

Wilk, A.L.; Greenberg, J.H.; Horgan, E.A.; Pratt, R.M.; and Martin, G.R. Detection of teratogenic compounds using differentiating embryonic cells in culture. *In Vitro* 16:269-276, 1980.

Wilson, J.G. Methods for administering agents and detecting malformations in experimental animals. In: Wilson, J.G., and Warkany, J., eds. *Teratology: Principles and Techniques.* Chicago: University of Chicago Press, 1965. pp. 263-277.

Wilson, J.G. *Environment and Birth Defects.* New York: Academic Press, 1973.

Woods, J.R.; Plessinger, M.A.; and Clark, K.E. Effect of cocaine on uterine blood flow and fetal oxygenation. *JAMA* 257:957-961, 1987.

World Health Organization. *Spontaneous and Induced Abortion.* World Health Organization Technical Report Series, Number 461. Geneva: World Health Organization, 1970.

Wuest, H.M.; Fox, R.R.; and Crary, D.D. Relationship between teratogeny and structure in the thalidomide field. *Experientia 24:993-*994, 1968.

ACKNOWLEDGMENT

This work was supported in part by funds from NIH grant HD07075, NIH grant HD18167, The Nemours Foundation, the Foerderer Foundation, and the Harry Bock Charities.

AUTHOR

Robert L. Brent, M.D., Ph.D.
Department of Medical Cell Biology
Alfred I. duPont Institute
P.O. Box 269
Wilmington, DE 19899

Drug Delivery Systems: Possible Applications in the Treatment of Drug Addiction

Stella T. Chao

During the past 25 years, there has been a large research effort directed at improving and developing new drug delivery technologies. This effort stems from the fact that improved drug delivery can significantly enhance the therapeutic value of drugs by improving efficacy, ease of administration, and compliance, and by reducing side effects. This concept of enhanced therapeutic value applies to all drugs, including those used to treat drug addiction.

Methadone, naltrexone, and levo-alpha-acetylmethadol (LAAM) are the medications approved by the Food and Drug Administration (FDA) for the treatment of heroin abuse/dependence. Buprenorphine and clonidine are currently under clinical investigation for treating drug addiction and may be officially approved in the future. Generally, the dosage forms available for these medications, except clonidine, have been conventional solutions or tablets designed primarily for oral administration. Most of these conventional dosage forms provide an immediate release of the drug. They deliver the drug in a first-order fashion; that is, drug delivery occurs initially at high rates that decline steadily afterward.

In order to achieve and maintain a drug concentration within the therapeutically effective range required, it is often necessary to administer the drug several times. In some cases, this results in a peaks-and-valleys profile of drug concentration in the blood and tissues, as shown in figure 1 (Zaffaroni 1991). When the concentration is above the upper limit of the therapeutic range (overmedication), efficacy is often accompanied by side effects. As the drug concentration declines, it passes through the therapeutic range required for efficacy, within which the desired therapeutic effect may be achieved without side effects. Concentrations less than therapeutic (undermedication) result in suboptimal therapy.

Significant advances in drug delivery have been made in the past 25 years primarily because rate of release control has been incorporated in delivery

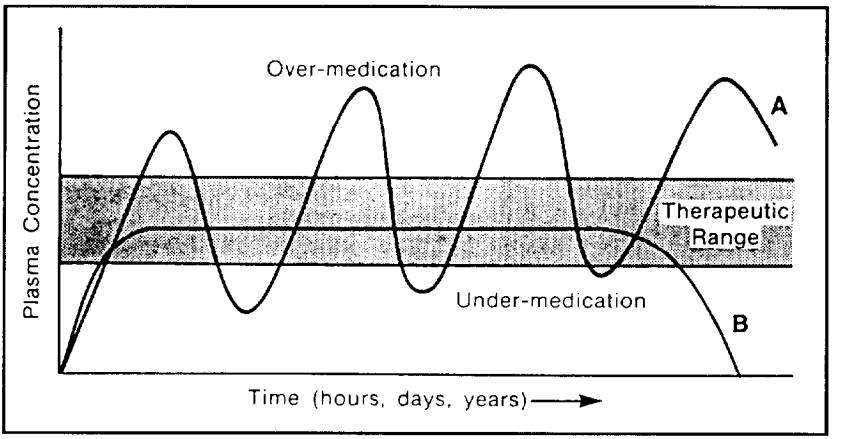


FIGURE 1. *Curve A shows the peaks-and-valleys plasma profile of a drug delivered from a conventional dosage form (repeated doses of solution or tablet). Curve B shows the more consistent profile of a drug from a controlled-delivery dosage form.*

systems. This new class of dosage form, the therapeutic system, administers medication precisely and automatically over predefined periods of time. These therapeutic systems control the quantity and rate of drug delivery so the profile of drug concentration achieved in the body is smoother, lacking the peaks-and-valleys profile of conventional dosage forms (figure 1) (Zaffaroni 1991). Therapeutic systems that incorporate rate control include transdermal drug delivery systems, oral osmotic drug delivery systems, and bioerodible polymer drug delivery systems. All of these systems have potential applications in the treatment of drug addiction.

TRANSDERMAL DRUG DELIVERY SYSTEMS

Transdermal drug delivery is defined as the administration of a drug through intact skin. A transdermal drug delivery system adheres to the skin and delivers the drug to the surface of the skin at a controlled rate. Transdermal delivery appears to be especially useful for administering drugs with poor oral bioavailability and short half-lives. When compared with an equipotent oral dosage form, transdermal systems have several advantages that include avoiding hepatic first-pass metabolism so that a lower total dose of the drug is required for efficacy; maintaining effective or relatively constant plasma levels for prolonged periods of time;

causing fewer adverse effects because less drug is administered; and reducing frequency of doses, leading to increased patient compliance.

Transdermal drug delivery systems have several components in common. A backing film provides a physical barrier to prevent drug loss and keep water out of the dosage form. The drug reservoir contains the drug in a stable form. The adhesive layer makes the system stick to the skin. A peelable protective liner ensures that the system does not deliver the drug until the liner is removed just before system application.

The two basic types of passive transdermal delivery systems currently on the market are matrix systems and membrane-controlled systems (Chien 1987; Ledger and Nichols 1989). In a matrix system, drug release from the reservoir as a semisolid solution or dispersion is determined by solution diffusion through a polymer matrix. For polymer matrix diffusion-controlled systems, the drug reservoir is formed by dispersing solid drug within a polymer. The nitroglycerin system (Nitro-Dur™) utilizes this technology. Two matrix systems that disperse the drug in an adhesive polymer are an isosorbide dinitrate tape (Frandol™) and a nitroglycerin system (Nitro-Dur II™).

Membrane-controlled systems, either multilaminate or form-fill-seal, have a rate-controlling membrane to limit drug release. Examples of products using the multilaminate design include scopolamine (Transderm Scop™) and clonidine (Catapres-TTS™). Examples of products that use form-fill-seal, membrane-controlled systems include nitroglycerin (Transderm-Nitro™) and estradiol (Estraderm™). All these systems have a rate-controlling membrane between the drug reservoir and the adhesive layer. This membrane controls the rate at which the drug is delivered to the skin surface. The rate of delivery from the system can be less than the rate of absorption by the skin; in this case it is the system, not the skin, that controls the rate at which the drug is absorbed.

A scopolamine transdermal system was the first commercially available transdermal drug delivery system. It is a 2.5 cm^2 circular flat disc with a thickness of 200 micrometers (μm) (Theeuwes 1981); it delivers 0.5 milligrams (mg) of scopolamine over a 3-day period to prevent motion sickness. This dose is approximately one-fifth the total daily dose of the usual intramuscular (IM) or oral regimens, which require 4 to 6 doses per day. To decrease the lag time, a loading dose of scopolamine is released from the adhesive for 2 hours after system application. Drug release then declines to a rate designed to maintain steady-state plasma

levels. In clinical trials the scopolamine transdermal system prevented motion sickness with a low incidence of side effects in 75 percent of susceptible subjects (Price et al. 1981), thereby successfully demonstrating that systemic drug therapy could be achieved through the transdermal route.

Since then, additional drugs such as estradiol, clonidine, fentanyl, nicotine, and nitroglycerin have been incorporated in transdermal delivery systems. Five transdermal nitroglycerin products are available in the United States: Transderm-Nitro™, Minitran™, Nitro-Dur®, Deponit NTG®, and Nitrodisc®. Experience with these products has established both the feasibility and patient acceptability of long-term transdermal drug delivery therapy.

Nicotine has been used for the treatment of addictive disorders and is another drug suitable for transdermal delivery. Previously, the only nicotine replacement therapy effective as an aid in smoking cessation was nicotine polacrilex (Nicorette® gum) (Hughes and Miller 1984). Cigarette smoking is a complex addiction with both behavioral and pharmacological components. The inhalation of tobacco smoke is the fastest and most efficient way to deliver nicotine to the brain. Upon abstinence from smoking, the rapid appearance of nicotine withdrawal symptoms often prevents even highly motivated smokers from quitting.

Transdermal nicotine replacement therapy products now include four brands: the Nicoderm® system, the Habitrol™ system, the Nicotrol™ system, and the ProStep™ system, all used as aids for smoking cessation in combination with behavioral therapy. A comparison of nicotine delivery rates, sizes, contents, and doses absorbed for the four transdermal systems is found in table 1 (Gorsline 1993). It is primarily the differences in design of the transdermal systems that affect the nicotine absorption and plasma concentration-versus-time profiles. One of these products, the Nicoderm system employs rate-control-membrane technology to deliver nicotine for 24 hours, while the other products use matrix systems. Three dosage strengths of the Nicoderm system are available, providing 7, 14, or 21 mg of nicotine over 24 hours. These doses were chosen because studies showed they provide plasma nicotine levels that have been effective in decreasing nicotine withdrawal symptoms in nicotine-dependent patients (Transdermal Nicotine Study Group 1991).

TABLE 1. *Nicotine Transdermal Systems*[a].

Product	Application Period (h)	Size (cm^2)	Nicotine Content (mg)	Delivery Rate ($\mu g/cm^2$-h)	Absorbed Dose (mg)
Nicoderm® System	24	22	114	40	21
Habitrol™ System	24	30	52.5	29	21
Nicotrol™ System	16	30	24.9	31	15
ProStep™ System	24	7[b]	30	130	22

[a]All data are from package insert information for each nicotine transdermal system.
[b]Size of the gel reservoir, actual patch size is larger.

SOURCE: Gorsline 1993.

Clinical studies with the Nicoderm system demonstrated that average steady-state plasma nicotine concentrations of 6, 12, and 17 nanograms per milliliter (ng/ml) were obtained for the 7, 14, and 21 mg/day systems, respectively (Gorsline 1993). When this nicotine transdermal system was compared to cigarette smoking ad libitum, plasma nicotine concentrations for the system were about half or less than half of the concentrations associated with smoking. Comparison of the 14 mg/day system with nicotine gum showed plasma nicotine levels for the system within the range of values achieved by administration of 10 to 15 pieces of the 2 mg gum during the day. These concentrations, for both the system and the gum, were within the effective concentration range for smoking cessation (Gorsline et al. 1992).

Clonidine, also used to treat addiction, is a potent hypotensive agent that acts on the central nervous system (CNS). It has been widely used as tablets administered orally 2 to 3 times a day. A clonidine transdermal system, Catapres-TTS®, provides controlled delivery of clonidine to hypertensive patients for 7 days after one application. A bioavailability

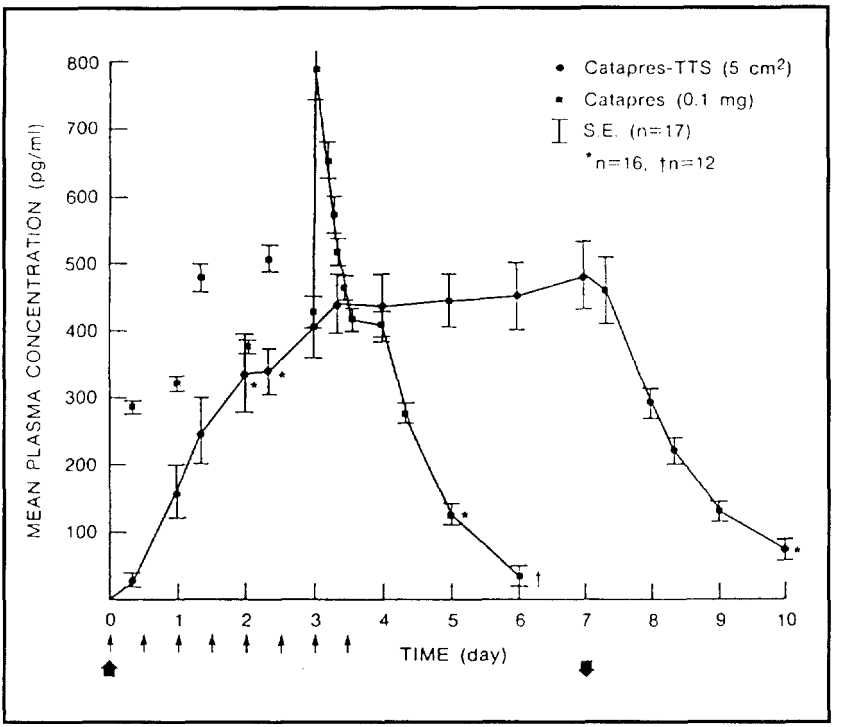


FIGURE 2. *Mean plasma concentrations of clonidine given both orally (squares, 0.1 mg) and transdermally (circles, 5 cm^2). Values are mean ± SE (n = 17).*

study (Shaw et al. 1987) demonstrated that repeated oral doses of clonidine produced a peaks-and-valleys profile of drug concentration in the plasma, whereas a smoother, more consistent plasma-level profile was produced by the transdermal dosage form over 7 days (figure 2).

With regard to the treatment of drug addiction, Roehrich and Gold (1987) described clonidine as providing a nonaddicting solution to an ancient problem: opiate withdrawal without opiates. Clonidine has been useful in treating the signs and symptoms of opiate withdrawal (Gold et al. 1980; Morgan and Wesson 1981; Stine and Kosten 1992) and has proven beneficial in the rapid detoxification of normotensive patients from opiates prior to the induction of naltrexone therapy (Senft 1991). In addition, clonidine has been used to treat the neonatal narcotic abstinence syndrome (Hoder et al. 1981, 1984).

In the past, clonidine treatment for opiate withdrawal involved a variety of oral dosage regimens. The introduction of a transdermal clonidine system made once-a-week dosing a new option. This transdermal product has been used to treat opiate withdrawal (Clark and Longmuir 1986), and the Haight-Ashbury Free Clinic in San Francisco has combined it with nicotine polacrilex gum to treat nicotine withdrawal (Sees and Stalcup 1989). For treating drug addiction, the transdermal drug delivery system significantly increases patient compliance. However, in the treatment of opiate withdrawal, steady-state drug levels of clonidine are not attained until 24 to 48 hours after the first system is applied, so patients must take an oral clonidine supplement during the first few days of therapy to control withdrawal reactions (Spencer and Gregory 1989).

