

Specialty Conference

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Heroin Addiction and Pregnancy

Pregnant heroin addicts tend to be younger than nonaddicted pregnant patients, unmarried or separated from spouses, and a disproportionately large number are members of minority ethnic groups. Heroin addiction during pregnancy is associated with several significant medical and obstetrical complications and may result in both acute and chronic abnormalities in neonates. Malnutrition, venereal disease, hepatitis, pulmonary complications, preeclampsia and third-trimester bleeding are the most common maternal complications, while fetal death, intrauterine growth retardation, prematurity and withdrawal symptoms affect the fetus and neonate. There is controversy about treating addicts with methadone during pregnancy. The findings of studies in animals suggest that there may be a long-lasting drug-induced syndrome, characterized by growth retardation, delayed motor development and behavior abnormalities in offspring of heroin-addicted or methadone-treated mothers.

RICHARD A. BASHORE, MD: * Historically, the emphasis in obstetrics has been on improving maternal welfare. With the development of antenatal care, hospital-based labor and delivery, improved anesthetic techniques, the ready availability of blood products, and the training of many professionals in obstetrics, maternal mortality and morbidity have been substantially reduced.

Perinatal loss, however, continues to be a prob-

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lem and, consequently, efforts to improve fetal outcome have increased. Tests for assessing fetal well-being are now available, fetal monitoring is possible during the course of labor, and techniques for detecting fetal chromosomal abnormalities have been developed. Also, professional and technical resources in neonatal intensive care facilities are more readily available, resulting in improved care for newborns.

There is a direct correlation between factors that jeopardize maternal health and poor fetal outcome, maternal drug abuse being one specific example. This symposium focuses on heroin ad-

diction during pregnancy. Our discussants will present psychiatric and epidemiologic implications, maternal complications, the fetal and neonatal consequences and results of animal experiments that may give insight into the problem of heroin addiction in humans.

Heroin Addiction and Pregnancy: Psychiatric Implications

JAMES S. KETCHUM, MD:* Narcotic addiction during pregnancy has become an important medical condition from which we are gaining insights into human pharmacology, pathophysiology and sociology. During the past decade a national epidemic of heroin addiction occurred which, although now in recession, has left us with the problem of caring for an estimated 100,000 heroin-dependent women of childbearing age and their heroin-dependent babies. It is estimated that about 10,000 such babies are born every year. Several large hospital centers have reported significant increases in the birth of addicted babies. At the Vancouver General Hospital in Washington state, for example, offspring of heroin addicts constituted about 1 in 250 live births in 1972, a sixfold increase in 20 years.¹ At the New York Medical College Metropolitan Hospital, an increase from 1 in 164 deliveries in 1960 to 1 in 27 in 1972 was recorded.² The latter hospital's tenfold higher overall rate reflects its proximity to the Harlem district of Manhattan, believed to have the highest concentration of heroin addicts in the United States.

Addicted mothers and their infants have many medical problems before, during and after delivery. Most of these problems, however, are not related directly to pharmacological factors. Heroin is a potent opiate, and, unlike many drugs of abuse, opiates can be administered at high levels for long periods without serious consequences and little or no impairment of intellectual and physiological function. A heroin addict is capable of developing a high level of tolerance with repeated administration of the drug ad lib, provided there is an unlimited supply. Wikler³ found that a detoxified morphine addict, when allowed to inject himself without restriction, increased his daily consumption from 30 mg to 1,200 mg during four months.

The appearance of pathological symptoms in an addict is related to fluctuations in narcotic levels that result in abrupt alterations in the steady

state of the user. Such fluctuations were virtually unavoidable before the advent of long-acting agonists, such as methadone and, more recently, L-acetyl-alpha-methadol (LAAM, or long-acting methadone), which are administered under controlled conditions. The average addict, therefore, depending on the availability and purity of his or her drug, experiences extreme emotional instability. For these persons to maintain even partial equilibrium requires a diversion of energy from normal pursuits, and personal care, nutrition, work and human relations are therefore neglected. Desperation breaks down social conformity and this leads to criminality, self-reproach and depression.

