SUDDING FUNCTION IN INFANTS:
THE EFFECTS OF MATERNAL DRUG ABUSE

By

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ABSTRACT

Infants of mothers who have received narcotics on a continuous basis during pregnancy are born physically dependent. Drug withdrawal, one of many detrimental effects, is initially the most apparent. Neonatal abstinence syndrome (NAS) was originally described as a generalized disorder characterized by signs of central nervous system hyperirritability, gastrointestinal dysfunction, respiratory distress, and a host of vague autonomic manifestations. Recent studies have suggested that these same signs follow withdrawal from other addicting drugs as well. Feeding problems are the most common and important concomitants of neonatal withdrawal, because sucking function is uncoordinated, ineffectual and poorly sustained.

Previous studies have shown a natural history of recovery of sucking dysfunction during recovery from NAS. A disposable and practical apparatus for monitoring nutritive sucking behaviour was developed, based on a prototype previously described in the literature. A weighted scoring system which encompasses the full spectrum of withdrawal signs was also designed. No significant difference in sucking rate was observed between normal and NAS babies on day 1 (p=0.8). There was a highly significant difference on day 2 (p=0.0001), day 3 (p=0.0005), and day 4 (p=0.006). No significant difference in nutrient consumption was observed between normal and NAS babies on day 1 (p=0.9) and day 2 (p=0.8). A significant difference was observed on day 3 (p=0.006) and day 4 (p=0.03). A significant inverse correlation was demonstrated between both sucking rate and nutrient
consumption with the classical clinical signs of withdrawal over the first two months of life (r=-0.57, -0.51, respectively).

The periodic monitoring of sucking rate of the passively addicted infant provides an objective gauge of the severity of withdrawal in NAS, eliminating the subjectivity of evaluating changes in clinical signs. Therefore, it is recommended that sucking rate measurements be instituted as a standard guide to the management of withdrawal in these infants.
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INTRODUCTION

It has been known for some time that drugs ingested by a pregnant woman may have adverse effects on her developing fetus. The significance of these effects was highlighted by the thalidomide tragedy. Over 10,000 infants were born with phocomelia or related congenital anomalies as a result of \textit{in utero} exposure to this drug.\textsuperscript{1}

The medical use of psychotropic agents, which are prescribed twice as often to women as to men, is on the increase.\textsuperscript{2,3} A recent survey of pharmacists revealed that psychoactive drugs are one of the five most frequently prescribed drugs in Canada, of which diazepam is the most popular.\textsuperscript{4} Over the past 25 years, abuse of psychotropic drugs has reached epidemic proportions, with women almost twice as likely to be abusers within each class of psychotropic drug.\textsuperscript{5}

In 1976, the Province of British Columbia had 17.7\% of the Canadian convictions for cannabis offences, 32.5\% of the convictions for cocaine offences, 1.2\% of the convictions for PCP (phencyclidine) offences, and 19.1\% of the convictions for offences related to other drugs. Considering that B.C. had 10.7\% of Canada's population in 1976, all but the PCP offences were disproportionately high. Surveys of illegal drug use among Vancouver secondary school students suggest a progressively escalating trend over the past several years. Overall, a greater frequency of use of one drug was associated with an increased likelihood of use of other drugs.\textsuperscript{6} A 1987
survey of B.C. adolescents revealed that alcohol, cannabis, tobacco, prescription depressants, hallucinogens, non-prescription stimulants including cocaine and crack, and inhalants, were the drugs abused, in order of decreasing frequency.\textsuperscript{7}

An increasing trend is evident from 1977-1979 in the officially recorded number of narcotic users in Canada, about 93\% of whom were illicit users. As of 1980, the prevalence of users in B.C. was greater than in any other province, and most (35.6\%) were 25 to 29 years of age. The usual drug of abuse at this time was heroin. Heroin use has since declined from 65\% of all drugs abused in 1977 to 39\% in 1982. An increase in cocaine use (from 10\% of all drugs abused to 26\%) in the same time period has been reported.\textsuperscript{4} Cocaine abuse among adolescents, but especially among young adults, has increased appreciably in the past decade.\textsuperscript{8} It is among the 3 most commonly used illicit drugs by American high school students.\textsuperscript{9}

With the widespread use of psychoactive drugs, it may be assumed that many women with childbearing potential also consume these substances. Average intakes of four to ten drug preparations by gravid females, up to 80\% of them self-prescribed, have been reported.\textsuperscript{10-14} In Baltimore, a study of one hundred adolescents of low socioeconomic class who were entering prenatal care revealed the following incidence of drug intake: heroin or methadone (3\%), barbiturates/depressants (8\%), marijuana (10\%), alcohol (25\%), and tobacco (50\%).\textsuperscript{15}
**Drug pharmacokinetics**

The pharmacological action of a drug results from an interaction between the drug and an active site on the tissue, the receptor. Using an isolated ileum from 12 to 24 week old fetuses, the presence and activity of autonomic receptors during the second trimester have been demonstrated.\(^{16}\) The presence of opioid receptors in the human fetus is suggested by the release of endogenous opioids in response to fetal and neonatal distress.\(^{17}\)

Most drugs are lipid-soluble weak organic acids that are not easily eliminated from the body. Biotransformation into more polar compounds facilitates their excretion. The kidney is the most important organ for elimination of drugs and their metabolites.\(^{18,19}\) Biotransformation of the majority of drugs occurs in the hepatic microsomal and nonmicrosomal enzyme systems; other organs such as the kidney and gastrointestinal epithelium are thought to have some activity as well.\(^{18}\) It has been established that the fetus can actively metabolize several xenobiotic or foreign chemical substances via the hepatic microsomal enzyme system by the sixteenth week of gestation.\(^{20,21}\)

**Response of the pregnant woman to drugs**

The effects of pregnancy on drug pharmacokinetics are complicated by the changes in metabolic and functional parameters in both mother and fetus. Drug disposition is modified in the gravid female, but information regarding the nature of these modifications is incomplete. Similarly, much remains to be learned about drug absorption in pregnancy. The total serum protein concentration, particularly albumin, is known to decrease, thus influencing the distribution of drugs, as many of them are avidly protein bound.\(^{22}\) Total
water content and blood volume increase gradually, presumably influencing the volume of distribution of any drug in the tissues. Renal function also changes in pregnancy, resulting in a reduction of the normal clearance values, which in turn modifies renal drug excretion.19

Drug dependence in pregnancy also predisposes women to a multitude of medical and obstetrical complications, resulting primarily from their characteristic lifestyle and neglect of health care in general. Malnutrition is a serious problem in many of these pregnancies. Food intake is minimal, due to inhibition of central hunger control mechanisms. Medical complications include anemia, cardiac disease (secondary to subacute bacterial endocarditis), cellulitis, poor dental hygiene, edema, phlebitis, pneumonia, tuberculosis, hepatitis, and acquired immunodeficiency syndrome.23,24 Sharing of "dirty" needles is often the route of acquisition of infections. Prostitution is quite common among these women, thus sexually transmitted diseases such as condyloma acuminatum, gonorrhea, herpes simplex and syphilis, as well as urinary tract infections including cystitis, urethritis, and pyelonephritis are prevalent.23