Another transdermal product in clinical use is the fentanyl (Duragesic®) transdermal system. Fentanyl is an opioid used in the management of chronic pain. This narcotic analgesic is available in four dosage strengths that range in drug delivery rate from 25 to 100 micrograms per hour (µg/hr). Higher doses can be achieved if a person wears more than one system. Application of a new fentanyl system every 72 hours can provide the sustained and relatively constant serum fentanyl concentrations associated with continuous intravenous (IV) delivery but without the invasive procedures or special equipment. Evaluation of transdermal fentanyl in clinical trials of cancer patients demonstrated that it was well tolerated and that adverse effects (mild erythema at the site of system application) were minimal (Portenoy et al. 1993). Transdermal delivery of fentanyl has changed an IV drug previously limited to inpatient use into a noninvasively administered analgesic appropriate for outpatient use.

The potential value of transdermal fentanyl delivery in the treatment of adults and neonates addicted to opiates has been raised in previous National Institute on Drug Abuse (NIDA) meetings. Such a therapeutic use of fentanyl should be explored further in clinical studies.

Since plasma concentrations of a particular drug may not reach the desired therapeutic levels soon enough with a transdermal delivery system, transdermal drug absorption can be enhanced to a certain degree by various chemical and physical methods. Examples of chemical methods for enhancing transdermal drug absorption include the addition

of permeation enhancers, lipophilic analogs, or prodrugs. Examples of physical methods include phonophoresis (ultrasound) and electrotransport.

Electrotransport, also known as electrically assisted delivery or iontophoresis, is defined as transdermal transport enhanced by application of an electrical field. An electrotransport system is applied to the skin in the same way as a transdermal system. This technology has potential for delivering peptide and protein drugs as well as conventional drugs, including some drugs used to treat drug addiction. While electrotransport drug delivery systems bypass the gastrointestinal (GI) tract, thus avoiding hepatic first-pass metabolism as passive (no electrical current) transdermal systems do, they have additional advantages because drug delivery rates are typically proportional to the magnitude of the applied current (figure 3). Not only can drug delivery be started or stopped by turning the current on or off, the drug delivery rate also can be readily modulated by varying the current (figure 4). This control enables electrotransport drug delivery systems to be engineered to meet a variety of therapeutic needs. Patterned drug delivery (figure 5) and on-demand delivery that allows the patient to control the dosing are two examples of drug delivery profiles that could be achieved using electrotransport systems.

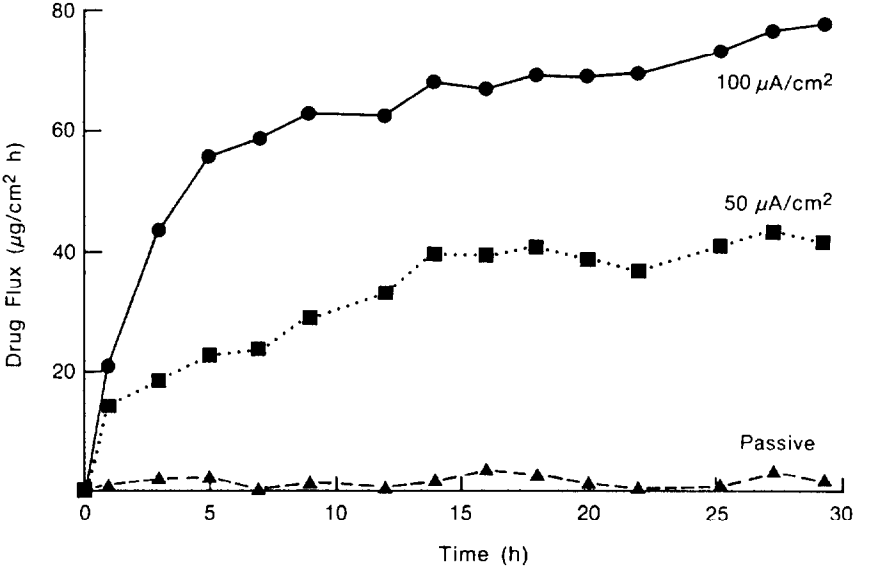


FIGURE 3. *Drug delivery rates are proportional to current density. "Passive" means no current applied.*

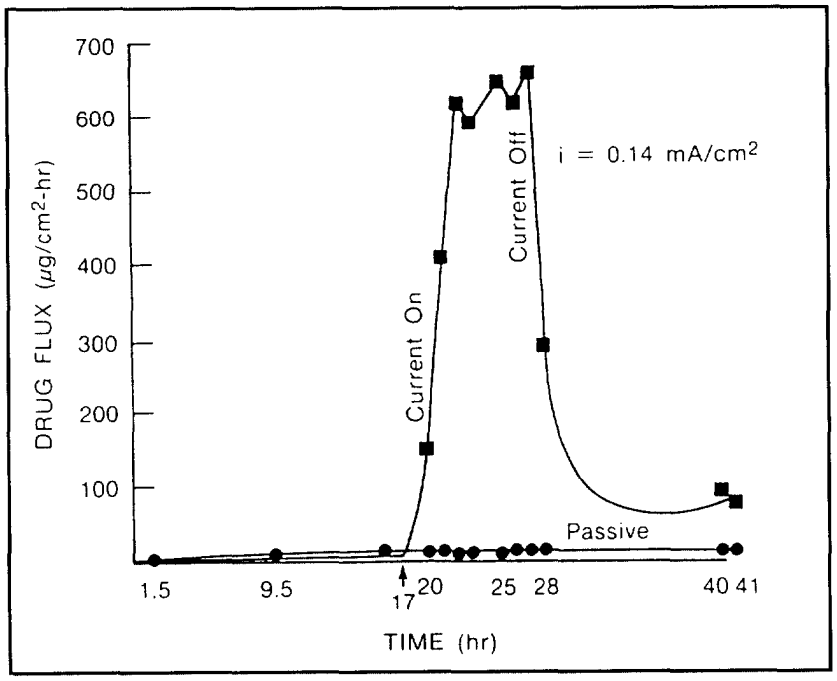


FIGURE 4. *Drug delivery can be started or stopped by turning the current on or off*

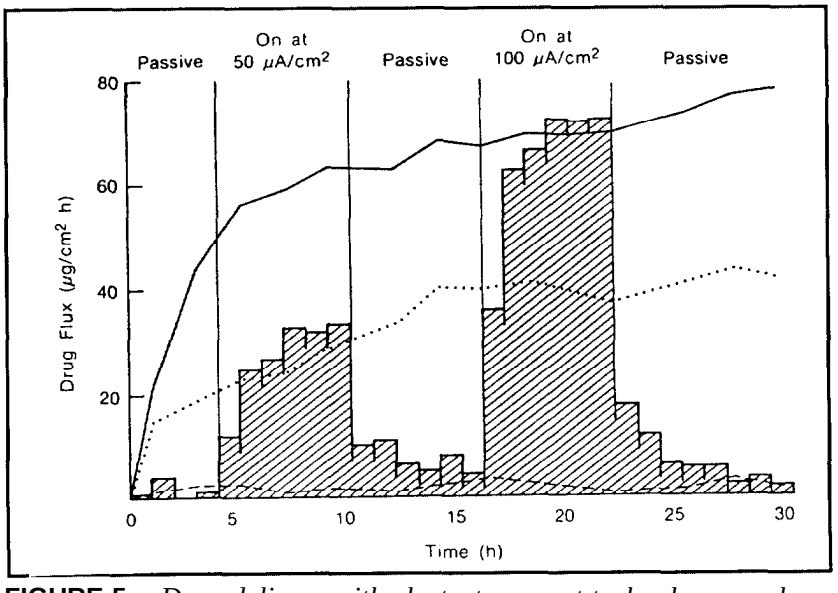


FIGURE 5. *Drug delivery with electrotransport technology can be patterned over time.*

ORAL DRUG DELIVERY SYSTEMS

Advancements in the development of oral drug delivery systems include the class of OROS® osmotic systems. These systems resemble ordinary tablets and they are taken with a glass of water like tablets, but they function in a dramatically different way compared with conventional tablets or slow-release preparations. Drug release is controlled by an osmotic process that can produce steady-state (zero-order) plasma concentration profiles. The technology uses the principle of osmosis, the natural movement of water through a membrane, to make drug administration more precise, reliable, and convenient. The drug release rate is not affected by the motility, acidity, or alkalinity of the GI tract. The release rate is dependent on the osmotic properties of the tablet core and the membrane's permeability to water. Excellent in vitro/in vivo correlations between delivery rates in vitro and absorption rates from the GI tract have been demonstrated for periods of up to 24 hours (Theeuwes et al. 1991). Two systems, the elementary osmotic pump and the push-pull osmotic pump, have been developed into commercial products.

The elementary osmotic pump has a tablet core containing the drug. This core is surrounded by a semipermeable membrane that has one or more laser-drilled holes. As water permeates the membrane, the drug in the core gradually dissolves and is then pumped out at a controlled rate through the small hole. The rate of water inflow and drug formulation outflow are controlled by the properties of the semipermeable membrane. The elementary osmotic pump also can be overcoated with a drug loading dose to provide an immediate pulse of the drug.

The push-pull osmotic system is a bilayer tablet; one layer contains the drug, and the other layer contains a polymeric osmotic agent. The tablet is surrounded by a semipermeable membrane with a laser-drilled hole on the side containing the drug compartment (figure 6). As the push-pull system moves down the GI tract, both compartments draw water across the membrane, slowly liquefying the drug formulation in the drug compartment on one side and expanding the polymeric osmotic compartment on the other side, which slowly and steadily pumps out the drug through the hole in the system to the GI tract.

A gastrointestinal therapeutic system (GITS), nifedipine (Procardia XL®), employs the push-pull osmotic technology for once-daily, constant (or zero-order) nifedipine delivery to treat angina and hypertension. In figure 7, the plasma concentration profile of nifedipine from the typical

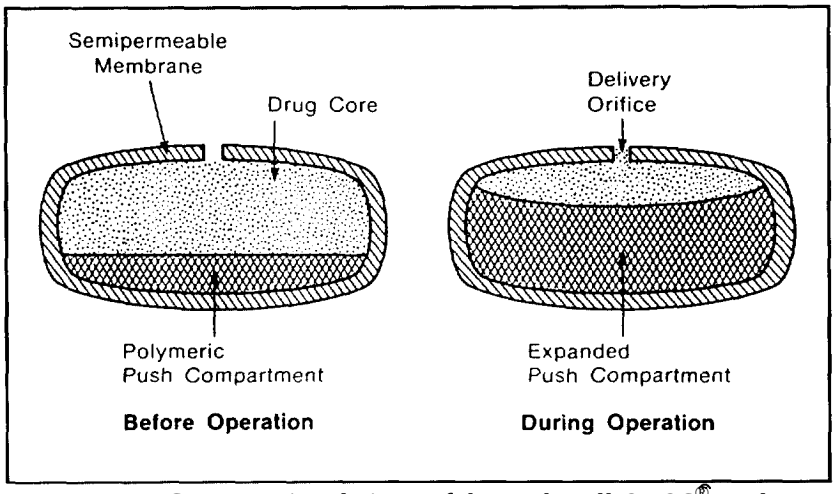


FIGURE 6. *Cross-sectional views of the push-pull OROS® oral osmotic system, before and during operation.*

three times a day oral dosing tablets is compared to that for the once-daily dose of nifedipine delivered at a constant rate by GITS nifedipine (Pfizer, unpublished data; Zaffaroni 1991). A much more consistent nifedipine plasma concentration is obtained with GITS nifedipine compared with

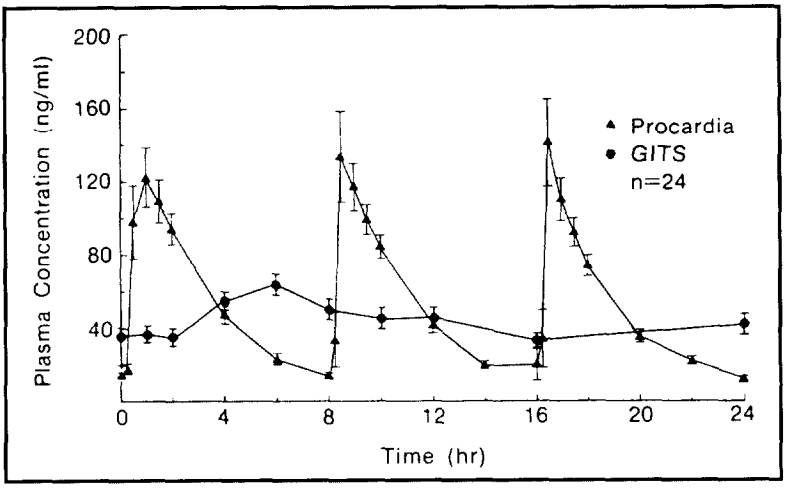


FIGURE 7. *Comparison of plasma nifedipine concentrations for nifedipine tablets (Procardia® versus GITS (nifedipine) (Procardia XL® system)) (Swanson et al. 1987).*

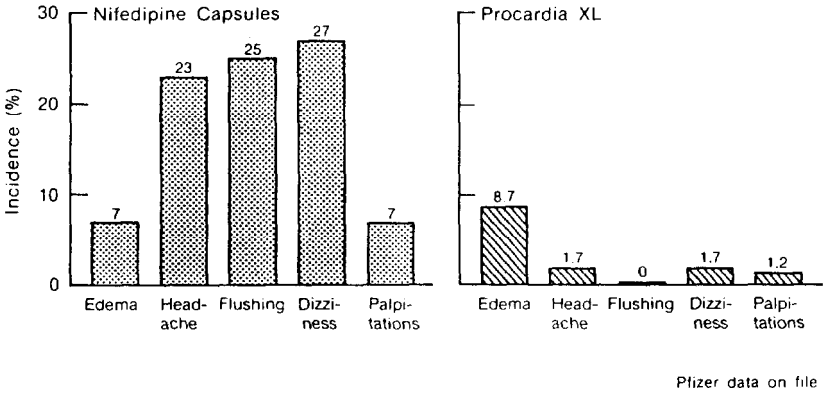


FIGURE 8. *Reduced side effects resulting from administration of the push-pull OROS® oral osmotic system (Procardia XL®) compared with tablets (Procardia®).*

conventional nifedipine tablets. Clinical studies have shown that GITS nifedipine effectively controls hypertension and angina while also significantly reducing side effects (figure 8).

Osmotic systems technology potentially could be suitable for therapies in drug addiction. A once-daily system offering controlled drug delivery would maintain the therapeutic effect throughout the dosing interval by producing a steady plasma concentration level for 24 hours. The technology allows more than one drug in a delivery system; for example, a small amount of naloxone could be mixed with an orally administered narcotic agent. Not only would this permit continued daily therapy with the narcotic, but it also would limit the diversion potential of any take-home medication. Naloxone, poorly absorbed after oral administration (Gilman et al. 1990), would not affect the efficacy of the narcotic. The narcotic could not be extracted easily from the system for IV use without also extracting the naloxone; this safeguard would help prevent diversion of the narcotic.

BIOERODIBLE POLYMER DRUG DELIVERY SYSTEMS

Bioerodible polymer technology involves the use of polymers that can be implanted or injected within the skin, muscles, or other tissues to administer drugs from a bioerodible matrix. Depending on their composition, bioerodible polymers can degrade over periods of time

ranging from several hours to several months. Release rates are controlled by the amount of drug incorporated into the polymer, drug diffusion through the polymer, and bioerosion of the polymer. This drug release control is an important feature for the treatment of drug addiction because bioerodible drug delivery systems could provide therapy over longer time periods and eliminate the need to give patients enough oral doses to use at home for several days. A bioerodible drug delivery system also would eliminate the need for daily visits to a treatment clinic to receive drug therapy. Patients could still go to the treatment clinic for psychosocial support services, but daily trips would not be required as before.