Despite the sharp increase in the number of heroin addicts, the daily consumption per street addict has declined from an average of about 200 mg in 1950 to around 25 mg in 1974. Because the frequency and severity of the withdrawal symptoms in newborns from both of these eras are similar, it is believed that chronicity of use contributes more than daily dosage to the onset of symptoms. This is also true for methadone users.

Demographically, the pregnant addicts in most series were young (median age about 22), unmarried or separated, lacking in social supports and disproportionately concentrated in minority ethnic groups. We do not know with certainty the percentage of addicted women who become pregnant, but two opposing phenomena may have an influence: sexual drive, although suppressed under conditions of chronic use, and the costly habit, which drives as many as 50 percent of women addicts into prostitution. In the Vancouver, Washington series, parity was close to that of the general population, possibly reflecting effects of lower age, higher base rates and a short history of addiction (median of two years in one large series) in this socioeconomic category.

The cause of addiction is still unknown, although it is clearly a learned behavior requiring the acquisition of responses that result in the procurement and self-administration of the drug. These responses are presumably reinforced by both direct and indirect classic and operant mechanisms.⁴ Although certain subpopulations are especially at risk, it seems that socioenvironmental circumstances are more important than constitutional or genetic influences, as witnessed by the high prevalence of addiction within the medical and pharmaceutical professions, and historically

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among middle-class and upper-class women. Instability of personality or psychiatric illness may increase the likelihood of drug abuse because impulsiveness and dysphoria may intensify the tendency to seek immediate gratification and relief from suffering. Alienation from societal norms, either as a result of social immaturity or mental disorder, makes antisocial behavior, including illicit drug use, more probable. Successful rehabilitation, therefore, entails more than the alleviation of tolerance and physical dependence.

The treatment of heroin addiction remains somewhat controversial. Since the introduction of methadone maintenance programs, polarization has developed within the medical community and is clearly reflected in the comments of various authors who have studied pregnant addicts and their offspring.^{1,2,5} These investigators express concern about the wisdom of treating prospective mothers with methadone, citing a higher occurrence of complications and greater severity of withdrawal symptoms in the newborns. Favorable judgments, however, have been rendered by others⁶⁻⁹ who found little or no neonatal mortality in a sizable series of methadone-maintained pregnant addicts. My own conclusion, after reading these reports, is that methadone is relatively safe and clearly less hazardous than heroin purchased on the street.

In the baby of a methadone-treated mother, withdrawal symptoms are qualitatively similar to those of heroin, although more delayed and persistent. Newborns presenting with these symptoms should be treated with gradually tapering doses of narcotic agonists. Although diazepam (Valium), barbiturates and phenothiazines have been described as effective in controlling neonatal abstinence, rational treatment dictates the use of opiates such as paregoric or, to obviate possible toxicity of camphor, a dilute solution of opium. When the mother has been receiving methadone under supervision, the use of methadone itself is recommended, beginning the day after delivery and gradually tapering during three to four weeks. There is no evidence that such treatment will increase the probability of later addiction. In adults, addiction should be viewed as a behavioral syndrome, requiring the learning of drug-seeking responses and the development of an awareness of, and preoccupation with, the reinforcing properties of the drug. None of these elements can be supposed to exist in a newborn infant. To refer to such infants as "addicts" and withhold all but

the minimum necessary medication in their supposed interest betrays a lack of pharmacological as well as psychological insight.

As to the fate of methadone-dependent mothers, it is most encouraging to note that in the series of 120 women in a study by Newman,⁶ 115 remained continuously in the treatment program after delivery. Thus, it seems that enrollment in a methadone program during or before pregnancy may prevent the high probability of reverting to the dismal life of obtaining heroin on the street after the birth of the baby. Therefore, a methadone maintenance program for the mother followed by a period of gradual methadone withdrawal for the newborn seems to be the best, if not the simplest, therapeutic strategy.

