Neonatal Drug Withdrawal

Symptoms of neonatal drug withdrawal consist of: W = wakefulness; I = irritability; T = tremulousness, temperature variation, tachypnea; H = hyperactivity, high-pitched persistent cry, hyperacusia, hyperreflexia, hypertonus; D = diarrhea, diaphoresis, disorganized suck; R = rub marks, respiratory distress, rhinorrhea; A = apneic attacks, autonomic dysfunction; W = weight loss or failure to gain weight; A = alkalosis (respiratory); L = lacrimation (Fig 1); also, hiccups, vomiting, stuffy nose, sneezing, yawning, photophobia, twitching, myoclonic jerks, opisthotonos, or seizures.

When these symptoms are seen in a newborn infant, the physician should consider a diagnosis of withdrawal from maternal drugs. Narcotics reported to cause these symptoms in the neonate are heroin, methadone, meperidine, morphine, codeine, pentazocine, and propoxyphene. A glossary of drugs is provided in Fig. 2.

The onset of symptoms may be present at birth or may begin within four days of delivery. In some instances, symptoms may not become obvious until 10 days of age. This depends upon the drug the infant was exposed to in utero and the pharmacokinetic excretion of the drug. Subacute symptoms of narcotic drug withdrawal may last for 4 to 6 months.

Rosen and Pippenger have demonstrated that infants born to mothers maintained on methadone do not begin to manifest withdrawal symptoms until the plasma level is less than 0.06 μg/mL. In utero exposure to multiple drugs may cause a biphasic pattern of withdrawal symptomatology in the neonate. Polydrug abusers frequently use as many as two to five drugs in combination; these might include phenobarbital, diazepam, marijuana, pentazocine, triptellamine, phencyclidine, and codeine. A physician who is unaware of a mother’s drug ingestion may initially make an erroneous diagnosis of colic in the infant; therefore, a detailed maternal drug history should be obtained, including prescription and nonprescription drugs received, social habits of the parents, and whether the mother is breast-feeding. In the event a negative drug history is obtained but infant symptomatology is consistent with drug withdrawal, a drug screen should be performed on the mother’s or infant’s blood and urine. Recently, screening of meconium for drugs has been reported to produce greater confirmation of fetal drug exposure than screening of urine.

TREATMENT OF NARCOTIC WITHDRAWAL FROM MATERNALLY ACQUIRED DRUGS

Treatment of the neonate should be primarily supportive, as unjustified pharmacologic administration will prolong hospitalization and subject the infant to additional exposure to drugs that are not indicated. Supportive care includes swaddling to decrease sensory stimulation; frequent small feedings of hypercaloric (24 cal/oz) formula to supply the additional caloric requirements; and observation of sleeping habits, temperature stability, weight gain or loss, or change in symptomatology which might suggest another disease process taking place (ie, infection). The clinical symptoms in 30% to 50% of infants who manifest drug withdrawal may be treated in the above manner without use of pharmacologic therapy.

Excess weight loss may represent inadequate provision of calories rather than the need for pharmacologic therapy. Besides the caloric expenditure caused by increased activity, crying, and decreased sleep, calories may be lost through vomiting, drooling, and diarrhea. Hyde et al have shown that infants withdrawing from maternal narcotics have an increased O2 consumption at the tissue level, which increases caloric need. Caloric intake should be calculated daily in order to provide the 150 to 250 cal/kg/24 h necessary for proper growth in babies suffering withdrawal from narcotics.

Each nursery should adapt one of the abstinence scoring methods to judge the need for drug therapy as nurses and doctors often become sympathetic with the jittery and frantic behavior observed in the infant and are prone to begin drug therapy for subjective reasons. An abstinence scoring sheet results in the use of more objective criteria for
that infection, hypoglycemia, hypocalcemia, hypomagnesemia, hyperthyroidism, CNS hemorrhage, and anoxia be ruled out as the etiology for the symptoms. The history of a drug abuser mother should be checked for evidence of past hepatitis or sexually transmitted disease.