Bioerodible drug delivery systems for naltrexone have been under development by several investigators (Atkins et al. 1992; Chiang et al. 1985; Maa and Heller 1990; Roskos et al. 1993). Heller and colleagues (1991) describe a 30-day bioerodible drug delivery system for naltrexone pamoate, a neutral salt of naltrexone. Their data show that naltrexone is released by an erosion-controlled process and that drug depletion and polymer erosion coincide over the 30-day period. Chiang and associates (1984, 1985) report clinical studies in normal volunteers using a biodegradable sustained-release dosage form of naltrexone. In their studies, constant plasma levels of naltrexone were maintained for about 1 month after volunteers received a 63 mg dose via subcutaneous implantation of naltrexone beads. However, tissue irritation from the naltrexone beads severely limits the usefulness of this particular dosage form. Other investigators also are working on 30-day delivery systems, but it appears that more research is necessary before a bioerodible drug delivery system for drug addiction can be commercialized.

CONCLUSION

While research and development continue on drug delivery systems, this work is only one part of the overall treatment of drug addiction. For pregnant women and newborns, prenatal care, postnatal care, and psychosocial support services are important components in the treatment of drug addiction. Integration of drug addiction treatment with these services can enhance compliance and improve perinatal outcomes.

REFERENCES

Atkins, T.J.; Lewis, D.H.; Rickey, M.E.; Wilbom, W.H.; Carter, M.L.; Strobel, J.D.; and Chiang, C.N. An injectable 30-day naltrexone delivery system. *Proc Intern Symp Control Rel Bioact Mater* 19:54, 1992.

Chiang, C.N.; Hollister, L.E.; Kishimoto, A.; and Barnett, G. Kinetics of a naltrexone sustained-release preparation. *Clin Pharmacol Ther* 36:704-708, 1984.

Chiang, C.N.; Hollister, L.E.; Gillespie, H.K.; and Foltz, R.L. Clinical evaluation of a naltrexone sustained-release preparation. *Drug Alcohol Dep* 16:1-8, 1985.

Chien, Y.W. Transdermal rate-controlled drug delivery: Theory and practice. *Drugs Today* 23:625-646, 1987.

Clark, H.W., and Longmuir, N. Clonidine transdermal patches: A recovery oriented treatment of opiate withdrawal. *Calif Soc Treatment Alcoholism Other Drug Dep News* 13:1-2, 1986.

Gilman, A.G.; Rall, T.W.; Nies, A.S.; and Taylor, P., eds. *The Pharmacological Basis of Therapeutics.* 8th ed. New York: Pergamon Press, 1990.

Gold, M.S.; Pottash, A.C.; Sweeney, D.R.; and Kleber, H.D. Opiate withdrawal using clonidine. A safe, effective and rapid non-opiate treatment. *JAMA* 243:343-346, *1980.*

Gorsline, J.; Benowitz, N.L.; Rolf, C.N.; Gupta, S.K.; and Garaud, J.J. Comparison of plasma nicotine concentrations for nicotine transdermal system (NTS), cigarette smoking and nicotine polacrilex (nicotine gum). *Clin Pharmacol Ther* 51:129, 1992.

Gorsline, J. Nicotine pharmacokinetics of four nicotine transdermal systems. *Health Values* 17:20-24, 1993.

Heller, J.; Maa, Y.F.; Wuthrich, P.; Ng, S.Y.; and Duncan, R. Recent developments in the synthesis and utilization of poly (ortho) esters. *J Controlled Rel* 16:3-14, 1991.

Hoder, L.E.; Leckman, J.F.; Ehrenkranz, R.; Kleber, H.; Cohen, D.J.; and Poules, J. Clonidine in neonatal narcotic-abstinence syndrome. [Letter to the editor] New *Engl J* Med 305:1284, 1981.

Hoder, L.E.; Leckman, J.F.; Poulsen, J.; Caruso, K.A.; Ehrenkranz, R.A.; Kleber, H.D.; and Cohen, D.J. Clonidine treatment of neonatal narcotic abstinence syndrome. *Psychiatry Res* 13:243-251, 1984.

Hughes, J.R., and Miller, S.A. Nicotine gum to help stop smoking. *JAMA* 252:2855-2858, 1984.

Ledger, P.W., and Nichols, K.C. Transdermal drug delivery devices. *Clin Dermat* 7:25-31, 1989.

Maa, Y.F., and Heller, J. Controlled release of naltrexone pamoate from linear poly *(ortho)* esters. *J Controlled Rel* 14:21-28, 1990.

Morgan, J.P., and Wesson, D.R. The use of clonidine (Catapres®) for opiate withdrawal. *Calif Soc Treatment Alcoholism Other Drug Dep* News 8:1-2, 1981.

Portenoy, R.K.; Southam, M.A.; Gupta, S.K.; Lapin, J.; Layman, M.; Intunisi, C.; and Foley, K.M. Transdermal fentanyl for cancer pain. *Anesthesiology* 78:36-43, 1993.

Price, N.M.; Schmitt, L.G.; McGuire, J.; Shaw, J.E.; and Trobough, G. Transdermal scopolamine in the prevention of motion sickness at sea. *Clin Pharmacol Ther* 29:414-419, 1981.

Roehrich, H., and Gold, M.S. Clonidine. *Adv Alcohol Subst Abuse* 7:1-16, 1987.

Roskos, K.V.; Tefft, J.A.; and Heller, J. A morphine-triggered delivery system useful in the treatment of heroin addiction. *Clin Mat* 13:109-119, 1993.

Sees, K.L., and Stalcup, S.A. Combining clonidine and nicotine replacement for treatment of nicotine withdrawal. *J Psychoactive Drugs* 21:355-359, 1989.

Senft, R.A. Experience with clonidine-naltrexone for rapid opiate detoxification. *J Subst Abuse Treat* 8:257-259, 1991.

Shaw, J.E.; Prevo, M.E.; and Amkraut, A. Testing of controlled-release transdermal dosage forms. *Arch Dermatol* 123:1548-1556, 1987.

Spencer, L., and Gregory, M. Clonidine transdermal patches for use in outpatient opiate withdrawal. *J Subst* Abuse *Treat* 6:113-117, 1989.

Stine, S.M., and Kosten, T.R. Use of drug combinations in treatment of opiate withdrawal. *J Clin Psychopharmacol* 12:203-209, *1992.*

Swanson, D.R.; Barclay, B.L.; Wong, P.S.L.; and Theeuwes, F. Nifedipine gastrointestinal therapeutic system. Supplement 6B. *Am J Med* 83:3-9, 1987.

Theeuwes, F. Drug delivery systems. *Pharmacol Ther* 13:149-191, 1981.

Theeuwes, F.; Yum, S.I.; Haak, R.; and Wong, P. Systems for triggered, pulsed and programmed drug delivery. *Ann N Y Acad Sci* 618:428-440, 1991.

Transdermal Nicotine Study Group: Transdermal nicotine for smoking cessation: Six-month results from two multicenter, controlled clinical trials. *JAMA* 266:3133-3138, 1991.

Zaffaroni, A. Overview and evolution of therapeutic systems. *Ann N Y Acad Sci* 618:405-421, 1991.

AUTHOR

Stella T. Chao, Ph.D.
Research Scientist
ALZA Corporation
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Clinical Trials of Pharmacologic Treatments in Pregnant Women-Methodologic Considerations

Richard S. Schottenfeld

INTRODUCTION

The proposed Food and Drug Administration (FDA) guidelines regarding inclusion of women of child-bearing potential in clinical trials of pharmacologic treatments are designed to increase knowledge about the efficacy and optimal use of medications to treat women (Food and Drug Administration 1993). As one illustration of the importance of including women in clinical trials of medications to treat drug dependence, data from a recent clinical trial comparing buprenorphine to methadone maintenance suggest that there may be important gender differences in response to these agents, with women subjects having fewer symptoms of withdrawal and less continued illicit drug use at lower doses of buprenorphine than men (Schottenfeld et al. 1993a).

While the proposed guidelines apply primarily to late Phase II and Phase III studies (i.e., after safety studies have been completed and after evidence of efficacy in humans has been established) and do not specifically call for studies to be conducted in pregnant women, there are two important reasons to consider conducting clinical trials of pharmacologic treatments for drug abuse in pregnant women. First, since drug-dependent women may become pregnant during clinical trials despite attempts to ensure adequate contraception, as occurred during a recent dose-ranging study of buprenorphine (Schottenfeld et al. 1993b), studies are needed to assess the risks and benefits of continued inclusion in the study, the risks and benefits of medication discontinuation, and optimal procedures for discontinuation. Investigators need to be able to assess the risk of having been on medication, make decisions about breaking the blind, and provide appropriate counseling about pregnancy risk and options. Second, considerations of the adverse effects of drug abuse during pregnancy on obstetrical outcome and fetal development suggest there may be a need to develop drug abuse treatment medications that are effective for pregnant women.

This chapter provides an overview of general issues regarding clinical trials of pharmacologic treatments for drug abuse and dependence. Topics covered include choice of pharmacologic agent based on rationale, safety, and preclinical and clinical evidence suggesting efficacy; ethical issues-informed, voluntary consent, consideration of risk-benefit ratio, and quality of scientific design; and the scientific design-the type of study and critical design features to ensure validity.

Special considerations regarding clinical trials in pregnant women are also covered. The discussion highlights issues regarding medication safety, especially with regard to obstetrical complications, fetal malformations, and behavioral teratogenesis; clinically important outcome measures, including reductions in obstetrical complications and adverse effects on the fetus in addition to reduction of maternal drug use and potential conflict among the various outcomes; and special problems regarding risk-benefit analysis and human subjects.

These issues are relevant to discussion of four medications that have been proposed or are under consideration for use with pregnant drug-dependent women: buprenorphine maintenance for opioid-dependent women, nicotine replacement for women who continue to smoke cigarettes during pregnancy, and desipramine and bromocriptine treatment for cocaine-dependent pregnant women. Finally, based on these considerations, the author suggests some guidelines for deciding whether, when, and how to conduct clinical trials of promising therapeutic agents in pregnant women.

GENERAL ISSUES REGARDING CLINICAL TRIALS OF PHARMACOTHERAPIES

Choice of Pharmacologic Agent

The rationale for investigating a medication for use in the treatment of drug dependence is based on consideration of its pharmacologic actions with regard to potential targets for drug abuse treatment as well as preclinical and clinical evidence regarding safety and possible efficacy.

Targets of Pharmacologic Treatments

Potential targets of pharmacotherapies for the treatment of drug abuse (based on Meyer 1989) include the following:

1. Reversal of the acute effects of drugs (reversal of intoxication or overdose);
2. Prevention or amelioration of withdrawal symptoms;
3. Antagonism or blockade of the euphoric or rewarding effects of drugs;
4. Elimination or dimunition of drug craving;
5. Amelioration of symptoms caused by drug use (e.g., paranoia or agitation associated with stimulant use); and
6. Treatment of underlying psychiatric disorders.

Naltrexone maintenance treatment for opioid dependence or abuse works by blocking heroin- or other opioid-induced euphoria. Methadone is used to prevent or ameliorate symptoms of opioid withdrawal. The rationale underlying methadone maintenance is more complex. Relatively low doses (25 to 40 milligrams [mg] per day) are sufficient to prevent or ameliorate symptoms of withdrawal. Higher doses lead to decreased craving and, via cross-tolerance, to blockade of heroin-induced euphoria (Dole 1988).

Craving, or an intense desire or compulsion to use a drug, is a complex biobehavioral construct (Bauer 1992; Childress 1992). Craving is intense during periods of withdrawal. It can occur spontaneously or be evoked by external (environmental) conditioned cues, such as exposure to the drug or drug paraphernalia; people, places, or things associated with drug use; or internal (emotional) cues such as feelings of elation or dysphoria. Use of a small quantity of a drug, such as occurs during a "slip," can have an appetizing effect, precipitate intense craving, and lead to relapse.

Pharmacologic treatments can target drug craving through a number of different mechanisms. Since craving diminishes significantly when drugs are not available, medications that effectively make the drug unavailable decrease drug craving (Meyer and Mirin 1991). This is one of the principles underlying the use of medications that block the euphoric or rewarding effects of a drug (such as naltrexone or methadone with regard to heroin) or that prevent a person from using the drug (such as disulfiram for alcohol).

Craving appears to be mediated by central noradrenergic, serotonergic, and opioid pathways. The priming effects of a drug on craving may be mediated in part through central opioid pathways. Several recent studies document the clinical efficacy of the opioid antagonist naltrexone in the treatment of alcoholism (O'Malley et al. 1992; Volpolicelli et al. 1992). One of the postulated mechanisms for the efficacy of naltrexone is that naltrexone blocks the priming effects of alcohol administration so that patients are less likely to continue drinking to the point of relapse following a slip. Some alcoholic patients treated with naltrexone have reported a decreased compulsion to drink or relapse to heavy use following an initial slip.

Finally, craving may reflect persistent central nervous system (CNS) alterations that follow drug discontinuation. The decision to investigate desipramine for the treatment of cocaine dependence followed recognition of discrete phases of abstinence symptomatology resulting from cocaine discontinuation, with episodic, intense cocaine craving occurring during a period of anhedonia that could persist for weeks after cocaine discontinuation (Gawin et al. 1989). While there is controversy about the validity of discrete phases of cocaine abstinence (Satel et al. 1991; Weddington et al. 1990), desipramine and other tricyclic antidepressant medications have demonstrated some efficacy in ameliorating these symptoms (Gawin et al. 1989; Levin and Lehman 1991). Presumed alterations in dopaminergic functioning are the rationale for using bromocriptine and amantadine during the early phases of cocaine abstinence (Tennant and Sagherian 1987).

It is important to note that since a variety of biological, psychological, and social factors contribute to relapse, pharmacologic treatments addressing biological factors often require psychosocial augmentation to be effective. The need for adjunctive therapy is illustrated most vividly in methadone maintenance treatment. Despite being the most thoroughly documented and effective pharmacologic treatment for opioid dependence, psychosocial interventions are essential to achieve maximal effects (McLellan et al. 1993). The implications of these findings for clinical trials of pharmacologic treatments for addictive disorders are of critical importance: Pure pharmacologic trials, which stringently limit adjunctive psychosocial treatments, may fail to establish efficacy of medications that may be efficacious when used with other interventions.

Safety and Efficacy

The safety of medications to be used in clinical trials of drug-dependent patients must first be established in animal studies. Many of the medications used to treat drug dependence have established indications for the treatment of other medical conditions and thus have been rather extensively tested for safety in nondrug-dependent humans before being tested in drug-dependent patients.

Additional safety precautions need to be taken when testing medications in drug-dependent patients because their health is often impaired and because of the possibility of toxic interactions between the medication and drugs of abuse if patients continue alcohol or other drug use during the clinical trial. Medical problems of drug-dependent patients may include hepatic abnormalities, infectious diseases (human immunodeficiency virus [HIV] infection, tuberculosis, syphilis, endocarditis), cardiac abnormalities (conduction defects, hypertension, microinfarcts associated with cocaine), impaired pulmonary function, and CNS abnormalities (e.g., seizures) (Novick 1992; Wartenberg and Liepman 1990).