Maternal Consequences of Heroin Addiction

KLAUS J. STAISCH, MD:* Regular prenatal care is the key to prevention of complications during pregnancy, but 75 percent of pregnant heroin addicts give birth without prenatal care. However, most women enrolled in methadone maintenance programs tend to participate in regular prenatal care.^{10,11} Although methadone reduces the maternal complications resulting from heroin, it has the same fetal side effects as heroin. Both drugs cause adverse effects, mainly intrauterine growth retardation and neonatal withdrawal after birth. The experience of most specialists in drug addiction suggests that a pregnant drug user is unlikely to continue in a standard prenatal program unless it is specifically adapted to her needs as an addict. The typical addict presents with medical, obstetrical and social problems. Because of the complex interrelation of these problems, pregnant women who are drug dependent need the special care of a health team consisting of an obstetrician, pediatrician and social worker, if treatment is to be successful.

It was previously thought that addicts had a reduced reproductive capacity. Findings of studies done in New York have shown that the average age of the pregnant addict is 23 years, with a mean parity of three. This indicates that women using narcotics have the same capability of becoming pregnant as those who are not addicted. The rate of spontaneous abortions and the frequency of women who seek elective abortions are the same in addicts as in the general population.¹²

The incidence of stillbirths in addicts has been

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reported to be between 17 and 60 per 1,000 births¹³; the rate in the general population is 14 per 1,000 births. Reports of stillbirths in women undergoing abrupt complete cessation of heroin use (cold turkey detoxification) are alarmingly high. During withdrawal, women report an increase in fetal movements often followed by the cessation of quickening. Serial measurements have shown that catecholamines in the amniotic fluid increase steadily during withdrawal. These changes are thought to reflect increased psychomotor activity of the fetus during the state of withdrawal. Zuspan and associates¹⁴ have postulated that fetal death occurs during intrauterine withdrawal as a consequence of increased motor activity, leading to a relative oxygen deficit in the hyperactive fetus. Many investigators, therefore, do not recommend detoxification during pregnancy. Instead, the pregnant heroin addict should be switched to a methadone dose sufficient to prevent withdrawal. This usually requires admittance to hospital as the dose is tapered to the minimal effective maintenance dosage.

Meconium staining of the amniotic fluid, a possible sign of hypoxia, is seen three times more frequently with drug abuse and may indicate episodes of hypoxia preceding or during labor. Pregnancy in an addict can be complicated by numerous infections and other disease processes that can affect almost any area of the body. Fetal demands for growth and nourishment put further stress on an already physically debilitated addict. Because of the crisis intervention type of therapy that addicts seek and receive, it is difficult to know the true incidence of maternal and fetal morbidity.^{10,15}

Malnutrition is common among heroin addicts because maintaining the drug habit usually requires that money be used for purchasing drugs and not food. In pregnant addicts, malnutrition usually causes anemia (in about 60 percent of patients), premature labor and intrauterine growth retardation. Inadequate maternal weight gain results in infants of low birth weight and high perinatal mortality. Women who register in methadone maintenance programs tend to have a more balanced diet than heroin addicts.

Many young women support their addiction by prostitution and, therefore, venereal disease occurs commonly. A positive serologic test for syphilis occurs in about 27 percent of patients. Hepatitis, usually in its chronic form, which results from the use of unclean or communal needles, is found

in approximately 80 percent of the addicts. Acute hepatitis during pregnancy can cause abortion during the first and second trimesters and premature labor in the third. Although hepatitis antigen is often found in the umbilical cord blood at birth, the clinical symptoms of hepatitis are rarely seen in the neonates.¹⁶

X-ray studies of the chest show abnormalities in almost 90 percent of all drug addicts. Common findings include hilar lymphadenopathy and foreign body granuloma, the latter being caused by the injection of contaminated drugs. Talc, cornstarch and cotton fibers are frequently found at autopsy. Pulmonary edema and aspiration pneumonia are usually a result of drug overdose. Septic emboli from peripheral thrombophlebitis can cause pulmonary abscesses. Pulmonary fibrosis and pulmonary hypertension are examples of long-range complications of continued drug use. Bacterial endocarditis is usually related to peripheral phlebitis. The use of heroin may result in non-specific glomerulosclerosis, a direct toxic effect of the drug on the kidneys. This condition requires symptomatic treatment and careful observation to detect superimposed preeclampsia. Skin abscesses may occur. Attempts at injecting drugs through a fibrotic vein can lead to leakage of the drug into subcutaneous tissue. Quinine, a drug used to cut heroin, causes necrosis, which in turn can be the focus of infection. Therefore, chain reactions of cellulitis, lymphangitis and lymphadenitis are commonly seen. Tetanus is an uncommon infection, but when present it carries a high mortality. In New York 75 percent of all reported cases of tetanus were related to addicts.¹⁷ Therefore, a tetanus booster immunization in drug-dependent patients is strongly indicated.