Obstetrical complications also abound. Chasnoff et al25 report an increased incidence of abruptio placentae (resulting in fetal hypoxia) and spontaneous abortions in association with cocaine use. Studies with heroin addicts report, in addition, such complications as gestational diabetes, pregnancy induced hypertension, septic thrombophlebitis, placental insufficiency, intra-uterine death, breech presentation, greater numbers of caesarian sections, chorioamnionitis, premature labour, premature rupture of membranes, and
Despite these complications, detoxification during pregnancy has been contraindicated in the first third or half of pregnancy, because it may precipitate a fetal crisis or even death, and might be undertaken only if the fetus is monitored biochemically in hospital for indicators of fetal stress. Monitoring by more modern noninvasive methods such as imaging of fetal activity or by fetal electrocardiography does not appear to have been reported. Studies suggest, however, that supervised low dose methadone maintenance with good patient compliance is compatible with an uneventful pregnancy and delivery. With appropriate management of the abstinence syndrome, the outcome of these infants is generally very good. Methadone programs provide a continuous supply of a long-acting pure narcotic, freedom from mood swings, and greater opportunities for prenatal care. Such programs are particularly advantageous because they may be instituted at any time during the pregnancy. The baby, however, will still be born drug dependent.

The placenta
The placenta is a unique organ which in some respects isolates the fetus but also allows bidirectional transfer of water, electrolytes, nutrients and organic wastes. Substances from the maternal arterial circulation are transferred across the trophoblast to fetal villous capillaries. The transplacental passage of pharmacological agents involves a complex series of processes governed by several factors. Four mechanisms: simple diffusion, facilitated diffusion, active transport and special processes are involved in the transfer of substances across the placenta. Drugs and other exogenous compounds are thought to cross primarily by simple diffusion.
These substances cross the placenta from a region of higher to a region of lower concentration at a rate dependent on surface area available for transfer, membrane thickness, and physicochemical properties of the drug. Facilitated diffusion and active transport probably apply only rarely and only where drugs have structural similarity to endogenous material normally transported by these means from maternal to fetal circulations.\textsuperscript{18,30,31}

Placental cell membranes are assumed to be comprised of lipoproteins, similar to other biological membranes. Compounds with a high degree of lipid solubility or large lipid:water partition coefficients and low ionic strength are generally thought to permeate the placenta readily. Substances with molecular weights of less than 600 are freely permeable, whereas those of greater than 1000 are not. Blood flow is a major rate-limiting factor governing placental transfer of the more lipid-soluble drugs. Protein binding may affect the transplacental transfer of drugs, especially if the agent has a relatively high affinity for components of a specific tissue. This may also lead to unusual and unanticipated drug distribution patterns in the fetus. Selective drug uptake by specific tissues due to nonspecific lipid solubility, permeability of specialized membranes, and distribution of the fetal circulation, may also influence distribution patterns. In addition, drug transfer may be influenced by metabolic and functional changes of the placenta which occur during gestation, such as the decrease in thickness of the trophoblastic epithelium with placental maturity.\textsuperscript{32-34}

Drug effects on placental function itself are also significant, as they may either enhance or inhibit placental enzyme activities. Some drugs decrease
the utilization of glucose by the placenta, thus modifying the primary substrate utilized by the fetus.\textsuperscript{22} The placental circulation may be compromised by increased uterine contractility or by the vasoconstricting effects of some drugs, thus restricting the supply of oxygen and nutrients to the fetus and adversely affecting development. Cocaine, for instance, blocks uptake of norepinephrine at peripheral adrenergic receptors and thus increases blood levels of catecholamines, which in turn cause placental vasoconstriction, decreased blood flow to the fetus, and increased uterine contractility.\textsuperscript{18,35,36} \emph{In vitro} studies have also demonstrated placental vasoconstriction with narcotics such as meperidine, morphine and codeine, and hallucinogens such as lysergic acid diethylamide (LSD).\textsuperscript{19}

It is a commonly held misconception that the placenta protects the fetus from maternally consumed drugs by preventing their transport to the fetus. There are very few examples of drugs which do not cross the placenta. Any substance which has pharmacologic activity after oral ingestion can cross the placenta to some extent because the gastrointestinal mucosa and placental membranes have similar characteristics. The fetus is exposed to essentially all drugs taken by the mother. Repeated use of a psychoactive drug by a pregnant woman will result in fetal drug levels equivalent to those in the mother. Adverse effects on the fetus, if any, are determined by the dosage, interval between doses, gestational age, route of administration, maternal health, genetic makeup of mother and fetus, and numerous environmental factors including concomitant exposure to alcohol and cigarette smoking.
Fetal and neonatal effects

The pattern of drug distribution in the fetus resembles that of the mother, although regional differences in concentrations may occur. The majority of the blood flow through the umbilical vein passes into the inferior vena cava at the liver through the ductus venosus. Pharmacologically active drugs perfuse the fetal right heart and reach the central nervous system via that portion of the venous flow which is shunted through the foramen ovale.

The fetal brain receives a much greater proportion of the cardiac output than the neonatal brain. Furthermore, the blood brain barrier develops late in fetal life. Thus, cerebral blood flow is the only limitation to permeation of the central nervous system by highly lipid soluble drugs. Drug distribution is also dependent on the extent of its binding to protein. If a drug has accumulated in a given tissue, the latter may serve as a reservoir, prolonging drug action. Drug metabolism in fetal and infant tissues is less well developed than in the adult, and the capacity to detoxify drugs is much lower. This lesser capacity is important in neonates and particularly in premature infants leading to a much slower elimination of drugs. Once the umbilical cord is occluded, the infant no longer receives any assistance from maternal and placental enzyme systems in the metabolism and excretion of drugs.

Several factors affect the response of the newborn to drugs, including absorption, volume of distribution, plasma binding, receptor sensitivity, metabolism and excretion. There are relatively few differences in drug absorption between neonates and adults. There are few studies of drug
distribution in the newborn, and studies on adults cannot be considered valid
for infants because of differences in body composition between infants and
adults. Total body water and extracellular fluid volume are greater in the
newborn infant than in the adult, and fat content is lower in the premature
than in the full-term infant. The drug-binding capacity of plasma is also
affected by age related variables. The concentration of neonatal plasma
protein is lower than in the adult, and endogenous substances such as
hormones, free fatty acids and bilirubin may compete for drug binding sites on
proteins. This effect is significant, since it is the unbound fraction of drugs
that is free to cross membranes and exert its action. Receptor function has
been demonstrated in the newborn, and there appears to be a positive
correlation between the degree of function and the gestational age and birth
weight. The capacity of the newborn to metabolize drugs is incomplete.
Perhaps the best example of this lesser capacity is the gray-baby syndrome in
infants caused by high doses of chloramphenicol. The activity of the hepatic
microsomal enzyme systems is also low in the neonate, particularly in
premature infants. Activity of nonmicrosomal enzymes is also reduced.
Finally, renal function in the newborn infant is not yet fully developed so
excretion of drugs and their metabolites is impaired. Their
underdeveloped blood brain barrier, poor drug metabolizing activity, and
immature excretory mechanisms render neonates highly sensitive to the toxic
effects of drugs. The morbidity and mortality of passively addicted infants
is higher than any other high risk maternal and infant population.
Fetal toxicity

Teratogenesis refers to any birth defect, morphological, biochemical or behavioral, induced at any stage of gestation. Causes of congenital malformations are usually multifactorial; they are the consequence of interactions between genetic and environmental factors. The deformities produced by a teratogen depend on the nature and mode of action of the agent. In addition, certain tissues may be more sensitive to particular drugs. Some drugs are selectively taken up by fetal organs and cause specific malformations. Teratogenic effects are also highly dependent on the frequency of use and plasma levels of a drug. A single dose may be more or less damaging than repeated doses because of such effects as enzyme inhibition or induction. The developmental stage of the embryo at the time of exposure and the genotype of mother and fetus are very important in modifying the severity, localization and frequency of malformations.