Increased toxicity of medications used to treat drug-dependent patients may result from alterations in hepatic metabolism associated with drug use or from combining the effects of the medication with abused drugs. Following a standard dosing regimen, desipramine plasma levels were reported to be elevated in methadone-maintained patients treated for cocaine abuse compared to cocaine-dependent patients not on methadone (Kosten et al. 1990). The cardiovascular toxicity of cocaine also appears to be increased during the initial phases of induction onto desipramine (Fischman et al. 1990). Neuroadaptation following prolonged desipramine administration may make the cardiovascular toxicity associated with cocaine use less problematic. The potential for drug interactions to lead to increased toxicity has appropriately prompted evaluation of many potential pharmacologic treatments in hospital settings using drug administration paradigms.

In addition to considering a medication's potential target and its safety, evidence of efficacy from preclinical or clinical studies may be important in deciding to investigate a medication for treatment of drug abuse or dependence. Animal models that have been used to suggest possible efficacy include drug reinforcement studies, drug discrimination (DD) studies, and studies of conditioned place preference. Fortuitous findings

in humans treated with a medication for other purposes, such as reports of reductions in cocaine use among buprenorphine-treated subjects in a study of short-term opiate detoxification, may also suggest novel uses for a medication (Kosten et al. 1992c).

ETHICAL ISSUES INVOLVING HUMAN SUBJECTS

Respect for persons, beneficence, and justice are the three basic ethical principles articulated in the Belmont Report (Department of Health, Education and Welfare 1979) that underlie Department of Health and Human Services (DHHS) regulations governing the protection of human subjects in research (Aikens, this volume). Respect for persons is ensured through insistence on the informed, voluntary consent of individuals to participate in a research protocol. Beneficence refers to the obligation to protect subjects from harm by maximizing potential benefits and minimizing possible risks. Risks involved in clinical trials of pharmacologic treatments include both the medical risks of the medication or drug interactions and nonmedical risks such as the potential for breaches of patient confidentiality. Potential benefits of participation must be evaluated by comparing the likelihood, potential magnitude, and importance of potential benefits in the context of the risks of the untreated disease and the risks and benefits of alternative treatments. To maximize societal benefits, it is critical that the scientific design and conduct of the research protocol ensure the validity of the study results.

SCIENTIFIC DESIGN

Although randomized, controlled, double-blind clinical trials have become the standard for establishing efficacy of an intervention, open-label and nonrandomized studies as well as a variety of quasiexperimental studies may provide important information regarding safety, optimal dose, adverse reactions, and possible efficacy. Efficacy can be strongly supported if the natural history of a condition is completely described and hard outcomes (e.g., death) are virtually certain for the untreated disease, so that any improvement following treatment can be attributed to treatment rather than natural recovery.

A number of critical design features have been identified to ensure the validity of randomized, controlled, double-blind clinical trials (Blame et

al., in press; Feinstein 1985; Lavori 1992; Satel and Kosten 1991). These design features include the following:

1. Baseline assessments must be sufficient to ensure comparability of treatment groups, homogeneity of subject sample, and evaluation of potential predictors of differential outcome.

2. Inclusion and exclusion criteria must be specified, including diagnosis, severity of disorder, patterns of use, clinical staging, and comorbid conditions.

3. When indicated, prerandomization stratification should be employed on selected subject characteristics such as depression. This practice allows inclusion of a sufficiently heterogeneous sample to ensure generalizability of the study while maintaining sufficient homogeneity and comparability of subject groups to detect treatment effects.

4. Experimental and control interventions must be defined, including:

    - Specification of optimal dose and duration of experimental treatment and control treatment (placebo or alternative active medication). A shorter study duration is usually associated with higher retention and facilitates data analysis, but longer duration is often necessary to assess sustained or clinically important effects;
    - An active medication control should be considered if the side-effect profile of the study medication is likely to lead to inadvertent breaking of the double blind or if there is a need to compare the study medication with a known efficacious medication;
    - The number of pills administered to controls should be yoked (equal) to the number of pills administered to subjects receiving the study medication if the dose of the study medication is adjusted based on blood levels or response; and
    - Compliance should be monitored using blood levels, pill counts, direct observation, riboflavin markers, and other appropriate methods.

5. The amount and type of other interventions (e.g., psychosocial), should be specified, limited, and monitored, and should include plans to limit increased interventions precipitated by patient needs. Failure

to specify, limit, and monitor other interventions may confound the interventions' effects with the effects of the medication group (e.g., placebo-treated subjects may require and obtain more interventions than subjects on active medications, leading to dilution of medication effects). Overly stringent limitations of psychosocial interventions may lead to problems with retention of subjects and difficulties generalizing study results to usual clinical practice settings.

6. Predetermined criteria for removal of subjects from the study must be established based on compliance with the study protocol or safety considerations (e.g., criteria for protective transfer). Criteria are needed for early termination of the study based on unacceptable levels of adverse outcomes in a treatment group. Caution is required in deciding to terminate a study prior to completion of the planned initial protocol, since multiple looks at the data necessitate correction for significance levels.

7. Adequate plans must be in place to ensure retention of subjects in the clinical trial and to follow all subjects throughout the planned duration of the study. While pure pharmacologic trials provide the clearest test of medication efficacy, psychosocial services may be necessary to facilitate sufficient subject retention and compliance to allow assessment of medication efficacy .

8. Major outcomes, frequency of assessment, and methods to assess and ensure the reliability and validity of measures to be used must be specified.

    - The most common outcome domains used in studies of drug abuse treatment include retention in treatment and abstinence or reduction in drug use as measured by urine toxicology and self-report. Additional outcome domains include reduction of symptoms and improved psychiatric, medical, social, family, vocational, or legal functioning.
    - Use objective, observer-rated, and self-report measures to improve reliability, validity, and sensitivity of measures (e.g., observed urine for toxicology testing obtained at sufficient intervals to detect any drug use; use of interviews, observation, and self-report as more sensitive measure of frequency and quantity of use).
    - Use a sufficient range of measures to evaluate primary outcomes, additional outcomes, and adverse effects.

- Use raters who are blind to the treatment group to minimize interviewer bias.
- Keep clinicians blind to research assessments to minimize bias in subject self-reports.
- Evaluate adequacy and maintenance of double-blind.

9. Plans for data analysis must include primary outcome measures specified in advance of the trial, and intention to treat analysis or predetermined minimum dose/duration of treatment.

10. The adequacy and feasibility of the sample size must be ensured. Power calculations need to be based on estimated effect size (optimally from pilot data), study design, and planned data analysis.

SPECIAL CONSIDERATIONS FOR CLINICAL TRIALS IN PREGNANT WOMEN

Safety Issues-Focus on Pregnant Woman and Developing Fetus

In addition to the general safety issues in clinical trials of pharmacologic agents for the treatment of drug abuse and dependence, the use of medications to treat drug-dependent pregnant women may pose significant safety risks for the pregnant woman and the developing fetus. The toxicity of the medication alone, or combined with alcohol or other drugs, may be affected by alterations of drug metabolism and drug disposition during pregnancy, and potential adverse obstetrical effects of the medication (e.g., premature labor or precipitation of other pregnancy complications) represent major risks for the pregnant woman. The teratogenic potential of the medication must be assessed, including possible fetal malformations, vascular disruptions, or long-term adverse behavioral effects. Since most potential pharmacologic agents for addictive disorders act on the CNS and neuroregulatory systems, the potential long-term behavioral teratogenicity of these medications is a critical concern.

Outcome Measures

In addition to measuring effects on drug use, primary outcome measures for drug-dependent pregnant women need to include obstetrical outcomes (reduction in obstetrical complications) and neonatal outcomes, including

congenital abnormalities (malformations, disruptions), intrauterine growth retardation (IUGR), prematurity, behavioral teratogenesis, and neonatal withdrawal.

Inclusion of these additional outcome domains raises two important considerations. First, some of the critical outcomes (e.g., behavioral teratogenesis) can only be assessed through long-term followup, but randomized, controlled clinical trials are an expensive and inefficient means to ascertain delayed, as opposed to acute, effects (Feinstein 1985). Second, some of the outcome domains may be in conflict. What is best or most desired for the mother, for example, may not always be what is best for the fetus, To illustrate this potential conflict, consider the use of a teratogenic medication to relieve abstinence symptoms in a pregnant woman (e.g., anhedonia following cessation of cocaine use) that are not physiologically damaging to the fetus. As another example, high-dose methadone maintenance may be needed to reduce illicit opiate use, but is more likely to lead to significant neonatal withdrawal. In this latter example, the benefits to the neonate of the mother's reduction in illicit drug use (e.g., reduced risk of infectious disease) may outweigh the risks of neonatal withdrawal.

Risk-Benefit Assessment

Assessment of the risk-benefit ratio of a clinical trial of a pharmacologic treatment for drug-dependent pregnant women is complicated by the need to evaluate the risks of obstetrical complications and teratogenesis associated both with drug abuse and with the medications used to treat drug abuse. At present, relatively limited human data are available regarding the optimal use during pregnancy of most of the medications that are under investigation for the treatment of drug dependence. Of additional concern, the problems caused by the untreated disease (drug abuse) with regard to obstetrical complications and neonatal outcomes are not always clearly established and may not be susceptible to therapeutic intervention (Zuckerman et al. 1989). Some adverse effects may be pregnancy phase-specific and irreversible; for example, treatment of maternal cocaine use after organ malformation occurs in the first trimester will not affect this outcome (Volpe 1992).

In one study, discontinuation of cocaine use after the first trimester only partially reduced the risk of placental abruption (Chasnoff et al. 1989). Data from a general hospital prenatal clinic which serves primarily low-income women suggests that it may not be feasible to enroll drug-

dependent pregnant women in clinical trials early enough to prevent many of the adverse effects on obstetrical or neonatal outcome (Grossman et al. 1993). Drug-dependent women are significantly more likely to enter prenatal care in the third trimester or to receive no prenatal care than women who are not drug dependent. Cocaine abuse was documented in 24 percent of women enrolling for prenatal care in the third trimester compared with 3.5 percent of women enrolling in the first trimester (Lago et al. 1993).

In addition, unless tens of thousands of subjects are enrolled, clinical trials lack sufficient power to document the efficacy of an intervention to prevent extremely rare adverse outcomes such as anencephaly or severe genitourinary disruptions. While even the rare occurrence of these catastrophic outcomes may fuel therapeutic zeal, enthusiasm for testing pharmacologic treatments needs to be tempered by consideration of the potential for medications used to treat drug dependence to cause even more harm. From a risk-benefit standpoint, it makes no sense to conduct a clinical trial to investigate a medication's efficacy in preventing an extremely rare outcome if the medication might cause even a slightly increased risk of a more commonly occurring condition.

Particular caution is required in evaluating the significance and deciding to treat signs or symptoms of pathologic occurrences rather than pathologic events (hard outcomes). Using fetal monitoring techniques (Doppler) and ultrasound, some investigators have detected signs of fetal distress associated with abrupt cessation of cocaine in cocaine-dependent women (Christmas et al. 1992). It is not clear, however, that the clinical significance of these findings warrants pharmacologic intervention. Researchers need to be mindful of the earlier history of treatments for opiate withdrawal, many of which were considerably more lethal than the disease being treated.

Human Subject Issues

Conducting clinical trials of pharmacologic treatments for drug-dependent pregnant women raises a number of important issues regarding protection of human subjects. First, obtaining informed, voluntary consent from the woman may be problematic, given that many drug-dependent women experience considerable coercion to enter treatment because of concerns about retaining child custody or avoiding criminal prosecution. Second, mandatory reporting requirements in some states may discourage drug-dependent women from enrolling in clinical trials,

making it even less feasible to conduct these trials and presenting problems in safeguarding confidentiality. Third, because of the dangers of both drug abuse and medication use during pregnancy, risk-benefit discussions regarding proposed clinical trials of pharmacotherapies for drug-dependent women need to consider carefully the potential benefits of nonpharmacologic treatments. If the risks of continued drug use during pregnancy are believed so extreme as to justify experimentation with medication, these medical risks might also be sufficient to warrant involuntary commitment to a residential facility. Confinement will almost certainly lead to higher rates of abstinence and improved obstetrical and neonatal outcomes compared with any pharmacologic treatment alone.

Liability Issues

Clinical trials of pharmacologic treatments for drug-dependent pregnant women are likely to become the focus of legal disputes regarding liability for adverse obstetrical events or neonatal outcomes. In the event of a liability suit, it will be difficult to disentangle the adverse effects of the woman's drug use, the impact of other risk factors for adverse outcomes experienced by many drug-dependent women (such as comorbid infectious diseases or poor nutrition), and the adverse effects of the medications used to treat drug dependence. As a practical matter, concerns about liability are likely to have a chilling effect on the interest of pharmaceutical companies in sponsoring or being involved in clinical trials for drug-dependent pregnant women.

PREGNANCIES OCCURRING DURING THE COURSE OF CLINICAL TRIALS

The occurrence of a pregnancy during the course of a clinical trial raises questions about the risks and benefits of continued treatment, the potential risks of medication discontinuation, and the risks of medication use prior to detection of pregnancy. For women who have benefited from treatment and are abstinent while on the medication, the risk of relapse to drug use if the medication is discontinued will need to be weighed against the risk of harm from the medication. For women who have been maintained on an investigational opioid such as buprenorphine, discontinuation may lead to withdrawal symptoms and possible adverse obstetrical effects.

Currently, no information is available regarding optimal regimens during pregnancy for discontinuation of buprenorphine or for substitution with an approved medication such as methadone. For many medications, there is insufficient information available about the risks to the fetus to provide guidance to the woman about continuation of the pregnancy. It is critical to maintain adequate records about pregnancy outcome or adverse obstetrical or fetal effects associated with exposure to medications used to treat drug dependence.

POTENTIAL MEDICATIONS TO BE EVALUATED IN CLINICAL TRIALS

Alternative Opioid Maintenance Agents-Buprenorphine

Buprenorphine, a partial mu agonist and potent kappa antagonist, is currently being investigated as an alternative to methadone for maintenance treatment of opioid dependence. While the initial reports of buprenorphine leading to reductions in cocaine use (Kosten et al. 1989) have not been supported by subsequent randomized, double-blind, controlled clinical trials, its efficacy in reducing opioid use has been established in clinical trials (Johnson et al. 1990; Kosten et al. 1992c; Schottenfeld et al. 1993a), making it likely that buprenorphine will eventually gain FDA approval. Many women treated with buprenorphine in Phase II and Phase III studies will become pregnant, especially since there is some evidence suggesting that buprenorphine increases the likelihood of pregnancy in drug-dependent women (Schottenfeld et al. 1993b). Because pregnancies are likely to occur in women maintained on buprenorphine, it is important to evaluate the risks of teratogenicity and adverse effects on the fetus (e.g., neonatal withdrawal) and of medical and obstetrical complications associated with buprenorphine use during pregnancy. It will also be important to evaluate buprenorphine dosing requirements during pregnancy and any long-term behavioral teratogenicity associated with its use.