Neonatal mortality in addicts is four times higher than in the general population. The principal causes for infant death are prematurity and growth retardation. Both of these conditions tend to occur together in the same infant and are responsible for a third of the low birth weights in addicts. The mean birth weight of heroin-addicted babies, as well as of methadone-addicted infants, is about 2,700 grams, which is considerably lower than the 3,400 grams normal birth weight in the general population. Also, breech and other abnormal presentations are seen more frequently. These conditions predispose infants to birth trauma with vaginal delivery and, if these are to be avoided, a high rate of cesarean sections.

Respiratory distress is rare in premature infants

exposed to heroin but not in those exposed to methadone.¹⁸ The physiological basis for this finding is unclear but is thought to be due to a maturational effect of heroin on pulmonary surfactant production. Estriol values, a measure of fetoplacental function, are chronically low in methadone users and are of limited value in monitoring these high-risk pregnancies.¹⁹ Electronic fetal monitoring of the heart rate during the antepartum period to detect fetal hypoxia is also of limited value in drug users. The cardiovascular reflexes such as beat-to-beat variability of the baseline heart rate and heart rate accelerations in response to fetal movements are signs of fetal well-being. These reflexes are blunted because of the sedative effect of methadone and heroin. Congenital abnormalities are not increased in the opiate-addicted patients.¹²

There are many problems that drug-addicted patients can present with during labor and delivery. Investigators in major cities such as New York, Philadelphia and San Francisco have reported that obstetrical complications occur in about 17 percent to 33 percent of patients. In general, complications are managed in a similar manner as with nonaddicted patients; however, physicians must be aware of the high frequency of these problems. Premature rupture of the membrane is twice as common in addicts and can lead to intrauterine infection and neonatal sepsis. Presence of infection is particularly devastating to small infants. Preeclampsia is three times as high and hemorrhage from placenta previa and abruptio placentae is four times higher in the addicted population. Management of the discomfort of labor pains presents a special problem because of addicts' developed tolerance to narcotics. High doses of analgesics would be required to control pain but these can produce neonatal depression—therefore, their use should be avoided. Epidural block is the analgesic of choice. Paracervical blocks should be given only if the estimated fetal weight is greater than 2,500 grams because it can cause fetal bradycardia, which can present a major complication to the small infant as metabolism and excretion of anesthetic drugs is slow.

When a pregnant woman uses addictive drugs, the clinical situation can become extremely complicated. To deliver effective care, physicians must be aware of the numerous medical and obstetrical problems that can arise in these women and their

unborn babies. Although many hospital centers that care for obstetrical patients at high risk are working to define these problems, and indeed some of the effects of prenatal stress resulting from addiction are reversible, much remains to be done in the treatment for addicted mothers and their infants.

Fetal and Neonatal Effects of Heroin Addiction

CYNTHIA T. BARRETT, MD:* Many areas of growth, metabolism and behavior are affected in the developing fetus and newly born infant of drug-dependent mothers. The effects of heroin and methadone differ in these variables. This is thought to be true partly because of the differing direct effects of these agents and partly because of the differences in nutrition, antenatal care and general life-styles among women addicted to these two agents. In both heroin and methadone addicts there is a noticeable prevalence of abuse of other agents, including tobacco, alcohol and barbiturates, all of which have notable effects on the fetus and newly born infant.