The blastocyst has an all-or-none response to drugs; it is either unharmed or killed by the drug. The interval from approximately the twentieth to the eightieth day of gestation, the period of embryogenesis, is considered the period of greatest teratogen sensitivity for structural anomalies. Each organ has a period of maximum sensitivity, thus the type of congenital malformation is dependent on the gestational age of the fetus. When the period of organogenesis is complete, in most respects the fetus is no longer susceptible to dysmorphogenesis; it responds to teratogenic insults by intrauterine growth retardation and an assortment of functional and behavioural defects. The central nervous system matures in the latter half of pregnancy, therefore exposure to psychotropic drugs at this time may produce
modifications of postnatal behaviour. Neuropathologic studies in infants of opiate dependent mothers have demonstrated gliosis, old foci of infarction, developmental brain retardation and mild microcephaly, damage thought to be due to anoxic-ischemic injury to the fetal brain. These are specific effects of addictive drugs on the developing nervous system. Other lesions common to such high risk neonates include subependymal germinal plate hemorrhage, acute brain necrosis with and without hemorrhage, germinal plate cysts, and focal subarachnoid hemorrhages.

In addition to the specific damage to the central nervous system, there are other more general or nonspecific complications of drug use on the newborn. The infants may be born prematurely, and are nearly always small for gestational age. In the case of heroin the growth retardation is thought to be consequent to a subnormal number of cells rather than simply the result of undernutrition. Cytogenetic studies with infants exposed prenatally to heroin and methadone have shown significant increases in the frequency of chromosomal aberrations as compared to normal controls. Several instances of acute infection, stillbirth and sudden infant death syndrome (SIDS) in association with opiate dependence have also been reported in the literature.

Other detrimental factors may have an additive influence on the effects of maternal drug abuse, but it has been difficult to discriminate between them. Smoking is almost universal among substance users, and smoking during pregnancy has been associated with a dose-dependent reduction in fetal birth weight. An overall depression of fetal growth is manifested by newborns
who are shorter and have a smaller head circumference than those born to non-smokers. Increased incidences of spontaneous abortions and SIDS have also been reported. Concomitant use of alcohol, the rule rather than the exception for most drug users, has been shown to increase the incidence of neonatal seizures and death. It has been difficult to isolate the respective causes and effects because these women often abuse alcohol and other drugs together.

Of particular concern when dealing with street addicts are the unpredictable effects of drug interactions on the fetus and neonate because of the tendency towards multiple drug abuse. Narcotic analgesics potentiate all of the depressant effects on the central nervous system of other classes of depressants including barbiturates, hypnotics, sedatives, general anesthetics, alcohol, antihistamines, and tranquilizers. Furthermore, the lack of quality control of street drugs and the tenuous nature of their supply exposes the fetus to repeated episodes of withdrawal and overdose. Either extreme may result in fetal hypoxia or death. Severe withdrawal episodes are associated with increased muscular activity, excessive fetal movements, and increased oxygen requirements. These effects may manifest as fetal distress culminating in abnormally severe birth asphyxia and meconium aspiration syndrome. Drug synergism and impure preparations may also lead to severe neonatal problems. The medical complications of neonatal abstinence syndrome (NAS) can be severe, and may include respiratory depression, hypothermia, coma and death. In addition, biochemical disturbances such as hypoglycemia, hypocalcemia, other electrolyte imbalances, dehydration, and shock may result from regurgitation, vomiting, diarrhea, poor intake, and
increased resting metabolic rate.\textsuperscript{62} Respiratory distress, aspiration pneumonia, and infection are also encountered not infrequently.\textsuperscript{63}

**Neonatal Abstinence Syndrome**

The biochemical and physiological processes of withdrawal are poorly understood. Physical dependence is defined as "an altered physiological state produced by repeated administration of a drug which necessitates the continued administration of the drug to prevent the appearance of a stereotypical syndrome, the withdrawal or abstinence syndrome, characteristic for the particular drug."\textsuperscript{18} The infants of mothers who have consumed drugs repeatedly during pregnancy can be expected to have developed a passive physiologic dependence. The fetus undergoes a biochemical adaptation to the presence of these agents, and the onset of withdrawal signs is precipitated by the abrupt removal of the source of the substance at birth. The neonate continues to metabolize and excrete the drug and abstinence signs ensue when a critically low tissue concentration is reached.\textsuperscript{63}

Drug withdrawal, although only one of the many detrimental effects of maternal drug abuse on the neonate, is the most apparent. Sixty to ninety percent of infants born to narcotic addicted mothers exhibit withdrawal signs, usually within 72 hours after delivery.\textsuperscript{26,63} Withdrawal signs are characterized by rebound effects in those same physiological systems that were initially modified by the drug. They are referred to as rebound
hyperexcitability. Whether all the complex patterns of clinical signs during withdrawal should be considered rebound effects, however, is not clear.18

NAS is a generalized disorder characterized by signs of central nervous system hyperirritability, respiratory distress, gastrointestinal dysfunction, and vague autonomic manifestations. The infants generally develop tremors, a high-pitched cry, hyperactive reflexes, including deep tendon reflexes and an exaggerated Moro reflex, increased muscle tone, restlessness and hyperactivity. Extremely excessive movement against bedclothes results in skin abrasions, especially of the knees, elbows and nose. These infants are very difficult to comfort. They hold themselves stiffly against the caregiver, refusing to cuddle. Sleep patterns are also disturbed, in that they sleep fewer hours and less peacefully than normal infants. Respiratory distress is also common. Tachypnea, probably due to a heightened sensitivity of the respiratory centre to carbon dioxide,64 often accompanies withdrawal in the first week of life, and may result in a primary respiratory alkalosis.65 Nasal congestion may lead to mild retractions, intermittent cyanosis, and irregular respirations. Gastrointestinal dysfunction is also common, evidenced by the occurrence of loose or even explosive watery stools, decreased intake and regurgitation, all of which render the infant susceptible to dehydration and electrolyte imbalance. For several reasons, these infants fail to thrive. Their sucking pattern is disorganized and poorly sustained. Therefore their caloric intake may be inadequate, resulting in excessive weight loss. The calories expended in increased activity and crying, in addition to the calories lost through vomiting and diarrhea, may exacerbate the weight loss. Less common manifestations include frequent yawning, nasal stuffiness, sneezing, profuse
sweating, projectile vomiting, mottling, convulsions, and very high fever.26,40,66,67