A second reason for investigating buprenorphine as a treatment for pregnant opioid-dependent women is that its pharmacologic profile suggests that it may be safer than methadone for use during pregnancy. While methadone and other full agonists cause increasing respiratory depression at higher doses, there is a flattening of respiratory depression and other mu agonist effects at higher doses of buprenorphine, making the lethality of overdose less for buprenorphine than for methadone. In

addition, abrupt discontinuation of buprenorphine leads to less severe withdrawal than abrupt discontinuation of methadone.

Based on these properties, one might speculate that buprenorphine maintenance during pregnancy may be associated with decreased effects on CNS regulation of respiratory functioning in the fetus and consequently a potentially decreased risk of sudden infant death syndrome (SIDS) associated with infants exposed prenatally to methadone (Kandall and Gaines 1991). Additionally, there may be fewer problems with neonatal withdrawal in children of buprenorphine-maintained pregnant women.

Although there are important reasons to evaluate buprenorphine maintenance in pregnant opioid-dependent women, insufficient data are available from preclinical or clinical investigations to evaluate its safety. In a literature search using both MEDLINE and TOXLINE, the author identified only two studies on buprenorphine toxicity during pregnancy. In one study, which compared subcutaneous administration of methadone (4 or 8 milligrams per kilogram [mg/kg]), buprenorphine (1 or 2 mg/kg), and vehicle in rats, methadone 8 mg/kg led to significant reductions of enkephalin levels in the striatum of rat pups while the lower dose of methadone and neither dose of buprenorphine had any effect on enkephalin levels (Tiong and Olley 1988). Buprenorphine, however, was associated with significantly decreased survival of rat pups (53 percent and 65 percent mortality by day 5 for buprenorphine 1 or 2 mg/kg, compared with 2 percent vehicle-treated, 13 percent methadone 4 mg/kg, and 0 percent methadone 8 mg/kg). Cause of death was not reported.

The lack of data regarding the safety of buprenorphine as a maintenance agent during pregnancy points to an urgent need to conduct preclinical studies evaluating buprenorphine toxicity and teratogenicity during pregnancy. Until these studies are completed, it would not be prudent to conduct clinical trials of buprenorphine for the treatment of pregnant opioid-dependent women.

It is not clear what should be done in situations when a woman becomes pregnant while maintained on buprenorphine. It may be prudent to withdraw her from buprenorphine and transfer her to methadone maintenance, but an argument could also be made that women who have responded well to buprenorphine should be continued on it throughout pregnancy. If the decision is made to substitute methadone for buprenorphine, close monitoring of the woman and the fetus for signs of

withdrawal or distress during this transition period is indicated. If the safety of buprenorphine for use during pregnancy is supported by preclinical studies, investigations in pregnant women will be needed to establish data regarding optimal dose and adverse effects.

Nicotine Replacement

Benowitz (1991) presented a cogent analysis arguing in favor of using nicotine replacement during pregnancy to facilitate abstinence from cigarette smoking. Although cigarette smoking leads to substantially increased risk of spontaneous abortion (odds ratio of 1.2 to 1.8), prematurity, low birth weight, and perinatal mortality, 20 to 25 percent of pregnant women continue to smoke throughout pregnancy with heavier smokers less likely to quit than light smokers. In a meta-analysis of studies of nicotine gum, nicotine replacement was associated with 27 percent cigarette abstinence at 6 months compared with 18 percent for placebo. Somewhat greater efficacy has been reported for transdermal nicotine replacement (the "patch").

In Benowitz's risk-benefit analysis, the benefits of replacement with regard to abstinence from continued cigarette smoking far outweigh the risks of continued smoking and the risks of replacement. As noted by Benowitz, the risks of smoking result from exposure to nicotine, carbon monoxide, and other components of cigarette smoke. While the risks of exposure to nicotine alone include effects on uteroplacental circulation leading to low birth weight and possible behavioral teratogenicity, nicotine replacement (approximately 15 to 20 mg nicotine) leads to nicotine levels (10 to 15 nanograms per milliliter [ng/ml]) slightly lower than that caused by smoking 1 pack of cigarettes per day (20 to 35 ng/ml with each cigarette delivering approximately 1 mg nicotine). Depending on the particular delivery system, nicotine levels at night during transdermal replacement may slightly exceed levels found in smokers. Thus there will be a net decrease in overall risk if nicotine replacement leads to abstinence from cigarette smoking. There is a question of potential increased toxicity if a woman continues to smoke while receiving nicotine replacement (especially the patch), but even this additional risk may be lessened somewhat by the development of tolerance to nicotine effects and the relatively flat dose-response curve for cardiovascular effects.

Desipramine Treatment for Cocaine Dependence

Although intensive efforts are underway to develop effective pharmacologic treatments for cocaine dependence, at present no medications are clearly indicated for the treatment of this disorder. Of all the medications tested to date, desipramine has shown the most promise. While the efficacy of desipramine has been supported by both open-label, nonrandomized studies and some randomized, controlled, double-blind clinical trials (Levin and Lehman 1991), negative findings have also been reported (Kosten et al. 19926).

In a recent me&analysis, Levin and Lehman (1991) identified seven randomized controlled clinical trials of desipramine that provided data regarding treatment retention and abstinence. They concluded that desipramine had no effects on treatment retention, but that desipramine-treated subjects were more likely to abstain from cocaine compared with placebo-treated subjects.

Data from even the most positive of the early studies of desipramine (Gawin et al. 1989) points to desipramine's limited efficacy. Significant differences were obtained only after excluding subjects who dropped out within 2 weeks from the analysis (about 30 percent). Six-month followup data documented persistent abstinence in about half of subjects who achieved 3 weeks continuous abstinence during the 8-week trial, but by the 6-month followup, no differences were evident between desipramine- and placebo-treated subjects (Kosten et al. 1992a).

Because desipramine's efficacy in treating cocaine dependence has not been clearly established and the magnitude of its effects (if any) is likely to be small, there would be little enthusiasm for conducting clinical trials of desipramine in cocaine-dependent pregnant women even if the safety of desipramine use during pregnancy were established. The limited information regarding the safety of desipramine use during pregnancy probably precludes further investigation at this time.

Desipramine is a metabolite of imipramine and is the major drug found in fetal circulation following treatment with imipramine. Although no human data have been reported regarding potential behavioral teratogenicity associated with desipramine use, Ramin and colleagues (1992) reported, "Of the numerous reports of imipramine use during pregnancy, none had more than 20 pregnancies exposed to this agent." There are case reports of limb reduction defects and other fetal

malformations in humans. Preclinical studies report a variety of fetal effects, including transient respiratory, circulatory, and neurologic adaptive abnormalities and increased frequency of CNS malformations in offspring of animals treated with high doses of imipramine. Two studies have documented behavioral effects of desipramine administration during pregnancy on the neonatal rat (Ali et al. 1986; Jason et al. 1981). In addition to these complications, data from nonpregnant humans suggest that there may be an increased likelihood of cardiovascular complications associated with cocaine use during initiation of desipramine treatment.

Bromocriptine Treatment for Cocaine Dependence

Like desipramine, the rationale for using bromocriptine to treat cocaine dependence is based on the hypothesis that bromocriptine reverses CNS alterations of catecholaminergic functioning associated with heavy cocaine use and thus facilitates maintenance of abstinence following cocaine cessation (Clow and Hammer 1991; Giannini et al. 1989; Hoffman 1993; Hubner 1990; Markou and Koob 1992; Taylor and Gold 1990). The evidence of bromocriptine's efficacy in treating cocaine dependence is even less compelling than the evidence for desipramine (Moscovitz et al. 1993; Preston et al. 1992), but the safety of bromocriptine use during pregnancy is somewhat better established; bromocriptine has been used to treat prolactin-secreting pituitary adenomas in pregnant women. Adverse effects of bromocriptine include hypotension, nausea, and fainting, and there is a case report suggesting an increased risk of cardiovascular complications (hypertension, vasospasm, pulmonary edema) associated with bromocriptine treatment of a cocaine-abusing postpartum woman (Bakht et al. 1990). Thus, at the present time, there are insufficient data regarding bromocriptine's efficacy and too great a risk of toxicity to justify clinical trials in pregnant women.

SUMMARY AND PROPOSED GUIDELINES

The many problems and pitfalls involved in conducting clinical trials in drug-dependent pregnant women suggest the need for stringent guidelines and the likelihood that few studies will be conducted of drug-dependent pregnant women. It is likely, however, that a substantial number of women enrolled in pharmacologic trials will become pregnant during these trials. Guidelines for determining what to do in these circumstances involve assessment of the risks and benefits of continued treatment, the potential risks of medication discontinuation, and the risks associated

with medication use prior to detection of pregnancy. For women who have benefited from treatment and are abstinent while on the medication, the risk of relapse to drug use if the medication is discontinued will need to be weighed against the risk of harm from the medication. Sufficient information is often not available to assess the risks of fetal medication exposure or to provide guidance to the woman about continuation of the pregnancy. To assess these risks, adequate records of adverse obstetrical or fetal effects associated with exposure to medications used to treat drug dependence are critical.

A number of relatively simple principles can be used as guidelines for conducting clinical trials in drug-dependent pregnant women. Clinical trials of pharmacologic agents to treat drug dependence should only be conducted in pregnant drug-dependent women after the following conditions have been met:

- the safety and efficacy of the medication has been documented in nonpregnant patients;
- safety studies, including teratological study (developmental toxicity) in animals or experience with use of the medication during pregnancy, have established the safety of medication use during pregnancy;
- investigation of the pharmacologic effects of the medication alone or in combination with illicit drug use has established that there is minimal risk for use in pregnancy;
- the potential benefits of the medication are of sufficient clinical significance to outweigh the potential risks; and
- the safety and efficacy of alternative, nonpharmacologic treatments have not been established or are considered likely to be inferior to the proposed pharmacologic treatment.

If all these conditions are met, controlled studies will be needed to establish the proper dosage regimen during pregnancy, adverse effects, and potential safety issues in pregnant women. There may be no need for randomized, placebo-controlled, double-blind clinical trials to assess efficacy of a pharmacologic treatment for drug abuse in pregnant women.

REFERENCES

Ali, S.F.; Buelke-Sam, J.; Newport, G.D.; and Slikker, W. Early neurobehavioral and neurochemical alterations in rats prenatally exposed to imipramine. *Neurotoxicology* 7:365, 1986.

Bakht, F.R.; Kirshon, B.; Baker, T.; and Cotton, D.B. Postpartum cardiovascular complications after bromocriptine and cocaine use. *Am J Obstet Gynecol* 162:1065-1066, 1990.

Bauer, L.O. Psychobiology of craving. In: Lowinson, J.H.; Ruiz, P.; Millman, R.B.; and Langrod, J.G., eds. *Substance Abuse: A Comprehensive Textbook.* 2nd ed. Baltimore: Williams & Wilkins, 1992. pp. 51-55.

Benowitz, N.L. Nicotine replacement therapy during pregnancy. *JAMA* 266:3174-3177, 1991.

Blaine, J.D.; Ling, W.; Kosten, T.R.; O'Brien, C.P.; and Chiarello, R.J. Establishing the efficacy and safety of medications for the treatment of drug dependence and abuse: Methodological issues. In: Prien, R., and Robinson, E., eds. *Clinical Evaluation of Psychotropic Drugs. Principles and Guidelines.* New York: Raven Press, 1994. pp. 593-624.

Chasnoff, I.J.; Griffith, D.R.; MacGregor, S.; Dirkes, K.; and Bums, K.A. Temporal patterns of cocaine use in pregnancy. *JAMA* 261:1741-1768, 1989.

Childress, A.R.; Eheman, R.; Rohsenow, D.J.; Robbins, S.J.; and O'Brien, C.P. Classically conditioned factors in drug dependence. In: Lowinson, J.H.; Ruiz, P.; Millman, R.B.; and Langrod, J.G., eds. *Substance Abuse: A Comprehensive Textbook.* 2nd ed. Baltimore: Williams & Wilkins, 1992. pp. 56-69.

Christmas, J.T.; Knisely, J.S.; Scholl, S.H. and Ruddy, S. Fetal stress associated with cocaine withdrawal. In: Harris, L., ed. *Problems of Drug Dependence* 1991. National Institute on Drug Abuse Research Monograph No. 119. DHHS Pub. No. (ADM) 92-1888. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1992.

Clow, D.W., and Hammer, R.P. Cocaine abstinence following chronic treatment alters cerebral metabolism in dopaminergic reward regions. Bromocriptine enhances recovery. *Neuropsychophannacology* 4(1):71-75, 1991.

Department of Health, Education and Welfare. "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." *Federal Register* April 18, 1979.

Dole, V.P. Implications of methadone maintenance for theories of narcotic addiction. *JAMA* 260(20):3025-3029, *1988.*

Feinstein, A.R. *Clinical Epidemiology: The Architecture of Clinical Research.* Philadelphia: W.B. Saunders Company, 1985.

Fischman, M.W.; Foltin, R.W.; Nestadt, G.; and Pearlson, G.D. Effects of desipramine maintenance on cocaine self-administration. *J Pharmacol Exp Ther* 253(2):760-770, 1990.

Food and Drug Administration. *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs.* Food and Drug Administration, Department of Health and Human Services. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1993.

Gawin, F.H.; Kleber, H.D.; Byck, R.; Rounsaville, B.J.; Kosten, T.R.; Jatlow, P.I.; and Morgan, C. Desipramine facilitation of initial cocaine abstinence. *Arch Gen Psychiatry* 46:117-121, 1989.

Giannini, A.J.; Folts, D.J.; Feather, J.N.; and Sullivan, B.S. Bromocriptine and amantadine in cocaine detoxification. *Psychiatry Res* 29:11-16, 1989.

Grossman, J.; Schottenfeld, R.S.; Viscarello, R.; and Pakes, J. Cocaine abuse during pregnancy. In: Harris, L., ed. *Problems of Drug Dependence, 1992: Proceedings of the 54th Annual Scientific Meeting.* National Institute on Drug Abuse Research Monograph No. 132. NIH Pub. No. 93-3505. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1993.

Hoffman, J.R. Treating drug abuse: Beyond bromocriptine. *J Gen Intern Med* 9(1):1-4, 1993.

Hubner, C.B., and Koob, G.F. Bromocriptine produces decreases in cocaine self-administration in the rat. *Neuropsychopharmacology* 3(2):101-108, 1990.

Jason, K.M.; Copper, T.B.; and Friedman, E. Prenatal exposure to imipramine alters early behavioral and beta adrenergic receptors in rats. *J Pharmacol Exp Ther* 217:461, 1981.

Johnson, R.E.; Jaffe, J.H.; and Fudala, P.J. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA* 267(20):2750-2755, 1990.

Kandall, S.R. and Gaines, J. Maternal substance use and subsequent sudden infant death syndrome (SIDS) in offspring. *Neurotoxicol Teratol* 13(2):235-240, 1991.

Kosten, T.R.; Kleber, H.D.; and Morgan, C. Role of opioid antagonists in treating intravenous cocaine abuse. *Life Sci* 44:887-892, 1989.

Kosten, T.R.; Gawin, F.H.; Morgan, C.; Nelson, J.C.; and Jatlow, P. Evidence for altered desipramine disposition in methadone-maintained patients treated for cocaine abuse. *Am J Drug Alcohol Abuse* 16(3&3):329-336, 1990.

Kosten, T.R.; Gawin, F.H.; Kosten, T.A.; Morgan, C.; Rounsaville, B.J.; Schottenfeld, R.; and Kleber, H.D. Six-month follow-up of short-term pharmacotherapy for cocaine dependence. *Am J Addict* 1(1):41-49, 1992a.