Intrauterine growth retardation and prematurity are well-recognized complications in infants of narcotic-addicted mothers. These conditions have generally been attributed to poor nutrition of the mother, but Naeye, Blanc and Leblanc²⁰ and coinvestigators²¹ have evidence from autopsy specimens that heroin has a primary effect on antenatal growth. In addition, they found a very high prevalence of intrauterine infection, which accounted for poor growth as well as prematurity. In infants of methadone-addicted mothers, intrauterine growth retardation occurs less frequently. There are reports, however, of diminished linear growth and head circumference during the first year of life as well as slightly decreased birth weight.² In 1971 Glass, Rajegowda and Evans¹⁸ reported that respiratory distress syndrome did not occur in 33 infants prematurely delivered of heroin-addicted women. However, in 1972 Tausch and associates²² studied lung development in fetal rabbits and confirmed that heroin had a direct inhibitory effect on fetal growth unrelated to maternal nutrition, with some indices compatible with acceleration of lung maturation. At the time of delivery, most infants with antenatal exposure to either heroin or methadone are

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vigorous and have good Apgar scores. Respiratory depression may occur but it can be reversed by treatment with naloxone (Narcan).

After delivery, withdrawal symptoms are present in about 75 percent of infants of heroin addicts and in almost all infants of methadone-addicted mothers. Symptoms usually seen include hyperactivity and hyperirritability with coarse tremors and poor feeding, leading to skin abrasions and poor weight gain. Sneezing, yawning, sweating, vomiting, diarrhea and hyperthermia are present less frequently. Seizures occur in about 5 percent of infants of heroin addicts and in about 15 percent of infants of methadone addicts after therapy has been instituted. In infants of methadone addicts, one can expect more severe symptoms of withdrawal, developing later and lasting longer, than in heroin addicts. However, if the mother has been receiving a dosage of less than 20 mg per day of methadone, symptoms of withdrawal are milder and occur less frequently.

In addition to narcotic withdrawal, the differential diagnosis in an infant with symptoms of hyperactivity and hyperirritability must include hypoglycemia, hypocalcemia, hypomagnesemia and hyperthyroidism. In the presence of hyperthermia, sepsis should be ruled out, and with seizures, hyponatremia, pyridoxine dependency, meningitis and intracranial trauma must be added to the list of possible diagnoses. Even in the presence of known narcotic withdrawal, any one of the above abnormalities may be present, and laboratory studies should include all tests necessary to rule them out. In addition, examination of the urine should be done for toxic substances (often findings are negative) and of the serum for hepatitis-associated antigen (serial determinations during the first three to four months) and for serologic findings (there is an increased prevalence of syphilis in heroin addicts).

Recognizing the withdrawal state of an infant is critical because most deaths are due to dehydration, which occurs when the baby is discharged from a hospital nursery in undiagnosed narcotic withdrawal. With proper diagnosis and use of current techniques in caring for these high-risk infants, neonatal mortality need not reach 5 percent, with the major causes of death being prematurity, infection and perinatal asphyxia, and not withdrawal.

The care of an infant during withdrawal involves supportive measures aimed at decreasing

physical stimuli to the baby and providing as calm an environment as possible in the high-risk nursery setting. Often by holding and rocking a baby and giving it a pacifier, one can alleviate much of the hyperactivity and hyperirritability that occurs during withdrawal, thereby eliminating the need for pharmacological intervention. Normal fluid balance can be maintained by use of gavage feeding. In the presence of notable vomiting or diarrhea, however, it may be necessary to give fluids intravenously.

The pharmacological agents used in the management of the withdrawal state include sedatives and narcotic substitutes. Various regimens using both groups of drugs have proved effective. The sedatives most frequently used are diazepam, phenothiazine and phenobarbital. Diazepam usually requires the shortest duration of therapy, often less than a week, but it does not reduce diarrhea. This agent is not recommended for patients with jaundice because the sodium benzoate in the diluent will displace bilirubin from albumin and increase the risk of bilirubin encephalopathy. Phenothiazine and phenobarbital often require courses of therapy as long as three weeks for complete withdrawal. There is a noticeable prevalence of extrapyramidal signs associated with phenothiazine that may occasionally be confused with signs of withdrawal.

Phenobarbital, in doses required to provide symptomatic relief, may produce lethargy and augment the nutritional problem. Also, it is ineffective against diarrhea. Phenobarbital may be used in babies with jaundice because it induces activity of glucuronyl transferase and may thus reduce the severity and duration of neonatal jaundice. It does not displace bilirubin from albumin. Diazepam and phenobarbital should never be used together in management of newly born infants because of increased risk of respiratory arrest. Jaundice is a less prevalent problem in infants with antenatal exposure to heroin than in the normal population because heroin is thought to induce glucuronyl transferase activity. The effects of methadone on this enzyme system are not known. Infants with glucose-6-phosphate dehydrogenase deficiency, however, may have increased severity of neonatal jaundice because quinine is frequently used to cut heroin.