**PHARMACOLOGIC AGENTS USED TO TREAT NARCOTIC WITHDRAWAL**

**Narcotics**

*Paregoric.* Many physicians prefer paregoric for therapy of the narcotic abstinence syndrome because of the ease in administration of the drug. Infants treated with paregoric for narcotic withdrawal symptoms have a more physiologic sucking pattern, higher nutrient consumption, higher percentage of sucking time, greater sucking pressure exerted at nursing, and more weight gain than infants treated with diazepam or phenobarbital.¹⁹

Paregoric contains anhydrous morphine (0.4 mg/mL). In addition, it contains opium alkaloids which consist of isoquinoline derivatives (narcotine and papaverine) which are antispasmodics and phenanthrene derivatives (morphine and codeine) which are analgesics and narcotics. Paregoric contains camphor, a CNS stimulant that is eliminated from the body slowly because of its high lipid solubility and the need for glucuronic conjugation for urinary excretion. Paregoric contains a high concentration of alcohol (44% to 46%), which is a CNS depressant, and anise oil, which may cause habituation. Benzoic acid (4 mg/mL), an oxidative product of benzyl alcohol, is present in paregoric. Severe acidosis, CNS depression, respiratory distress, hypotension, renal failure, seizures, and death have been reported to occur in small premature infants who receive benzyl alcohol in amounts of 99 to 234 mg/kg/24 h.²⁰⁻²² Glycerine is another component.

The dose of paregoric administered to a full-term infant for treatment of neonatal narcotic withdrawal is from 0.2 mL (0.08 mg morphine equivalent) to 0.5 mL (0.2 mg morphine equivalent) per dose every 3 to 4 hours until the symptoms of withdrawal are controlled. A neonatal abstinence score is helpful in determining the need for increasing or decreasing the dose. The dose of paregoric should be tapered after symptomatology has been stabilized for three to five days.

**Tincture of Opium.** The United States Pharmacopeia preparation of tincture of opium also contains opiate alkaloids and morphine (10 mg/mL) but in a weaker alcohol preparation (17% to 21%). There is concern about stocking tincture of opium in hospital pharmacies because doctors and nurses may inadvertently mistake this preparation for paregoric and thus administer an excess dose of opium. A 25-fold dilution of tincture of opium contains the
same concentration of morphine equivalent as pare- 
goric (0.4 mg/mL morphine equivalent) without 
the additives (camphor, anise oil, benzoic acid, or 
glycerine) found in paregoric. A recent study has 
shown that the diluted solution remains stable for 
least 2 weeks (S. Segal, unpublished data, 1983). 
Because of the danger of mistaking tincture of 
opium for paregoric, tincture of opium should be 
dispensed to the nursery only in a dilution that 
contains a concentration of morphine equivalent to 
that concentration in paregoric. A suggested name 
for the preparation is “neonatal opium solution.” 
Diluted tincture of opium should be administered 
according to the same morphine equivalent dosage 
schedule used for paregoric.

Morphine. In the past, parenteral morphine has 
been used to treat the severe vasomotor collapse 
obsserved in infants with heroin withdrawal.15

The parenteral form of morphine contains so-
dium bisulfite (1 mg/mL), which has been reported 
to produce an anaphylactic reaction consisting of 
urtis, flushing, and acute wheezing in older pa-
tients.24 The parenteral form of morphine also con-
tains phenol (5 mg/mL). Absorption of phenol via 
the skin has been associated with jaundice in small 
infants.25 The dose of phenol that produces hyper-
ibilirubinemia is not known. The 8-mg/mL ampul 
of morphine also contains 7 mg/mL (0.12 mEq/ 
ML) of sodium chloride. Because morphine is used 
in such small doses, these additives may not have 
a significant effect on the infant.

An oral preparation of morphine (2 and 4 mg/
ML), which contains no additives and less alcohol 
than paregoric (10%), is now available. Oral mor-
phine has less analgesic effect than the same par-
enteral dose. To date there have been no studies in 
which morphine preparations with morphine equiv-
als similar to paregoric have been used to treat 
neonatal narcotic withdrawal. Oral morphine doses 
should be calculated to deliver to the full-term 
infant the same quantity of morphine equivalent 
usually supplied in paregoric.