Kosten, T.R.; Morgan, C.M.; Falcione, J.; and Schottenfeld, R.S. Pharmacotherapy for cocaine-abusing methadone-maintained patients using amantadine or desipramine. *Arch Gen Psychiatry* 49:894-898, 1992b.

Kosten, T.R.; Rosen, M.I.; Schottenfeld, R.; and Ziedonis, D. Buprenorphine for cocaine and opiate dependence. *Psychopharmacol Bull* 28(1):15-19, 1992c.

Lago, L.A.; Schottenfeld, R.S.; Pakes, J.; and Forsyth, B. Primary care-based interventions for pregnant cocaine-abusing women: comparison of treatment enrollees and refusers. In: Harris, L., ed. *Problems of Drug Dependence,* 1993. National Institute on Drug Abuse Research Monograph No. 140. NIH Pub. No. 94-3748. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1994.

Lavori, P.W. Clinical trials in psychiatry: Should protocol deviation censor patient data? *Neuropsychopharmacology* 6(1):39-48, 1992.

Levin, F.R., and Lehman, A.F. Meta-analysis of desipramine as an adjunct in the treatment of cocaine addiction. *J Clin Psychopharmacol* 11(6):374-378, 1991.

Markou, A., and Koob, G.F. Bromocriptine reverses the elevation in intracranial self-stimulation thresholds observed in a rat model of cocaine withdrawal. *Neuropsychopharmacology* 7(3):213-24, 1992.

McLellan, A.T.; Amdt, 1.0.; Matzger, D.S.; Woody, G.E.; and O'Brien, C.P. The effects of psychosocial services in substance abuse treatment. *JAMA* 269(15):1953-1959, 1993.

Meyer, R.E. Prospects for a rational pharmacotherapy of alcoholism. *J Clin Psychiatry* 50(11):403-412, 1989.

Meyer, R.E., and Mirin, S.M. A psychology of craving: Implications of behavioral research. In: Lowinson, J.H., and Ruiz, P., eds. *Substance Abuse: Clinical Problems and Perspectives.* Baltimore: Williams & Wilkins, 1991. pp. 57-62.

Moscovitz, H.; Brookoff, D.; and Nelson, L.A. Randomized trial of bromocriptine for cocaine users presenting to the emergency department. *J Gen Intern Med* 8:1-4, 1993.

Novick, D.M. The medically ill substance abuser. In: Lowinson, J:H.; Ruiz, P.; Millman, R.B.; and Langrod, J.G., eds. *Substance Abuse: A Comprehensive Textbook.* Baltimore: Williams & Wilkins, 1992. pp. 657-674.

O'Malley, S.; Jaffee, A.J.; Chang, G.; Schottenfeld, R.S.; Meyer, R.E.; and Rounsaville, B. Naltrexone and coping skills therapy for alcohol dependence: A controlled study. *Arch Gen Psychiatry* 49:881-887, 1992.

Preston, K.L.; Sullivan, J.T.; Strain, E.C.; and Bigelow, G.E. Effects of cocaine alone and in combination with bromocriptine in human cocaine abusers. *J Pharmacol Exp Ther* 262(1):279-29, 1992.

Ramin, SM.; Little, B.B.; and Gilstrap, L.C. Psychotropics in pregnancy In: Gilstrap, L., and Little, B., eds. *Drugs and Pregnancy. New* York: Elsevier, 1992. pp. 145-173.

Satel, S.L., and Kosten, T.R. Designing drug efficacy trials in the treatment of cocaine abuse. *J Nerv Ment Dis* 179(2):89-96, 1991.

Satel, S.L.; Price, L.H.; Lalumbo, J.M.; and McDougle, C.J. Clinical phenomenology and neurobiology of cocaine abstinence: A prospective inpatient study. *Am J Psychiatry* 149(12):1761-1762, 1991.

Schottenfeld, R.S.; Kosten, T.R.; Pakes, J.; Ziedonis, D.; and Oliveto, A. Buprenorphine vs. methadone maintenance for combined cocaine and opioid dependence. *College on Problems of Drug Dependence*, Toronto, 1993a.

Schottenfeld, R.S.; Pakes, J.; Zideonis, D.; and Kosten, T.R. Buprenorphine: Dose-related effects on cocaine and opioid use in cocaine-abusing opioid dependent humans. *Biol Psychiatry* 34:66-74, 19936.

Taylor, W.A., and Gold, M.S. Pharmacologic approaches to the treatment of cocaine dependence. *West J Med* 152(5):573-577, 1990.

Tennant, F.S., and Sagherian, A.A. Double-blind comparison of amantadine and bromoctiptine for ambulatory withdrawal from cocaine dependence. *Arch Intern Med* 147:109-111, 1987.

Tiong, G., and Olley, J.E. Effects of exposure in utero to methadone and buprenorphine on enkephalin levels in the developing rat brain. *Neurosci Lett* 93:101-106, 1988.

Volpe, J.J. Effect of cocaine use on the fetus. N *Eng J Med* 327(6):399-407, 1992.

Volpolicelli, J.R.; Alterman, A.I.; Hayashida, M.; and O'Brien, C.P. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psy* 49:876-880, 1992.

Wartenberg, A.A., and Liepman, M.R. Medical complications of substance abuse. In: Lemer, W.D., and Barr, M.A., eds. *Handbook of Hospital-Based Substance Abuse* Treatment. New York: Pergamon, 1990. pp. 45-65.

Weddington, W.W. Jr.; Brown, B.S.; Haertzen, C.A.; Cone, E.J.; Dax, M.; Heming, R.I.; and Michaelson, B.S. Changes in mood, craving, and sleep during short-term abstinence reported by male cocaine addicts. A controlled, residential study. *Arch Gen Psychiatry* 47(9):861-868, 1990.

Zuckerman, B.; Frank, D.A.; Hingson, R.; Amaro, H.; Levenson, S.M.; Kayne, H.; Parker, S.; Vinci, R.; Aboagye, K.; Fried, L.E.; Cabral, H.; Timperi, R.; and Bauchner, H. Effects of maternal marijuana and cocaine use on fetal growth. N *Eng J Med* 320(12):762-768, 1989.

AUTHOR

Richard S. Schottenfeld, M.D.
Associate Professor of Psychiatry
Yale University School of Medicine
Department of Psychiatry
34 Park Street
New Haven, CT 06519

Legal and Ethical Issues

Diane Aiken

The Public Health Service Act requires the Department of Health and Human Services (DHHS) to issue regulations for the protection of human subjects in research and to implement a program of instruction and guidance in the ethical issues associated with such research. The regulations are codified as Title 45 part 46 of the *Code of Federal Regulations*, known as 45 CFR 46.

The history of human subject protection goes back to the Nuremberg Code. Most researchers are aware of the medical experiments conducted during the Nazi regime and of the Nuremberg trials that followed. The Nuremberg Code has 10 principles for the protection of human subjects in research, including basic principles governing the ethical conduct of research. The provision that is the most germane to this chapter states that the voluntary participation of human research subjects is absolutely essential. Freely given consent to participate in research is the cornerstone of ethical experimentation involving human subjects. Other provisions include the capacity to consent; freedom from coercion; comprehension of the risks and benefits involved; the requirement for the minimization of risks and harm, a favorable risk-benefit ratio, and qualified investigators using an appropriate research design; and freedom of subjects to withdraw at any time without losing any benefits that they would otherwise accrue.

These are minimal regulations in effect worldwide. The United Nations Charter was cosigned by 184 countries, including the United States as well as less-developed countries that also follow these minimum regulations. Similar recommendations were made in the Declaration of Helsinki, which further distinguished therapeutic from nontherapeutic research. This declaration was revised three times, the last time in 1989, and differs from DHHS regulations in that it does not require written informed consent. DHHS regulations require written informed consent unless a waiver is requested from and approved by the institutional review board (IRB).

BACKGROUND

From about 1966 to 1974, DHHS (then the Department of Health, Education and Welfare) operated according to policies for the protection of human subjects. In May 1974 these policies were upgraded to regulations. In July 1974 the National Research Act was signed into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the mandates of the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects. The result of the deliberations of the Commission, the Belmont Report and its three ethical principles, is enforced in all research funded by DHHS. Some institutions already had protections for human subjects. Some universities and medical schools realized that when they conducted research they needed to protect human subjects, but there was no overall code and people just did what they thought was best for their institutions. What changed this situation was the Tuskegee Syphilis Study.

From 1932 to 1972, the Public Health Service conducted a natural-history study of syphilis in black men in Tuskegee, Alabama. Even after medications became available for the treatment of syphilis, treatment was withheld because the researchers thought that it was much more important to follow the natural history of the disease. The discussions go on even today, and this author believes it is a very poor reflection on the Public Health Service that this research continued for 40 years. People who were responsible still say it was important, and both sides still argue.

When the Tuskegee situation became known, other instancesof human-subject abuses also became known. Research had been conducted on nursing-home patients who were injected with live cancer cells. At Willowbrook, a facility for retarded children, parents had to agree to have a child injected with live hepatitis virus to get the child admitted; the rationale was that the child was going to get hepatitis in this situation anyway and might as well be part of the research experimentation. These are examples of coercion; as the regulations state, coercion is not allowed.

There had been discussions about establishing IRBs. IRBs, which are similar to human ethics committees, consider the ethics of research. Not much was done until the early 1970s, when these infractions were brought forth during the Kennedy hearings. Three basic principles of

ethics were outlined in the Belmont Report in the late 1970s and these principles have not changed.

THE BELMONT REPORT

The first principle of the Belmont Report is respect for persons, which is recognition of personal dignity and the autonomy of individuals to choose whether to enter a clinical trial or a research program. The regulations contain special protections for persons with diminished autonomy such as pregnant women, fetuses, prisoners, children, and economically and educationally disadvantaged persons, among others.

The second principle is beneficence. This speaks to the obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks or harm. When a research protocol is conceived, the risk-benefit ratio is carefully assessed. One responsibility of the IRB is to determine whether the risk-benefit ratio is favorable to the research subjects.

The third principle is justice: fairness in the distribution of research benefits and burdens (distributive justice). This means ensuring that all the benefits are not accrued by one class of people and all the burdens are not borne by one class of people.

The regulations apply to all research involving human subjects that is conducted, funded, or supported in whole or in part by DHHS. Therefore the regulations may apply to institutions or individuals, including students who participate in research, even if no actual transfer of funds occurs. The regulations define exactly what research is. Often investigators assume that the research is not covered by the regulations if they are not actually interacting with a research subject, but research is defined as a systematic investigation designed to develop or contribute to generalizable knowledge. That is, even if secondhand data are being analyzed, the research comes under the regulations and not under one of the exemptions to the regulations if the investigator is privy to identifiable information (i.e., a research record number, a medical number, or a code name). A human subject is defined as a living individual about whom an investigator conducting research obtains data through intervention or interaction or obtains private identifiable information.

DHHS REGULATIONS

DHHS regulations require that each institution where research involving human subjects is conducted provide written assurance of compliance with the regulations (called assurances). Major institutions that have a history of engaging in DHHS-supported research that involves human subjects have what was formerly called a general or blanket assurance and is now called a multiple project assurance. These institutions have an M number, which must be noted on the face page of every National Institutes of Health (NIH) grant application and on continuing applications for noncompetitive support. Each assurance sets forth the commitment of the institution to follow the basic ethical principles of the Belmont Report and to comply with the regulations.

In 1990 a policy was issued by NIH and then by the Alcohol, Drug Abuse, and Mental Health Administration that required grants and contracts involving human subjects to include provisions for women and minorities so that research findings could be beneficial to all. These groups may be excluded only for compelling reasons, not because including them is difficult or costly. NIH has refused to fund projects with good priority scores that did not include women.

Because clinical trials may expose women of childbearing potential or pregnant women to additional risks, every effort must be made to reduce risks as much as possible and to maximize benefits. Over the years, women and minorities have demanded greater participation in drug trials; one reason for this may be the acquired immunodeficiency syndrome trials, where state-of-the-art medication and treatment are available through drug trials that may not be available to the general population. The Food and Drug Administration (FDA) has expanded access and created a parallel track so that people who are not allowed on drug trials or do not meet the inclusion criteria are sometimes able to get the drugs used in the drug trial. The focus is changing from the protection from research risks and the burdens that research entails to the potential benefits to be accrued from participating in a study. Conflict exists because there is increasing demand for accelerated drug approval processes and inclusion of more vulnerable groups in trials.

Elderly people, children, women, and minorities generally have not participated in clinical trials, and there has not been adequate premarket testing in these populations. There are conflicting demands on investigators and the pharmaceutical industry for the inclusion of women,

women of childbearing potential, pregnant women, and minorities in clinical research. Often, guidelines for safe conduct of clinical trials are being challenged by a population that is much more aware of procedures for clinical trials than in the past.

FDA has reversed its recommendation against including women of childbearing potential in early trials, but the need exists to balance the exposure of vulnerable groups with their access to new modalities.

INSTITUTIONAL REVIEW BOARDS

Part of the DHHS regulations require the establishment of IRBs, which are responsible for protecting the rights and welfare of human subjects. The IRBs determine if the selection of subjects is equitable; this does not refer to the inclusion or exclusion of women or minorities but rather to the fairness and the appropriateness of subject selection. The pivotal role of the IRB in the research process is becoming more apparent.

Most Federal Government agencies that conduct human-subject research have now signed on to subpart A of the general regulations called the Federal Common Rule, which was published in the *Federal Register* in June 1991. Subpart A of these regulations was altered slightly to accommodate other agencies. Subparts B, C, and D have not been signed on to, probably because it took 10 years for all the signing agencies to agree on subpart A.

As already noted, there are provisions in the regulations that address the need for additional safeguards for vulnerable populations. Subpart B addresses pregnant women in research. The IRB must determine whether adequate consideration is given to how potential subjects will be selected, how the informed consent process will be monitored, and how individual consent will be secured, either by approving all accruals or by verifying through sampling that approved procedures have been followed. Monitoring is required to ensure that the process is carried through. The regulations require that the IRB review research at least yearly, depending on the degree of risk. The more risky the research, the more often review is needed.

The regulations also state that no award may be issued until the applicant has certified to the Office for Protection From Research Risks (OPRR, acting for the Secretary of DHHS) that the IRB has determined that the

requirements of subpart A and subpart B have been met. No activity may be undertaken unless appropriate studies on animals and nonpregnant women have been completed, except when the purpose of the activity is to meet the health needs of the particular mother or fetus and the risk to the fetus is minimal. In all cases, activities should have the least possible risk for achieving the objective. Individuals engaged in the research activity should have no part in the decisions of timing, method, or procedures used to terminate a pregnancy and should have no part in determining the viability of fetuses.

The regulations describe activities directed toward pregnant women as subjects. No pregnant woman may be involved as a subject in an activity covered by this subpart unless the purpose of the activity is to meet the health needs of the woman and the fetus will be placed at risk only to the minimum extent necessary to meet such needs. The activity permitted under this section may be conducted only if the mother and father are legally competent and have given their informed consent. The father's informed consent need not be secured if the purpose of the activity is to meet the health needs of the mother, if his identity or whereabouts cannot reasonably be ascertained, or if he is not reasonably available.