Paregoric, which is a camphorated tincture of opium, is the narcotic substitute most frequently used. This agent is particularly effective in

infants with diarrhea and may even produce constipation. When paregoric is used to treat withdrawal symptoms, the most common side effect is lethargy, which tends to decrease nutrition; weaning is often prolonged to six weeks. Methadone has not been widely used to treat withdrawal symptoms, although there are some reports of its being used with success. In one study, duration of time in hospital was not different among three groups of infants treated with methadone, diazepam and phenobarbital.²⁴ Recently, we treated two addicted infants with breast-feeding by their mothers who were in methadone maintenance programs; no pharmacological agent was used and neither baby had any notable withdrawal symptoms.

The effects of methadone and heroin, as well as the pharmacological agents used in treating withdrawal on neonatal adaptive behavior, have been investigated: methadone depresses adaptive behavior to a greater extent than heroin. When nutritive sucking was the variable studied, infants treated with paregoric during withdrawal had nearly normal adaptive behavior; those treated with phenobarbital had less normal behavior, and those with diazepam had very abnormal adaptive behavior.

Late signs of methadone and heroin withdrawal persist in about 5 percent to 10 percent of children and are more severe after methadone withdrawal, usually lasting as long as three months. After heroin withdrawal, more than 20 percent of infants are hyperactive and have a short attention span even at 1 year of age. Infants withdrawing from methadone have an increased frequency of all behavioral disturbances up to 18 months of age. Thereafter these abnormalities seem to resolve. Increased prevalence of behavioral disturbances has not been noted in infants whose mothers received less than 20 mg of methadone per day.

Sudden infant death syndrome has been reported in about 2 percent of infants after heroin or methadone withdrawal. This is seven times higher than in the normal population. The cause is unknown, but it may be related to an increased frequency of abnormal sleep states in these infants.

Despite the more severe and prolonged withdrawal symptoms in infants receiving methadone antenatally, this agent is preferable to heroin during the antepartum period because of the many social and legal complications involved with heroin use. Whereas most infants born to heroin-addicted women are removed from the mother and placed

in foster care, methadone-maintained women generally keep their babies. It is hoped that a heroin substitute will be found that will have fewer side effects than methadone in newly born infants exposed to heroin antenatally.

Research Methods in Drug Abuse

EMERY G. ZIMMERMANN, MD:* Adverse consequences of maternal narcotic addiction for the developing fetus and newborn have been noted with increasing frequency by clinicians⁵ during the past 25 years.²⁵ The increase in opiate abuse by women of childbearing age during the past decade has brought the problem of fetal and neonatal narcotic addiction into sharp focus. The problems experienced by pregnant addicts and their addicted offspring have been discussed by previous speakers at this conference. In this section I will briefly review recent experimental animal research in the problem of neonatal narcotic addiction.

Rats are used extensively for studying developmental effects of opiates because many of their responses to drugs resemble those of humans and because of their short life span. Findings of current studies in rats confirm results obtained in clinical investigations.

Administration of opiates, whether morphine or methadone, during fetal development results in increased intrauterine death,²⁶⁻²⁸ decreased body and brain growth^{27,29-31} and characteristic neonatal narcotic withdrawal.²⁶⁻²⁸ Additional findings include retardation of motor development and delayed behavioral maturation.^{28,31-33} Narcotics are not morphologically teratogenic in rodents or in humans except at high doses.³⁴ The effects of narcotics on the developing organism are more subtle in that they seem to alter the rate and extent of growth and functional maturation. It is difficult to study these variables of development in humans because of the many genetic and environmental factors involved. Animal studies are particularly valuable in that they allow systematic variation of experimental conditions.