The time of onset and severity of signs are said to depend on the types of drug(s), dosage, the timing of the dose before delivery, character of labor, type and amount of anaesthesia used, maturity, nutrition, and presence of intrinsic disease in the infant.63 The ability of the mother and infant to metabolize the drug, the duration of addiction, and genetic differences between mother and fetus may modify the manifestations. Multiple drug abuse may also modify the signs, but no correlation has been found with infant gestational age, sex, race, Apgar score, maternal age or parity.68 Conflicting evidence has been reported with respect to the correlation of severity of withdrawal manifestations with the level of drugs in the infant's urine, blood and amniotic fluid.18,68-70

A number of different pharmacological agents have been implicated in producing neonatal psychomotor behaviour consistent with the signs of NAS. These include alcohol, methadone, heroin, morphine, meperidine, codeine, barbiturates, diazepam, cocaine, chlordiazepoxide, and pentazocine.25,52,66,71-79 Those agents that are relevant to this study are reviewed in the following paragraphs. They are among the most commonly self-prescribed or nonmedically used drugs.

Opiate dependence is associated with a 3-4.5% neonatal mortality rate. Heroin readily crosses the placenta. The infants may have a low birth weight and are small for gestational age. Within hours of birth, they experience
central nervous system, gastrointestinal and respiratory disturbances, including hyperactivity, irritability, tremors, poor feeding, regurgitation of feedings, diarrhea, tachypnea, respiratory grunting, nasal congestion, and sneezing. Usually, their breathing is not depressed, implying a development of tolerance in utero to the narcotic effect on respiration. Methadone also readily crosses the placenta, but the birth weight of these infants, in contrast, is generally appropriate for gestational age. The withdrawal phase, however, may be severe. Withdrawal signs may include hypertonicity, seizures, excessive high-pitched crying, hyperthermia, irritability, tremors, jitteriness, hyperactivity, vomiting, diarrhea, perianal excoriation, respiratory distress, and friction burns on the knees. They also have a blunted ventilatory response to carbon dioxide. Other complications include a remarkably increased incidence of SIDS and alterations in behavioural development.

Phenobarbital is known to cross the placenta as well, and signs of withdrawal are similar to those seen with maternal opiate dependence, but are more prolonged and severe. Nonspecific central nervous system depression is manifested by decreased neurophysiologic responses and decreased sucking ability.

Minor tranquilizers, commonly the benzodiazepines, including chlordiazepoxide and diazepam, are frequently drugs of abuse, and there may be cross dependence with alcohol and barbiturates. Their withdrawal produces a syndrome similar to that of opiates. Characteristic features include lethargy, or hyperactivity in some infants, poor thermoregulation,
hyperreflexia, tremors, vomiting, respiratory problems including apnea and decreased respiratory rate, hypotonia and failure to suck effectively. Tranquilizer abuse may be further complicated by malformations because cleft lip and palate and cardiac defects have been reported with their use.52,77,84

Pentazocine is a partial narcotic agonist, and rapidly crosses the placenta. Withdrawal signs usually appear within 24 hours of birth. Decreased interactive behaviour, hyperactivity, hypertonicity, opisthotonus, tremulousness, convulsions, marked irritability, persistent high-pitched crying, vomiting, diarrhea, severe respiratory depression, apnea, and diaphoresis are commonly observed. In addition, several instances of SIDS have been reported. The infants are also small for gestational age with all of the neonatal complications of intra-uterine growth retardation (IUGR).4,40,60,76,78,85-89

Until recently, very little had been reported about the fetal effects of maternal abuse of cocaine. Cocaine is a local anesthetic and sympathomimetic, with significant central nervous system stimulant properties.18,90 It has been suggested that cocaine may affect neurological development. Wang et al91 raise the possibility of down regulation of adrenergic receptors of the developing fetal nervous system, similar to that of placental beta-adrenergic receptors, adversely affecting synaptic growth. Chasnoff et al25,92,93 and others94 report higher numbers of spontaneous abortions and fetal deaths, an increased risk of genitourinary malformations, a greater incidence of SIDS, fetal and postnatal tachycardia, depressed
interactive behaviour, poor organizational response, tremors, an increased Moro reflex, hypertension, and a case report of acute focal cerebral infarction in the perinatal period. Compared with infants of women maintained on methadone, this group experienced a higher incidence of abruptio placentae, fetal distress, fetal meconium staining, premature labour, and precipitous labour.\textsuperscript{93} These infants also have Apgar scores lower than normal, as well as a lower birth weight, length, and head circumference.\textsuperscript{94} The IUGR has been attributed to the effect of cocaine on placental vasoconstriction\textsuperscript{25} and decreasing maternal appetite.\textsuperscript{95}

诊断

None of the signs of withdrawal are pathognomonic of NAS, although the full complex is highly suggestive to the experienced observer. Nevertheless, other diagnostic possibilities must be considered, particularly as they may coexist with the effects of withdrawal. Neonatal hyperthyroidism, although rare and usually associated with a history of maternal disease, mimics the spectrum of signs associated with NAS. Tremors may be indicative of hypoglycemia or hypocalcemia, and convulsions should always be investigated as a possible indicator of meningitis, metabolic disturbance, and intracranial hemorrhage. Loose or watery stools and fever may occur due to abstinence, but the possibility of infectious gastroenteritis should be excluded first. Pneumonia and congenital heart disease, which may manifest as tachypnea, are other potentially fatal conditions that must also be considered in the differential diagnosis of NAS.\textsuperscript{26}
Management of the Neonatal Abstinence Syndrome

Current recommendations for treatment of the passively addicted newborn are both generally supportive and specifically pharmacologic, and based largely on subjective assessment of clinical signs. Recovery occurs gradually, as the infant’s metabolism adjusts to the absence of the drug. The prognosis is generally quite favourable. Twenty or thirty years ago, many infants did not survive the neonatal period because of obstetrical and medical complications, lack of prenatal care and low birth weight. With newer techniques at the disposal of neonatologists, however, the mortality rate has since declined significantly. It has been recommended that treatment should be primarily supportive, including swaddling, infrequent handling, protection from the stimulation of ordinary light and noise, and provision of the greatest possible caloric intake. If such conservative measures are not sufficient to control the clinical signs of withdrawal, drug therapy is instituted.