The activities directed towards fetuses generally come under the same type of guidelines. No fetus may be involved as a subject in an activity unless the purpose is to meet health needs.

The regulatory requirements that govern the participation of pregnant women in research deserve special attention from IRBs because of women's additional health concerns during pregnancy and because of the need to avoid unnecessary risks to fetuses. Minimal risk is defined as the probability and magnitude of anticipated harm or discomfort being no greater than those ordinarily encountered in daily life. The IRB has to carefully weigh exactly what the risks entail.

Pregnant women may be involved in several categories of research. IRB duties differ in each category, but the primary objectives are to assess whether the research is directed towards the mother's health or towards the fetus and whether the risk to the woman and fetus (or infant) is minimal.

CONCLUSION

To approve research, the IRB must determine that risks to the subjects are minimized. This goes back to the underlying ethical principles of the Belmont Report: to beneficence (that risks to the subjects are reasonable in relation to anticipated benefits), to selection of subjects being equitable, and to the informed consent being an educative document that is updated when new information becomes available, with subjects signing the updates as necessary. The IRBs have a tremendous responsibility and authority in reviewing a research protocol.

Before a research project is started, researchers may want to consider obtaining a certificate of confidentiality that protects research data from subpoena by law enforcement agencies. More and more States are forcing this issue in court, and two or three States are trying to undermine the certificates of confidentiality.

OPRR offers a free set of videotapes that explain IRB procedures and informed consent and can be ordered directly. In addition, OPRR has just issued an IRB guidebook that is available from the Government Printing Office.

AUTHOR

Diane Aiken, M.A.
Assurance Coordinator
Office of the Director
Office of Protection From Research Risks
National Institutes of Health
Building 31, Room 5B-63
9000 Rockville Pike
Bethesda, MD 20892

Testing Medications for the Treatment of Addiction in Pregnancy: One Reviewer's Opinion

Curtis Wright

INTRODUCTION

Society is at an impasse regarding the testing and development of new drugs for use during pregnancy. Concern over litigation has resulted in a near paralysis of new drug development, even for conditions for which lack of effective treatment results in a heavy toll of morbidity and mortality for both mother and child. One such area is in the development of new therapies for the treatment of the female or pregnant addict. This area is of intense interest to the Food and Drug Administration (FDA), and while the general problem is too complex for simplistic solutions, there are some situations in addiction treatment when the study of treatments for the pregnant addict may be appropriate. This chapter presents strategies for such studies.

Reproduction is a risky business for all members of the animal kingdom, including clinical researchers and pharmaceutical executives. Despite a quarter-century of legislation, regulation, reform, and dialog, individual and class-action tort cases are the feared result when any procedure or product with a possible adverse reproductive effect is involved in a case of poor reproductive outcome. There are surprisingly few such cases, but it is not known if this is due to the lack of liability or the rarity of such testing. With a baseline risk of birth defects of 1 percent even in low-risk pregnancies and a tendency for juries to attribute adverse outcomes to drugs taken before or during pregnancy, the fear of an adverse judgment is substantial even with drugs that do not have any adverse effect on the reproductive process. Since there is a risk of adverse judgments running to millions of dollars and the period of liability extends until the children are mature, the risk of developing new medications or conducting trials of new therapies in pregnant women is often considered prohibitive by commercial sponsors and academic institutions.

These risks of liability are so much greater than the possible reward that pregnant women as a group are at risk of becoming another member of an emerging new class of "orphan patients" avoided by researchers, the pharmaceutical industry, and institutional review boards (IRBs). It is always wise to avoid *unneeded* medications during pregnancy, and routine preclinical animal testing provides at least some warning of the rare products that pose a serious teratogenic problem. The testing of drugs in pregnancy should always be approached by trying to get enough information to allow an individual decision that weighs the potential benefits against the risk of injury.

THE PROBLEM OF THE ADDICTIONS

The problem of studying drugs in pregnancy is especially troubling in addictive disease, a group of conditions where lack of treatment *guarantees* that the mother and the child will be routinely exposed to teratogenic embryotoxins as a condition of the disease. Alcoholism, tobacco addiction, and cocaine and other drug dependencies are as a class the most prevalent disorders associated with preventable adverse reproductive outcomes in this society. Recent associations of intravenous drug use with prostitution, tuberculosis, and sexually transmitted diseases have added the possibility of human immunodeficiency virus, drug-resistant tuberculosis, and even a resurgence of congenital syphilis to the risks faced by addicted women and their children. In these patients, not only is there an ongoing risk of injury that will be expected to persist until treatment is provided, but the available treatment medications pose a potential risk of adverse effects on pregnancy, parturition, and the postnatal health of the infant.

The problem thus becomes one of an underlying disease that places both mother and child at risk, and therapies that reduce this risk but are simultaneously associated with adverse risks to the pregnancy. The choice of therapy becomes a choice between the risks of uncontrolled addiction and the risks of the therapy. In this setting the likelihood of the treatment being effective must be balanced against the risks of the treatment and the risks of the addiction. In some cases the choice is straightforward (methadone therapy is better than uncontrolled heroin use), while in others the relative risks are difficult to weigh (nicotine replacement may or may not be better than nondrug therapy in the management of the heavily nicotine-dependent pregnant smoker).

CASES WHEN STUDIES IN PREGNANCY ARE PROBABLY NOT DESIRABLE

In general, a medication for addiction treatment should not be used by pregnant women until reproductive studies in animals and some efficacy studies in nonpregnant populations have been completed. Medications that show serious teratogenic effects in animals, that are shown to be less effective or less well-tolerated than approved alternative treatments, or both, should not be used in pregnant populations. Studies in pregnancy are probably not warranted in cases when the baseline risk from the addiction is low, such as with women smoking less than half a pack a day of cigarettes or in certain forms of addiction to prescription medication.

CASES WHEN CONTROLLED STUDIES IN PREGNANCY MAY BE NEEDED

In cases of serious (risky) addiction when a new treatment is proven substantially more effective than the best of the existing therapies *and the* animal reproductive profile shows no adverse reproductive effects, controlled studies of the proper dose, duration, and conditions of use of the new medication are appropriate, if not mandatory. The focus of these studies should be to define how to use the drug safely and *effectively* in pregnancy, not to demonstrate basic efficacy that has already been shown in nonpregnant populations. Such studies should address the problem of effective use of the new therapy in the face of the known physiological changes of pregnancy as appropriate (Food and Drug Administration 1993).

AMBIGUOUS CASES

In cases when a new treatment does not appear to be much better than an existing treatment or when there are ambiguous animal safety data, controlled studies might not be appropriate. In such cases it is likely that the drug *will* be used by women who may become pregnant. In such a setting it is probably best to establish a registry of women who become pregnant while taking the drug and to monitor the children's development, looking for any evidence of injury not seen in suitable control populations. Current long-term studies of the effects of alcohol

use, cocaine use, or both have shown this to be an effective technology of reasonable sensitivity.

REGULATORY ACTION

Pregnant women are a subpopulation of great interest to FDA. Any drug that is used by women of childbearing potential will ultimately be used in pregnant women, whether such use is intended or not. In conditions when the disorder (in this case addiction) puts both the mother and child at risk of deformity or death, new treatments that are proven to be clearly better than existing treatments should be tested and proved safe in pregnancy, provided animal studies are favorable. Design of such studies should be left to the investigators and the local IRBs, but the focus of the work should be to optimize the treatment for pregnant women and to show its safety. It is unclear if any regulatory agency has or should have the power to mandate such testing, but sponsors should be strongly encouraged to seek investigators and institutions who feel that the benefits of the new therapy outweigh the risks.

In cases when a new treatment is roughly equivalent to existing therapy or is somewhat superior but has equivocal safety in animals, there are no compelling reasons to test the new treatment in pregnancy, but it is likely that some women taking the drug will become pregnant. In such cases the establishment of a suitable registry and long-term followup of the cohort (with a possible control cohort) is a reasonable way to protect both the sponsor and the treating professional while safeguarding the patient, the child, and the public health.

REFERENCE

Food and Drug Administration. "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." *Federal Register* July 22, 1993.

AUTHOR

Curtis Wright, M.D., M.P.H.
Medical Officer
Pilot Drug Evaluation Staff
Food and Drug Administration
Parklawn Building, Room 9B-45
5600 Fishers Lane
Rockville, MD 20857

While limited supplies last, single copies of the monographs may be obtained free of charge from the National Clearinghouse for Alcohol and Drug Information (NCADI). Please also contact NCADI for information about availability of coming issues and other publications of the National Institute on Drug Abuse relevant to drug abuse research.

Additional copies may be purchased from the U.S. Government Printing Office (GPO) and/or the National Technical Information Service (NTIS) as indicated. NTIS prices are for paper copy; add $3.00 handling charge for each order. Microfiche copies also are available from NTIS. Prices from either source are subject to change.

Addresses are:

NCADI
National Clearinghouse for Alcohol and Drug Information
P.O. Box 2345
Rockville, MD 20852
(301) 468-2600
(800) 729-6686

GPO
Superintendent of Documents
U.S. Government Printing Office
P.O. Box 371954
Pittsburgh, PA 15220-7954
(202) 738-3238
FAX (202) 5 12-2233

NTIS
National Technical Information Service
U.S. Department of Commerce
Springfield, VA 22161
(703) 487-4650

For information on availability of NIDA Research Monographs from 1975-1993 and those not listed, write to NIDA, Community and Professional Education Branch, Room 10A-39, 5600 Fishers Lane, Rockville, MD 20857.

26 THE BEHAVIORAL ASPECTS OF SMOKING. Norman A. Krasnegor, Ph.D., ed. (Reprint from 1979 Surgeon General's Report on Smoking and Health.)
NCADI#M26 NTIS PB #80-118755/AS (A09) $27.00

42 THE ANALYSIS OF CANNABINOIDS IN BIOLOGICAL FLUIDS. Richard L. Hawks, Ph.D., ed.
NCADI #M42 NTIS PB #83-136044/AS (A07) $27.00

50 COCAINE: PHARMACOLOGY, EFFECTS, AND TREATMENT OF ABUSE. John Grabowski, Ph.D., ed.
NCADI #M50 NTIS PB #85-150381/AS (A07) $27.00

52 TESTING DRUGS FOR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. Joseph V. Brady, Ph.D., and Scott E. Lukas, Ph.D., eds.
NCADI #M52 NTIS PB #85-150373/AS (A08) $27.00

53 PHARMACOLOGICAL ADJUNCTS IN SMOKING CESSATION. John Grabowski, Ph.D., and Sharon M. Hall, Ph.D., eds.
NCADI #M53 NTIS PB #89-123186/AS (A07) $27.00

54 MECHANISMS OF TOLERANCE AND DEPENDENCE. Charles Wm. Sharp, Ph.D., ed.
NCADI #M54 NTIS PB #89-103279/AS (A19) $52.00

56 ETIOLOGY OF DRUG ABUSE: IMPLICATIONS FOR PREVENTION. Coryl LaRue Jones, Ph.D., and Robert J. Battjes, D.S.W., eds.
NCADI #M56 NTIS PB #89-123160/AS (A13) $36.50

61 COCAINE USE IN AMERICA: EPIDEMIOLOGIC AND CLINICAL PERSPECTIVES. Nicholas J. Kozel, M.S., and Edgar H. Adams, M.S., eds.
NCADI #M61 NTIS PB #89-131866/AS (A11) $36.50

62 NEUROSCIENCE METHODS IN DRUG ABUSE RESEARCH. Roger M. Brown, Ph.D., and David P. Friedman, Ph.D., eds.
NCADI #M62 NTIS PB #89-130660/AS (A08) $27.00

63 PREVENTION RESEARCH: DETERRING DRUG ABUSE AMONG CHILDREN AND ADOLESCENTS. Catherine S. Bell, MS., and Robert J. Battjes, D.S.W., eds.
NCADI #M63 NTIS PB #89-103287/AS (A11) $36.50

64 PHENCYCLIDINE: AN UPDATE. Doris H. Clouet, Ph.D., ed.
NCADI #M64 NTIS PB #89-131858/AS (A12) $36.50

65 WOMEN AND DRUGS: A NEW ERA FOR RESEARCH. Barbara A. Ray, Ph.D., and Monique C. Braude, Ph.D., eds.
NCADI #M65 NTIS PB #89-130637/AS (A06) $27.00

69 OPIOID PEPTIDES: MEDICINAL CHEMISTRY. Rao S. Rapaka, Ph.D.; Gene Bamett, Ph.D.; and Richard L. Hawks, Ph.D., eds.
NCADI #M69 NTIS PB #89-158422/AS (A17) $44.50

70 OPIOID PEPTIDES: MOLECULAR PHARMACOLOGY, BIOSYNTHESIS, AND ANALYSIS. Rao S. Rapaka, Ph.D., and Richard L. Hawks, Ph.D., eds.
NCADI #M70 NTIS PB #89-158430/AS (A18) $52.00

72 RELAPSE AND RECOVERY IN DRUG ABUSE. Frank M. Tims, Ph.D., and Carl G. Leukefeld, D.S.W., eds.
NCADI #M72 NTIS PB #89-151963/AS (A09) $36.50

74 NEUROBIOLOGY OF BEHAVIORAL CONTROL IN DRUG ABUSE. Stephen I. Szara, M.D., D.Sc., ed.
NCADI #M74 NTIS PB #89-151989/AS (A07) $27.00

78 THE ROLE OF NEUROPLASTICITY IN THE RESPONSE TO DRUGS. David P. Friedman, Ph.D., and Doris H. Clouet, Ph.D., eds.
NCADI #M78 NTIS PB #88-245683/AS (A10) $36.50

79 STRUCTURE-ACTIVITY RELATIONSHIPS OF THE CANNABINOIDS. Rao S. Rapaka, Ph.D., and Alexandros Makriyannis, Ph.D., eds.
NCADI #M79 NTIS PB #89-109201/AS (A10) $36.50

80 NEEDLE SHARING AMONG INTRAVENOUS DRUG ABUSERS: NATIONAL AND INTERNATIONAL PERSPECTIVES. Robert J. Battjes, D.S.W., and Roy W. Pickens, Ph.D., eds.
NCADI #M80 NTIS PB #88-236138/AS (A09) $36.50

82 OPIOIDS IN THE HIPPOCAMPUS. Jacqueline F. McGinty, Ph.D., and David P. Friedman, Ph.D., eds.
NCADI #M82 NTIS PB #88-245691/AS (A06) $27.00

83 HEALTH HAZARDS OF NITRITE INHALANTS. Harry W. Haverkos, M.D., and John A. Dougherty, Ph.D., eds.
NCADI #M83 NTIS PB #89-125496/AS (A06) $27.00

84 LEARNING FACTORS IN SUBSTANCE ABUSE. Barbara A. Ray, Ph.D., ed.
NCADI #M84 NTIS PB #89-125504/AS (A10) $36.50

85 EPIDEMIOLOGY OF INHALANT ABUSE: AN UPDATE. Raquel A. Crider, Ph.D., and Beatrice A. Rouse, Ph.D., eds.
NCADI #M85 NTIS PB #89-123178/AS (A10) $36.50

87 OPIOID PEPTIDES: AN UPDATE. Rao S. Rapaka, Ph.D., and Bhola N. Dhawan, M.D., eds.
NCADI #M87 NTIS PB #89-158430/AS (A11) $36.50