Virtually all animal studies have shown that both morphine^{26,27,29,31,35-37} and methadone,^{30,38} when administered during intrauterine development, result in growth retardation in the neonate. Moreover, the growth lag persists, in most cases, for weeks to months after birth. The absence of catch-up growth suggests that nutritional impairment may not fully explain the growth retardation

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and that additional long-lasting drug-induced neurochemical alterations may be involved. The immature brain seems to be particularly vulnerable to actions of opiates. Opiate-specific receptors appear in the rat brain about midgestation.³⁹ Steele and Johannesson²⁹ found that morphine administered to maternal rats near term (21 days gestation) appeared in almost equal amounts in the fetal and maternal brains. Peters³⁸ found similar disbursement of methadone in pregnant rats and fetuses, with some delay in distribution to the fetal brain. Methadone appeared in higher concentrations in the blood of pregnant animals than in nonpregnant animals. Peters also noted that because of the lack of a blood-brain barrier in the developing organism, the concentration of methadone in the fetal brain approximated that found in the rest of the carcass. Zagon and McLaughlin^{27,30} reported that morphine and methadone administered to rats during pregnancy caused decreased brain weight and size in addition to decreased litter size, increased number of stillborns, increased pup mortality and decreased neonatal birth weight. The effects on growth and weight seem to be related to the dose of opiate administered.

Behavioral effects of perinatal exposure to opiates clearly outlast the presence of the drug or its metabolites in the body. Peters³⁸ correlated neurochemical changes and behavioral deficiencies in offspring of rats treated with morphine or methadone throughout gestation and lactation (21 days). Offspring exposed to morphine and methadone were slow to learn to run a maze and to acquire shock avoidance behavior. We found similar behavioral effects long after neonatal administration of morphine.^{33,35,36} Banerjee³² reported impaired acquisition of conditioned avoidance responses in rats seven weeks after exposure to morphine early in life, and we observed altered conditioned emotional responses as long as three months after neonatal exposure to morphine.^{33,35}

Delayed development of motor function has also been reported to follow early exposure to opiates.²⁸ Several spontaneous and reflex motor behaviors appeared later and developed more slowly in pups exposed to methadone during gestation and lactation. These effects seem to be related to the time and duration of drug exposure.

Other effects of early exposure to opiates have been observed in experimental studies using rodents. Several investigators have noted the development of tolerance to the analgesic action

of morphine or methadone.^{26,29,33} In our experiments we detected tolerance for as long as 230 days^{31,35} and evidence of drug dependence for up to 90 days³⁷ after administration of morphine to neonates. Alterations in neuroendocrine function have also been reported.^{31,33,36,37} Although the effects of perinatal opiate dependence are not clearly understood, they may help explain the persistent growth and behavioral effects of early exposure to opiates. In addition, findings of several studies have shown body-weight and motor deficits in the offspring of rats that were themselves treated with opiates early in life.⁴⁰ The significance of these carry-over effects into subsequent generations remains to be elucidated.

The mechanism by which perinatal opiate exposure exerts long-lasting effects on growth and development is not known with certainty but seems to involve altered neurochemical development. Steele and Johannesson⁴¹ were among the first to show that growth retardation is associated with decreased macromolecular synthesis in the brain. This suggests that prenatal administration of morphine causes a dose-dependent interference with cerebral protein synthesis by decreasing the availability of mRNA. Several other investigators have confirmed that chronic administration of morphine or methadone to rats during the perinatal period causes significant decrease of brain protein, RNA and DNA in the offspring.^{38,41,42} Further studies with rats should clarify the biochemical basis of the aforementioned effects of perinatal opiate addiction.

In summary, the advantages of methadone maintenance during pregnancy and the successful management of addicted newborns are noteworthy achievements. However, the long-term consequences for developing infants remain obscure. Such effects have recently begun to attract serious attention as a result of the growing awareness of an apparent long-lasting drug-induced syndrome consisting of growth retardation, delayed motor development and behavioral abnormalities. Although this syndrome is not limited to opiate use, the appearance of drug-specific features, such as tolerance and dependence, offer sufficient evidence to implicate opiates, including heroin and methadone, in the production of the generalized syndrome of drug-delayed development (3D syndrome). Results of clinical and experimental studies recently have been reviewed, and they show the urgent need for information about the long-term and perhaps permanent effects of

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abused drugs on developing fetuses.¹² For reasons of economy of time and dollars, well-established studies using rats should once again prove useful in this research.

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