Several medications have been used for the treatment of narcotic withdrawal. The most commonly used agents in the past have been phenobarbital, diazepam, paregoric, and tincture of opium; chlorpromazine, morphine and methadone have been used infrequently. Most of these medications have serious drawbacks. Phenobarbital causes generalized central nervous system depression and impairs sucking, and does not provide relief of gastrointestinal problems. Diazepam causes behavioral depression and severely depresses sucking, so its effectiveness in the management of NAS is also questionable. Paregoric controls many of the withdrawal signs and these infants demonstrate more physiological sucking behaviour. This effect may be because paregoric actually contains opium alkaloids.
including morphine (0.4 mg/ml), but it also contains other additives with a potential for serious side effects. These include anise oil (4%) which may cause habituation, camphor (4%) which is a central nervous system stimulant and is eliminated very slowly, and a high percentage of alcohol (44%) which acts as a central nervous system depressant. Both camphor and alcohol are known to have toxic effects on the infant’s liver. In Vancouver, the preferred treatment is with a preparation developed there called Pediatric Opium Solution. It contains no camphor or anise oil. It is a 25-fold dilution of tincture of opium resulting in the same opium concentration as paregoric, 0.4 mg of morphine equivalent/ml. In contrast to paregoric, the dilution consists of an alcoholic content of only 1.8%. It should be noted that it would be illogical to use narcotic antagonists in the passively addicted infant because they may precipitate an abrupt onset of withdrawal, with disastrous consequences.

Because of the individual variation in time of onset and severity of the syndrome, and the possibility that such medication may not be required, prophylactic drug therapy is not recommended. Indications for drug treatment include vomiting and diarrhea that threaten excessive weight loss or severe dehydration, inability of the infant to sleep, fever, or seizures. The objectives of drug therapy are to reduce the severity of the withdrawal process in order to avoid permanent physical, neurological, and physiological sequelae.

Several studies suggest that about 50% of infants exposed prenatally to dependency causing drugs emerge with long standing and permanent
disabilities. These include delayed speech development, poor coordination, sleep disturbances, abnormal muscle tone, growth impairment, impaired hearing, mental retardation, impulsiveness, aggressiveness, bursts of uncontrollable temper, hyperactivity, brief attention span, learning disabilities, defective communication skills, difficulty in making and keeping friends, poor self confidence, and disturbed behaviour. Removal of the child from the drug abusive environment does not necessarily prevent the development of these disturbances. Which of these disturbances are caused by permanent changes in the brain during prenatal exposure to maternal drugs and which are the result of the agony caused by the withdrawal effects after birth is not known. Most of the follow up studies do not provide conclusive long term data because of imperfect methodology and the difficulty of following an adequate sample size for a prolonged period.

Indications for treatment, the choice of pharmacotherapeutic agents, dosage schedules, and duration of treatment courses vary widely among those who have managed these infants. It has been generally accepted that the infants should be evaluated on an ongoing basis by utilizing objective assessment criteria. Several neonatal abstinence scoring systems have been described in the literature. These scoring systems provide a sensitive and reliable index of some characteristic behaviours of passively addicted infants. They provide a more precise assessment of the clinical status of the infants than by subjective impression alone. Their usefulness in comparing treatment regimens has also been demonstrated. They are valuable research tools, but their clinical applications are limited. Disadvantages include a focus on too few abstinence signs, lack of precision in distinguishing the
levels of withdrawal severity, and excessive observer subjectivity in grading. In addition, in most nurseries, it will be physicians and nurses with varying levels of experience and attention who will evaluate the infants. Furthermore, nursery schedules generally do not permit the examiner the time required to evaluate the infant at the specific time intervals specified by the schedule. Many physicians thus choose not to use them. Therefore a precise method to monitor the neonatal abstinence syndrome upon which therapeutic decisions can be based would be an important contribution to the care of the infant during withdrawal. The method should be uncomplicated and should involve a limited number of measurements but should provide an accurate assessment of the severity of the syndrome. The procedure should be defined in objective terms that are conducive to obtaining reproducible scores. Because sucking and swallowing engage the integration of several body systems affected by withdrawal, feeding difficulties in these infants may be most representative of overall clinical status. Therefore, sucking behaviour may be the sign most amenable to development of such a method.

Sucking behaviour

The mechanism for sucking develops during fetal life. Normal sucking behaviour consists of two components, expression and suction. The muscles of mastication and of the face, lips and tongue are involved in expression of milk from the nipple. A negative intra-oral pressure, created by dropping the tongue away from the palate, is required for suction of milk. Sucking requires the function of cranial nerves V, VII, and XII, and deglutition requires the function of cranial nerves IX and X. The concerted actions of sucking, swallowing and respiration are under medullary control. These complex motor
actions are highly developed in the normal newborn by 32 to 34 weeks gestation. The absence of coordination between the three systems in the neonate is indicative of central nervous system dysfunction.\textsuperscript{113-117} Measures of sucking performance provide quantitative estimates of some components of the infant's level of central nervous system excitation or depression.\textsuperscript{40,108,109,118}

All infants can suck in two modes, nutritive and nonnutritive.\textsuperscript{119} Nutritive sucking may be defined as repetitive mouthing on a nipple associated with a negative intra-oral pressure sufficient to withdraw liquid from the nipple. It has been described as a range from a continuous stream of sucks to a series of sucking bursts alternating with short pauses, as exemplified in figure 4a.\textsuperscript{112,113,119-22} Within limits, nutritive sucking is not affected by nipple shape or by the nutritional value of the fluid.\textsuperscript{119,120} Reproducibility of measures of nutritive sucking in consecutive feeds has been demonstrated, particularly when infant formula (as opposed to a corn syrup solution) is used as the nutrient.\textsuperscript{123,124} Nonnutritive sucking is defined as any repetitive mouthing activity on a nipple which does not deliver milk. The sucking rhythm is similar to that in nutritive sucking. It is characterized by an alteration between burst and rest periods of equal duration, but the sucking rate is typically twice that of nutritive sucking.\textsuperscript{119,120}

Both nutritive and nonnutritive sucking exhibit very distinct and stable temporal patterns. Nonnutritive sucking, in particular, is resistant to adverse prenatal and perinatal factors.\textsuperscript{120,121} Nutritive sucking, on the other hand, is altered in infants who exhibit central nervous system depression or
irritability as a result of adverse prenatal circumstances. Therefore, we elected to study nutritive sucking, because it is a more sensitive reflection of an essential physiological behaviour than nonnutritive sucking.

Previous studies have described the usefulness of sucking measurements in monitoring the severity of the neonatal narcotic abstinence syndrome. Of several parameters investigated, sucking rate appears to be the most sensitive in distinguishing infants undergoing narcotic abstinence from normal infants. It is hypothesized that objective measures of sucking rate and nutrient consumption of passively addicted infants can be developed, and that the qualitative and quantitative characteristics of these functions differ significantly from normal infants. It is also hypothesized that sucking rate and nutrient consumption can be correlated with the clinical signs of withdrawal. If such correlations are demonstrated, sucking measures would provide objective criteria by which to determine the effects of specific modes of withdrawal management, and whether the treatment should be introduced, increased, decreased, or discontinued. If the methods of measurement used are sufficiently simple, it would encourage the clinical use of the sucking apparatus as a routine procedure in guiding the management of the neonatal abstinence syndrome.
MATERIALS AND METHODS

The sucking apparatus used in these studies was a modification of the one originally designed by Kron and his colleagues. The disadvantages associated with their original equipment were that it required autoclaving prior to each study session, and assembly of the apparatus was tedious and time consuming. Some of the materials could not withstand the heat of autoclaving. Higher standards of sterility in newborn nurseries precluded the use of such a device. The apparatus that was developed for monitoring nutritive sucking behaviour consisted of disposable components. It was a simplified version of that used by Kron et al. These modifications were made to ensure that the study feedings were as similar as possible to customary feeding technique, to minimize the risk of external contamination, and to make the device more acceptable to busy nursery staff.