88 MECHANISMS OF COCAINE ABUSE AND TOXICITY. Doris H. Clouet, Ph.D.; Khursheed Asghar, Ph.D.; and Roger M. Brown, Ph.D., eds.
NCADI #M88 NTIS PB #89-125512/AS (A16) $44.50

89 BIOLOGICAL VULNERABILITY TO DRUG ABUSE. Roy W. Pickens, Ph.D., and Dace S. Svikis, B.A., eds.
NCADI #M89 NTIS PB #89-125520/AS (A09) $27.00

92 TESTING FOR ABUSE LIABILITY OF DRUGS IN HUMANS. Marian W. Fischman, Ph.D., and Nancy K. Mello, Ph.D., eds.
NCADI #M92 NTIS PB #90-148933/AS (A17) $44.50

94 PHARMACOLOGY AND TOXICOLOGY OF AMPHETAMINE AND RELATED DESIGNER DRUGS. Khursheed Asghar, Ph.D., and Errol De Souza, Ph.D., eds.
NCADI #M94 NTIS PB #90-148958/AS (A16) $44.50

95 PROBLEMS OF DRUG DEPENDENCE, 1989. PROCEEDINGS OF THE 5 1 st ANNUAL SCIENTIFIC MEETING. THE COMMITTEE ON PROBLEMS OF DRUG DEPENDENCE, INC. Louis S. Harris, Ph.D., ed.
NCADI #M95 NTIS PB #90-237660/AS (A99) $67.00

96 DRUGS OF ABUSE: CHEMISTRY, PHARMACOLOGY, IMMUNOLOGY, AND AIDS. Phuong Thi Kim Pham, Ph.D., and Kenner Rice, Ph.D., eds.
NCADI #M96 NTIS PB #90-237678/AS (A11) $36.50

97 NEUROBIOLOGY OF DRUG ABUSE: LEARNING AND MEMORY. Lynda Erinoff, Ph.D., ed.
NCADI #M97 NTIS PB #90-237686/AS (A11) $36.50

98 THE COLLECTION AND INTERPRETATION OF DATA FROM HIDDEN POPULATIONS. Elizabeth Y. Lambert, M.S., ed.
NCADI #M98 NTIS PB #90-237694/AS (A08) $27.00

99 RESEARCH FINDINGS ON SMOKING OF ABUSED SUBSTANCES. C. Nora Chiang, Ph.D., and Richard L. Hawks, Ph.D., eds.
NCADI #M99 NTIS PB #91-141119 (A09) $27.00

100 DRUGS IN THE WORKPLACE: RESEARCH AND EVALUATION DATA. VOL II. Steven W. Gust, Ph.D.; J. Michael Walsh, Ph.D.; Linda B. Thomas, B.S.; and Dennis J. Crouch, M.B.A., eds.
NCADI #M100 GPO Stock #017-024-01458-3 $8.00

101 RESIDUAL EFFECTS OF ABUSED DRUGS ON BEHAVIOR. John W. Spencer, Ph.D., and John J. Boren, Ph.D., eds.
NCADI #M101 NTIS PB #91-172858/AS (A09) $27.00

102 ANABOLIC STEROID ABUSE. Geraline C. Lin, Ph.D., and Lynda Erinoff, Ph.D., eds.
NCADI #M102 NTIS PB #91-172866/AS (A11) $36.50

106 IMPROVING DRUG ABUSE TREATMENT. Roy W. Pickens, Ph.D.; Carl G. Leukefeld, D.S.W.; and Charles R. Schuster, Ph.D., eds.
NCADI #M106 NTIS PB #92-105873(A18) $50.00

107 DRUG ABUSE PREVENTION INTERVENTION RESEARCH: METHODOLOGICAL ISSUES. Carl G. Leukefeld, D.S.W., and William J. Bukoski, Ph.D., eds.
NCADI #M107 NTIS PB #92-160985 (A13) $36.50

108 CARDIOVASCULAR TOXICITY OF COCAINE: UNDERLYING MECHANISMS. Pushpa V. Thadani, Ph.D., ed.
NCADI #M108 NTIS PB #92-106608 (A11) $36.50

109 LONGITUDINAL STUDIES OF HIV INFECTION IN INTRAVENOUS DRUG USERS: METHODOLOGICAL ISSUES IN NATURAL HISTORY RESEARCH. Peter Hartsock, Dr.P.H., and Sander G. Genser, M.D., M.P.H., eds.
NCADI #M109 NTIS PB #92-106616 (A08) $27.00

111 MOLECULAR APPROACHES TO DRUG ABUSE RESEARCH: RECEPTOR CLONING, NEUROTRANSMITTER EXPRESSION, AND MOLECULAR GENETICS: VOLUME I. Theresa N.H. Lee, Ph.D., ed.
NCADI #M111 NTIS PB #92-135743 (A10) $36.50

112 EMERGING TECHNOLOGIES AND NEW DIRECTIONS IN DRUG ABUSE RESEARCH. Rao S. Rapaka, Ph.D.; Alexandros Makriyannis, Ph.D.; and Michael J. Kuhar, Ph.D., eds.
NCADI #M112 NTIS PB #92-155449 (A15) $44.50

113 ECONOMIC COSTS, COST EFFECTIVENESS, FINANCING, AND COMMUNITY-BASED DRUG TREATMENT. William S. Cartwright, Ph.D., and James M. Kaple, Ph.D., eds.
NCADI #M113 NTIS PB #92-155795 (A10) $36.50

114 METHODOLOGICAL ISSUES IN CONTROLLED STUDIES ON EFFECTS OF PRENATAL EXPOSURE TO DRUG ABUSE. M. Marlyne Kilbey, Ph.D., and Khursheed Asghar, Ph.D., eds.
NCADI #M114 NTIS PB #92-146216 (A16) $44.50

115 METHAMPHETAMINE ABUSE: EPIDEMIOLOGIC ISSUES AND IMPLICATIONS. Marissa A. Miller, D.V.M., M.P.H., and Nicholas J. Kozel, M.S., eds.
NCADI #M115 NTIS PB #92-146224/ll (AO7) $27.00

116 DRUG DISCRIMINATION: APPLICATIONS TO DRUG ABUSE RESEARCH. R.A. Glennon, Ph.D.; Toubjörn U.C. Järbe, Ph.D.; and J. Frankenheim, Ph.D., eds.
NCADI #M116 NTIS PB #94-169471 (A20) $52.00

117 METHODOLOGICAL ISSUES IN EPIDEMIOLOGY, PREVENTION, AND TREATMENT RESEARCH ON DRUG-EXPOSED WOMEN AND THEIR CHILDREN. M. Marlyve Kilbey, Ph.D., and Kursheed Asghar, Ph.D., eds.
GPO Stock #017-024-01472-9 $12.00
NCADI #M117 NTIS PB #93-10210l/LL (A18) $52.00

118 DRUG ABUSE TREATMENT IN PRISONS AND JAILS. Carl G. Leukefeld, D.S. W., and Frank M. Tims, Ph.D., eds.
GPO Stock #017-024-01473-7 $16.00
NCADI #M118 NTIS PB #93-102143/LL (A14) $44.50

120 BIOAVAILABILITY OF DRUGS TO THE BRAIN AND THE BLOOD-BRAIN BARRIER. Jerry Frankenheim, Ph.D., and Roger M. Brown, Ph.D., eds.
GPO Stock #017-024-01481-8 $10.00
NCADI #M120 NTIS PB #92-214956/LL (A12) $36.50

121 BUPRENORPHINE: AN ALTERNATIVE TREATMENT FOR OPIOID DEPENDENCE. Jack D. Blaine, Ph.D., ed.
GPO Stock #017-024-01482-6 $5.00
NCADI #M121 NTIS PB #93-129781/LL (A08) $27.00

123 ACUTE COCAINE INTOXICATION: CURRENT METHODS OF TREATMENT. Heinz Sorer, Ph.D., ed.
GPO Stock #017-024-01501-6 $6.50
NCADI #M123 NTIS PB #94-115433/LL (A09) $27.00

124 NEUROBIOLOGICAL APPROACHES TO BRAIN-BEHAVIOR INTERACTION. Roger M. Brown, Ph.D., and Joseph Fracella, Ph.D., eds.

GPO Stock #017-024-01492-3 $9.00
NCADI #M124 NTIS PB #93-203834/LL (A12) $36.50

125 ACTIVATION OF IMMEDIATE EARLY GENES BY DRUGS OF ABUSE. Reinhard Grzanna, Ph.D., and Roger M. Brown, Ph.D., eds.

GPO Stock #017-024-01503-2 $7.50
NCADI #M125 NTIS PB #94-169489 (A12) $36.50

126 MOLECULAR APPROACHES TO DRUG ABUSE RESEARCH VOLUME II: STRUCTURE, FUNCTION, AND EXPRESSION. Theresa N.H. Lee, Ph.D., ed.
NCADI #M126 NTIS PB #94-169497 (A08) $27.00

127 PROGRESS AND ISSUES IN CASE MANAGEMENT. Rebecca Sager Ashery, D.S.W., ed.
NCADI #M127 NTIS PB #94-169505 (A18) $52.00

128 STATISTICAL ISSUES IN CLINICAL TRIALS FOR TREATMENT OF OPIATE DEPENDENCE. Ram B. Jain, Ph.D., ed.
NCADI #M128 NTIS PB #93-203826/LL (A09) $27.00

129 INHALANT ABUSE: A VOLATILE RESEARCH AGENDA. Charles W. Sharp, Ph.D.; Fred Beauvais, Ph.D., and Richard Spence, Ph.D., eds.

GPO Stock #017-024-01496-6 $12.00
NCADI #M129 NTIS PB #93-183119/LL (A15) $44.50

130 DRUG ABUSE AMONG MINORITY YOUTH: ADVANCES IN RESEARCH AND METHODOLOGY. Mario De La Rosa, Ph.D., and Juan-Luis Recio Adrados, Ph.D., eds.

GPO Stock #017-024-01506-7 $14.00
NCADI #M130 NTIS PB #94-169513 (A15) $44.50

131 IMPACT OF PRESCRIPTION DRUG DIVERSION CONTROL SYSTEMS ON MEDICAL PRACTICE AND PATIENT CARE. James R. Cooper, Ph.D.; Dorynne J. Czechowicz, M.D.; Stephen P. Molinari, J.D., R.Ph.; and Robert C. Peterson, Ph.D., eds.
GPO Stock #017-024-01505-9 $14.00
NCADI #M131 NTIS PB #94-169521 (A15) $44.50

132 PROBLEMS OF DRUG DEPENDENCE, 1992: PROCEEDINGS OF THE 54TH ANNUAL SCIENTIFIC MEETING OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE. Louis Harris, Ph.D., ed.
GPO Stock #017-024-01502-4 $23.00
NCADI #M132 NTIS PB #94-115508/LL (A99)

133 SIGMA, PCP, AND NMDA RECEPTORS. Errol B. De Souza, Ph.D.; Doris Clouet, Ph.D., and Edythe D. London, Ph.D., eds.
NCADI #M133 NTIS PB #94-169539 (A12) $36.50

134 MEDICATIONS DEVELOPMENT: DRUG DISCOVERY, DATABASES, AND COMPUTER-AIDED DRUG DESIGN. Rao S. Rapaka, Ph.D., and Richard L. Hawks, Ph.D., eds.
GPO Stock #017-024-01511-3 $11.00
NCADI #M134 NTIS PB #94-169547 (A14) $44.50

135 COCAINE TREATMENT: RESEARCH AND CLINICAL PERSPECTIVES. Frank M. Tims, Ph.D., and Carl G. Leukefeld, D.S.W., eds.
GPO Stock #017-024-01520-2 $11.00
NCADI #M135 NTIS PB #94-169554 (A13) $36.50

136 ASSESSING NEUROTOXICITY OF DRUGS OF ABUSE. Lynda Erinoff, Ph.D., ed.
GPO Stock #017-024-01518-l $11.00
NCADI #M136 NTIS PB #94-169562 (A13) $36.50

137 BEHAVIORAL TREATMENTS FOR DRUG ABUSE AND DEPENDENCE. Lisa Simon Onken, Ph.D.; Jack D. Blaine, M.D., and John J. Boren, Ph.D., eds.
GPO Stock #017-024-01519-9 $13.00
NCADI #M137 NTIS PB #94-169570 (A15) $44.50

138 IMAGING TECHNIQUES IN MEDICATIONS DEVELOPMENT: CLINICAL AND PRECLINICAL ASPECTS. Heinz Sorer, Ph.D., and Rao S. Rapaka, Ph.D., eds.

NCADI #M138

139 SCIENTIFIC METHODS FOR PREVENTION INTERVENTION RESEARCH. Arturo Cazares, M.D., M.P.H., and Lula A. Beatty, Ph.D., eds.

NCADI #M139

140 PROBLEMS OF DRUG DEPENDENCE, 1993: PROCEEDINGS OF THE 55TH ANNUAL SCIENTIFIC MEETING, THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE, INC. VOLUME I: PLENARY SESSION SYMPOSIA AND ANNUAL REPORTS. Louis S. Harris, Ph.D., ed.

NCADI #M140

141 PROBLEMS OF DRUG DEPENDENCE, 1993: PROCEEDINGS OF THE 55TH ANNUAL SCIENTIFIC MEETING, THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE, INC. VOLUME II: ABSTRACTS. Louis S. Harris, Ph.D., ed.

NCADI #M141

142 ADVANCES IN DATA ANALYSIS FOR PREVENTION INTERVENTION RESEARCH. Linda M. Collins, Ph.D., and Larry A. Seitz, Ph.D., eds.

NCADI #M142

143 THE CONTEXT OF HIV RISK AMONG DRUG USERS AND THEIR SEXUAL PARTNERS. Robert J. Battjes, D.S.W.; Zili Sloboda, Sc.D.; and William C. Grace, Ph.D., eds.

NCADI #M143

144 THERAPEUTIC COMMUNITY: ADVANCES IN RESEARCH AND APPLICATION. Frank M. Tims, Ph.D.; George De Leon, Ph. D.; and Nancy Jainchill, Ph.D., eds.

NCADI #M144

145 NEUROBIOLOGICAL MODELS FOR EVALUATING MECHANISMS UNDERLYING COCAINE ADDICTION. Lynda Erinoff, Ph.D., and Roger M. Brown, Ph.D., eds.

NCADI #M145

146 HALLUCINOGENS: AN UPDATE. Geraldine C. Lin, Ph.D., and Richard A. Glennon, Ph.D., eds.

NCADI #M146

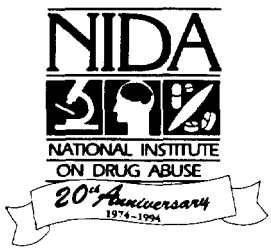
147 DISCOVERY OF NOVEL OPIOID MEDICATIONS. Rao S. Rapaka, Ph.D., and Heinz Sorer, Ph.D., eds.

NCADI #M147

148 EPIDEMIOLOGY OF INHALANT ABUSE: AN INTERNATIONAL PERSPECTIVE. Nicholas J. Kozel, M.S.; Zili Sloboda, Sc.D.; and Mario R. De La Rosa, Ph.D., eds.

NCADI # M148

* U.S. GOVERNMENT PRINTING OFFICE: 1995 386-912/00014



NIH Publication No. 95-3891
Printed 1995