Sucking Methods

The study was conducted in the nurseries of 2 hospitals. Separate but duplicate apparatus was used for the study at each of the hospitals. The apparatus consisted of the following items: sterile, disposable bottled nutrient formula, sterile, disposable nipples, sterile, disposable 18 gauge Cathlon IV catheters (Critikon, Burnaby, B.C.), sterile, disposable 0.6 m. pressure monitoring lines (Medex, inc., Coquitlam, B.C.), a differential pressure transducer (Sanborn 267BC, Cambridge, Mass., or Statham labs inc. model no. P23 Db, Puerto Rico, U.S.A.), and a standard pre-amplifier - recording galvanometer (S.E. Labs (Eng) Ltd.), transducer/converter type SE 905 (S.E. Labs (Eng) Ltd) with Gould recorder 2200 (Cleveland, Ohio), or
Sanborn carrier preamplifier with Sanborn 152 recorder (Cambridge, Mass.) or Hewlett Packard 7402A recorder (San Diego, California).

The catheter was inserted into the base of a sterile, disposable nipple and directed through the lumen to emerge adjacent to the nipple aperture, on the same side as it was originally inserted (Fig. 1). The needle was subsequently withdrawn from the catheter and discarded. The catheter remained situated at the side of the nipple to face the negative pressure within the infant's mouth (Fig.1). The catheter was connected to a sterile pressure monitoring line which in turn was attached to a differential pressure transducer. The closed system ending at the transducer displacement diaphragm and open only at the catheter tip, was important for prevention of milk or baby's secretions entering the tube leading to the transducer. An open catheter system would have allowed contamination of the transducer or possibly blockage of the tube. A fluid-free air-containing channel communicating pressure changes between the infant's mouth and the transducer was thus maintained. The pressure transducer was connected to a standard pre-amplifier - recording galvanometer for continuous registration of pressure changes on a standard speed of recording paper (1mm/sec) (Fig.2).

FIGURE 1. Schematic representation of catheter-nipple system.
All of the studies were conducted by one investigator, the author. The babies were fed by the mother or a nurse, in cooperation with the investigator. The studies with this apparatus were carried out during routine nursery feedings.

Two variables were computed from the data, including sucking rate (sucks per minute) and rate of nutrient consumption (ml/min). The first five minutes of each of the graphic recordings were used for the sucking rate analysis. The nutrient consumption was calculated over the entire duration of the feeding session. Sample tracings are shown in Fig. 4.

The initial intention was to calculate minute pressure (the average pressure per suck over 1 minute) as well, but the use of an imprecise pressure transducer which resulted in a wandering baseline precluded this calculation. Baseline shift was also a result of the use of a rigid nursing bottle which caused the hydrostatic pressure of the fluid in the bottle to vary with changes in nutrient level, a back-pressure developing as fluid was withdrawn (Fig. 3). Thus, there was variation in the effort required for nutrient flow throughout the feed. The quantity of nutrient delivered in each suck was therefore not
directly proportional to the pressure of that suck. As a result, measurements of minute pressure derived from the use of a standard rigid glass nursing bottle would not have been reliable.\textsuperscript{129} The sucking apparatus was calibrated with a pressure gauge prior to each study session. This practice was continued even after it became apparent that the minute pressure data would not be usable as a true reflection of intra-oral pressure.

Figure 3. Development of back-pressure within the measurement system. Note that the units of pressure are intended only as a guide, and are not necessarily accurate for any given point.

Subjects
Eighteen infants from the Special Care Nursery at B.C. Children's Hospital who had been born to drug dependent mothers comprised the experimental group. These infants, 8 male and 10 female, ranged in gestational age from 34 to 42 weeks, and their birthweights were all appropriate for gestational age. There were 21 infants born to drug dependent mothers but 3 were excluded from the study, 1 because of active hepatitis, and the other 2 because of prematurity (less than 34 weeks). Eight of the addict mothers were on the methadone program, but 7 of them had abused one or more additional drugs, including
benzodiazepines, heroin, phenobarbital, marijuana, and cocaine. The 10 not on the methadone program had abused any combination of the above drugs as well as LSD, analgesics, pentazocine and methylphenidate. This information was obtained from the history, and did not always correlate with the findings of the hospital toxicology screening service. A negative urine drug screen, however, does not negate tissue content of drugs.130,131

A population of 20 healthy infants drawn from the nurseries of the Salvation Army Grace Maternity Hospital served as the control group. These infants, 10 male and 10 female, ranged in gestational age from 36 to 42 weeks, and their birthweights were all appropriate for gestational age. This group was recruited from responses to a written description of the project distributed in the Grace Hospital to mothers who were bottle feeding their infants, inviting them to participate in the study. There were 60 forms issued (see appendix) and 29 responses. Nine were excluded, 1 because of possible drug exposure, 2 because of equipment malfunction, and the other 6 because mothers changed their minds about participating. Two of these infants were boarded in the observational nursery of the Grace Hospital for a period of 24 hours, but examinations of all of these infants by the staff indicated they were normal, healthy infants.

Mothers of the control group infants provided informed consent for the study on the form describing the procedure. Consent for the procedures in the study group was not sought because they were considered as a guide to the management of each of the patients involved. The UBC Screening Committee for Research and Other Studies Involving Human Subjects (Clinical) had
granted ethical approval for the study. The study infants were kept under observation in the Special Care Nursery of B.C.'s Children's Hospital and subsequently at Sunny Hill Hospital for Children. Treatment of the infants initially was primarily supportive. It included swaddling and protection from noise and light to decrease sensory stimulation, frequent small feedings of hypercaloric formula (81 cal/100 ml) to supply additional caloric requirements, and observation of sleeping habits, temperature stability, weight gain or loss, and any change in signs. Pharmacological therapy was instituted only if supportive treatment was not sufficient to control severe clinical signs of drug withdrawal.

In those infants in whom conservative management failed to control severe withdrawal manifestations, Pediatric Opium Solution (equivalent to 0.4 mg/ml of morphine activity), a 25-fold dilution of tincture of opium, was used exclusively. The medication was administered orally every 3 hours with feeds. The starting dose was 0.066 ml x body weight (kg) per dose (0.2 mg/kg/day). If vomiting was a problem, it was given 30 minutes prior to the feed. After withdrawal signs had stabilized for 2 to 3 days, the dose was tapered gradually by 0.02 ml per dose every second day if clinical signs remained mild. Otherwise the dosage was kept constant or increased to meet the withdrawal needs.

Procedure
The sucking behaviour of the control group was measured for up to 4 days consecutively, depending on the length of stay in hospital. The sucking behaviour of the experimental group was measured according to a schedule
determined by the investigator based on the changes in the clinical signs of withdrawal. This schedule was different for each infant, and was continued for up to 4 months, depending on the length of stay in hospital. The infants in the latter group were also subjected to an evaluation of the clinical signs of withdrawal exhibited over the course of each monitored feeding session (Table 1). Greater numerical values of clinical score reflect increased intensity of withdrawal. In determining the clinical parameters to be included in this evaluation, review was made of reports in the literature describing scoring systems for evaluation of NAS\textsuperscript{107,108} as well as our own clinical experience with NAS. The weighting assigned to each observational parameter had been assigned independently of the experimental results and prior to their objective interpretation. The weighting assignment was influenced by a clinician's perception of the significance each sign has had in the context of NAS. The data were statistically analyzed using the SAS (statistical analysis system) on an IBM personal computer.
Table 1. Neonatal Abstinence Syndrome clinical score sheet

<table>
<thead>
<tr>
<th>Signs</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>High pitched cry</td>
<td>2</td>
</tr>
<tr>
<td>Excessive, consolable cry</td>
<td>3</td>
</tr>
<tr>
<td>Continuous inconsolable cry</td>
<td>4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
</tr>
<tr>
<td>Continuous irritability</td>
<td>3</td>
</tr>
<tr>
<td>Excessive somnolence</td>
<td>3</td>
</tr>
<tr>
<td>Marked lethargy (not due to medications)</td>
<td>4</td>
</tr>
<tr>
<td>Increased muscle tone</td>
<td>2</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>3</td>
</tr>
<tr>
<td>Some hyperreflexia</td>
<td>1</td>
</tr>
<tr>
<td>Marked hyperreflexia</td>
<td>4</td>
</tr>
<tr>
<td>Tremors when handled</td>
<td>2</td>
</tr>
<tr>
<td>Tremors while undisturbed</td>
<td>3</td>
</tr>
<tr>
<td>Continuous tremors</td>
<td>4</td>
</tr>
<tr>
<td>Convulsions</td>
<td>6</td>
</tr>
<tr>
<td>Clinically weak sucking</td>
<td>2</td>
</tr>
<tr>
<td>Stops sucking prematurely</td>
<td>3</td>
</tr>
<tr>
<td>Voracious but insustained sucking</td>
<td>3</td>
</tr>
<tr>
<td>Absent sucking</td>
<td>5</td>
</tr>
<tr>
<td>Incoordinated swallowing</td>
<td>3</td>
</tr>
<tr>
<td>Facial abrasions</td>
<td>2</td>
</tr>
<tr>
<td>Knee, elbow redness</td>
<td>1</td>
</tr>
<tr>
<td>Knee, elbow denuding</td>
<td>2</td>
</tr>
<tr>
<td>Tachypnea &gt; 60/minute</td>
<td>2</td>
</tr>
<tr>
<td>Tachypnea with retractions</td>
<td>3</td>
</tr>
<tr>
<td>Medical Symptom</td>
<td>Score</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Occasional vomiting with feeds</td>
<td>3</td>
</tr>
<tr>
<td>Occasional vomiting anytime</td>
<td>4</td>
</tr>
<tr>
<td>Frequent vomiting</td>
<td>5</td>
</tr>
<tr>
<td>Watery stools</td>
<td>3</td>
</tr>
<tr>
<td>Continuous watery diarrhea</td>
<td>5</td>
</tr>
<tr>
<td>Diaper area redness</td>
<td>1</td>
</tr>
<tr>
<td>Perianal excoriation</td>
<td>2</td>
</tr>
<tr>
<td>Yawning</td>
<td>1</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>1</td>
</tr>
<tr>
<td>Mottling</td>
<td>1</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>1</td>
</tr>
<tr>
<td>Temperature instability</td>
<td>1</td>
</tr>
</tbody>
</table>
RESULTS

Differences in sucking behaviour: Normal versus NAS babies

There was a distinct and rather dramatic difference between the sucking behaviour of the normal and the NAS babies. Qualitatively, in each feeding, the normal infants spent a longer time sucking, and there was a regularity or pattern to their sucking (Fig. 4a). The sucking behaviour of the NAS babies was erratic (Fig. 4b) and they seemed to tire quite quickly (Fig. 4c). Once they had recovered from the withdrawal phase, their sucking patterns resembled those of normal infants (Fig. 4d).

Sucking rate. The sucking data from the experimental and control groups were summarized by averaging the minute scores on each of the first four days of life. The number of sucks in each minute was counted for each of the first five minutes. One way analysis of variance using the number of sucks per minute was performed to detect possible differences between the control and NAS groups during the first four days of life. P values less than 0.05 were considered to be significant. Given that the data were basically count data there were more sophisticated models for analysis, such as Poisson mixture models. However, the analysis of variance was sufficiently robust to detect the differences which were obvious graphically. The data demonstrate that control group infants had a significantly higher sucking rate on the second (p=0.0001), third (p=0.0005), and fourth p=(0.006) days of life. There was no significant difference on day one (Table 2, Fig. 5).
a) Sample tracings of regular sucking patterns of 2 normal infants, day 4.

b) Sample tracing of erratic sucking pattern of NAS infant, day 4.

c) Sample tracing of fatigue of sucking pattern of NAS infant, day 15.

Figure 4. Sample tracings of infant sucking behaviour. Note that the units of pressure are intended only as a guide, and are not necessarily accurate for any given point.
d) Sample tracing of sucking pattern of NAS infant, just before discharge.

Figure 4, continued.
Figure 5. Sucking rate: Notched box plots of control vs. experimental groups on day 1 (n=16,8; p=0.8), day 2 (n=19,15; p=0.0001), day 3 (n=16,13; p=0.0005), and day 4 (n=8,13; p=0.006), respectively.
Table 2. Significance of the differences between experimental and control groups in sucking rate and nutrient consumption.

<table>
<thead>
<tr>
<th></th>
<th>Sucking rate (sucks/min)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental</td>
<td>Control</td>
</tr>
<tr>
<td>day 1</td>
<td>37.1</td>
<td>36.1</td>
</tr>
<tr>
<td>day 2</td>
<td>24.5</td>
<td>46.6</td>
</tr>
<tr>
<td>day 3</td>
<td>27.1</td>
<td>51.5</td>
</tr>
<tr>
<td>day 4</td>
<td>27.2</td>
<td>48.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Nutrient consumption (ml/min)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental</td>
<td>Control</td>
</tr>
<tr>
<td>day 1</td>
<td>5.1</td>
<td>4.8</td>
</tr>
<tr>
<td>day 2</td>
<td>4.2</td>
<td>4.5</td>
</tr>
<tr>
<td>day 3</td>
<td>2.7</td>
<td>5.5</td>
</tr>
<tr>
<td>day 4</td>
<td>3.3</td>
<td>5.4</td>
</tr>
</tbody>
</table>

**Nutrient consumption.** One way analysis of variance using the average rate of nutrient consumption over the feeding time was performed to detect possible differences between the control and experimental groups. P values less than 0.05 were considered to be significant. Infants in the control group had a significantly greater average nutrient consumption on the third (p=0.006) and fourth (p=0.03) days of life. There were no significant differences on days one and two (Table 2, Fig. 6).

The data in figures 5 and 6 are represented as notched box plots. These plots give a quick look at the centre (50th percentile) and spread of the data. The upper and lower tails are the 95th and 5th percentile, respectively. The upper and lower boxes are the 75th and 25th percentile, respectively. The notches are constructed using the formula: Median ± 1.57 X (75th percentile -
25th percentile)/√n. If the notches of 2 boxes do not overlap, it may be assumed that the medians are significantly different (the centres are statistically significant).
Figure 6. Nutrient consumption. Notched box plots of control vs. experimental
groups on day 1 (n=16,9; p=0.9), day 2 (n=19,15; p=0.8), day 3
(n=16,14; p=0.006), and day 4 (n=8,13; p=0.03), respectively.
Correlations between sucking measures and clinical score

Within the experimental group, the clinical score items were inversely correlated with both sucking rate and nutrient consumption over the first two months of life (Table 3, Figs. 7,8). Ethically, medication to control severe withdrawal could not have been withheld. Therefore, to determine whether there was any difference within the experimental group, those infants who required opium and those who did not, were divided into two subgroups. Separate regressions of score versus average sucking rate and score versus average nutrient consumption were fitted to the 'opium' and 'no opium' babies. These lines were essentially identical (p>0.99) for both variables (Table 3, Figs. 9,10).

Table 3. Correlations between sucking measures and clinical score

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucking rate:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) opium</td>
<td>-0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>b) no opium</td>
<td>-0.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nutrient consumption</td>
<td>-0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>a) opium</td>
<td>-0.42</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>b) no opium</td>
<td>-0.58</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure 7. Correlation between sucking rate and clinical score within the experimental group (n=16) over the first 2 months of life (r=-0.57, p<0.0001).
Figure 8. Correlation between nutrient consumption and clinical score within the experimental group (n=18) over the first 2 months of life ($r = -0.51$, $p<0.0001$).

Nutrient Consumption (ml/min) = 9.8 - 0.23 clinical score
Figure 9. Correlation between sucking rate and clinical score within the experimental group (n=18) over the first 2 months of life: Opium ($r=-0.46$, $p<0.0001$) and no opium ($r=-0.64$, $p<0.0001$) subgroups.
Figure 10. Correlation between nutrient consumption and clinical score within the experimental group (n=18) over the first 2 months of life: Opium (r=-0.42, p<0.0001) and no opium (r=-0.58, p<0.001) subgroups.
DISCUSSION

This study sought to confirm a difference in neonatal sucking behaviour between normal and drug dependent infants, and to determine whether a relationship between sucking behaviour and the classical clinical signs of withdrawal could be demonstrated. A number of instruments have been described in the literature for quantifying infant sucking behaviour.\textsuperscript{128,134-6} None of these, however, was compatible with current sanitary standards in a nursery. Thus, an instrument was designed which satisfied the requirements of sterility, and was acceptable to the busy nursery staff and mothers. Monitoring sucking rate by observation using a stopwatch and hand counter was considered. These observations were found to be unreliable, however. When these results were compared with those from the tracings it was evident that many sucks had not been perceived by clinically experienced nurses, likely due to the weak sucking behaviour of the NAS infants. Also, a clinical score sheet was designed for this study because the scoring systems in the literature were not considered sufficiently precise.

Central nervous system irritability associated with withdrawal has been shown to depress nutritive sucking behaviour. The findings in this study indicate that sucking rate is a valid indicator of the severity of the neonatal abstinence syndrome. These observations are also consistent with those reported in the literature.\textsuperscript{74,96,127} Sucking rate and nutrient consumption are significantly reduced in drug dependent infants in comparison with these measurements in normal infants during the early neonatal period. Sucking rate is more discriminating than nutrient consumption, however, in
distinguishing between these two groups of infants. The lack of statistically
significant differences in sucking rate and nutrient consumption in the first
day or two between the study group and the control group may be due to tissue
storage and delayed excretion of the drug in the NAS infants, and possibly to
the effects of obstetrical analgesia and anesthesia. It is less clear, however,
why on day 2 the differences in sucking rate are highly significant but not the
nutrient consumption. A significant correlation was also demonstrated
between both sucking rate and nutrient consumption with the clinical signs of
withdrawal over the first 2 months of life. Over this period there was no
difference in the response of infants requiring pharmacotherapy from those
judged clinically not to require it.

Several prenatal and perinatal factors were considered which may have
adversely affected sucking behaviour of the NAS infants, but it was not felt
that any of them was sufficient by themselves to explain the findings. As
mentioned previously, protection from noise and light stimulation was an
important part of the treatment of NAS. Due to physical constraints, this
could not be provided in the first few days of life, while the infants were
boarded in a special care nursery requiring lighting for the detection of any
clinical deterioration of sick infants. Stress caused by the light stimulation
may have adversely affected sucking behaviour and may be a potential source
of error.

Use of sucking rate alone seems to be both practical and valid as an indicator
of the severity of withdrawal. Using only the sucking rate parameter, which
required no calibration prior to measurement, the entire procedure including
interpretation of results may be conducted by a general duty nurse. The services of a technician or professional interpreter would not be required. Therefore, the periodic monitoring of sucking rate of the passively addicted infant would be a practical and useful method by which to guide the management of the withdrawal syndrome. It would also provide a basis for development of uniform criteria for assessment and treatment of these infants. Data such as would be available from this monitoring system would allow more objective judgements regarding institution or changes in therapy of withdrawal; it would guide decisions such as when more intensive pharmacotherapy is needed, when dosages may be reduced, whether lesser signs are indications that therapy is needed at all, and when the infant may be removed from light and sound protection. Furthermore, where there may be options in withdrawal management, the objective recording of sucking behaviour may assist in determining which management method would be more effective in alleviating withdrawal manifestations.

This study has investigated the effect of maternal drug abuse on sucking behaviour of the passively addicted infant. Future studies could investigate the specific effects of individual narcotic and nonnarcotic drugs on sucking behaviour. To do so would require a greater number of infants in the experimental group. Other parameters of sucking behaviour could also be investigated, such as sucking patterns and time spent sucking, using this apparatus. Analysis of these additional parameters by hand would be a tedious chore, justifying the addition of a computer to the instrumentation.
This instrument may have other applications in studies of infant behaviour. With the ever increasing understanding of neonatal physiology, introduction of intensive therapy of neurologically compromised neonates at an earlier time may improve their prognosis. The morphologic and physiologic immaturity of the newborn infant's nervous system often precludes a conclusive diagnosis of central nervous system damage using standard neurological tests. Studies suggest that perinatal brain injury may manifest as a low sucking rate and dysrhythmic sucking pattern. Therefore, an objective, sequential analysis of sucking behaviour of high risk infants using a simple and noninvasive procedure may indicate the presence of central nervous system dysfunction.
REFERENCES