There is some concern regarding safety in use of 
opiate preparations in neonates due to their marked 
respiratory depressant effect. This concern is ac-
ccentuated in the report by Mitchell et al26 of life-
threatening reactions in infants less than 3 months 
of age who were premedicated with morphine. They 
found that morphine doses of 0.1 mg/kg may cause 
respiratory cessation in non-narcotic-habituated 
infants. Infants manifesting narcotic withdrawal 
will be more refractory to this dose.

Methadone. The neonatal abstinence syndrome 
has been treated with methadone. The prolonged 
plasma half-life of methadone (t1/2 = 26 hours) 
makes difficult the adjustment of the dose of meth-
adone in the infant during decreasing require-
ments.9 The multiple-dose vial of methadone con-
tains chlorobutanol (0.5 mg/mL), which is a seda-
tive, and 8% ethyl alcohol in the oral form.

Neuroleptics

Diazepam. Rapid suppression of narcotic with-
drawal symptoms has been observed in infants 
treated with diazepam (1.0 to 2 mg every 8 hours). 
The newborn infant has a limited capacity to me-
tabolize and excrete diazepam. Total elimination of 
diazepam and its metabolites may take 1 month or 
more.27 The infant’s suck reflex may also be de-
pressed, and late-onset seizures have been observed 
in infants treated with diazepam.28 Parenteral di-
azepam contains benzyl alcohol (1.5%) and sodium 
benzoate (5%), which may displace bilirubin for 
conjugation and excretion; therefore, use of diaze-
pam is contraindicated in a jaundiced infant or a 
premature infant.29 Nathenson et al30 measured albumin 
binding capacities of addicted infants 
treated with diazepam and found some decrease in 
albumin binding capacity.

In addition, parenteral diazepam contains ethyl 
alcohol (10%) and significant quantities of propyl-
ene glycol (40%). Cerebral and hepatic dysfunction 
and hyperosmolation with an osmolar gap have been 
reported in infants receiving large quantities (10 
ML/24 h) of parenteral multivitamins which con-
tain 30% propylene glycol.31,32

Chlorpromazine. The CNS and gastrointestinal 
symptoms produced by narcotic withdrawal are 
abbreviated by chlorpromazine. A dosage of 2.2 to 3 
mg/kg/24 h in divided doses every 6 hours intra-
muscularly or orally has been used in infants. Oc-
casionally, hypothermia may develop. The abnor-
malities in rapid eye movement (REM) sleep ob-
served during withdrawal are not alleviated by 
chlorpromazine. Some chlorpromazine metabolites 
are eliminated slowly over an 18-month period in 
adults; therefore, a prolonged excretion time may 
be anticipated in the neonate.31 Chlorpromazine 
contains sodium chloride (6 mg/mL), sodium bis-
ulfite, and sulfite (2 mg/mL). The multidose vial 
contains benzyl alcohol (2%).

Sedatives

Phenobarbital. Hyperactive behavior in the in-
fant who manifests narcotic withdrawal is modified 
by administration of phenobarbital, but the drug 
does not relieve the gastrointestinal symptoms. 
Large doses of phenobarbital may significantly sup-
press the CNS of the infant, may impair the suck 
reflex, and may delay the bonding between mother 
and infant. Elixirs of phenobarbital contain 14% to 
25% alcohol. The parenteral forms contain propyl-
ene glycol (67.8%), ethyl alcohol 10%, and benzyl alcohol 1.5%. The therapeutic blood level of phenobarbital necessary for control of narcotic withdrawal is not known. Finnegan et al used a neonatal loading dosage of 16 mg/kg/24 h of phenobarbital that produced blood levels of 20 to 30 µg/mL, which effectively controlled symptoms of narcotic withdrawal. A blood level should be obtained 24 to 28 hours later and the maintenance dose adjusted according to the infant’s symptomatology as determined by the abstinence score and the phenobarbital plasma level. Finnegan et al reported that maintenance doses of 2 to 8 mg/kg/24 h were required to control withdrawal symptomatology and maintain phenobarbital plasma levels. After the infant’s condition has stabilized, the maintenance dose should be decreased to allow the drug level to decrease by 10% to 20% per day.

**Antihypertensive Agent**

Clonidine has been shown to reduce withdrawal symptoms in adult opiate addicts. It has been administered to two neonates withdrawing from maternal methadone. More data are required to define the role of clonidine in the treatment of neonatal withdrawal.

**GENERAL CARE OF THE NEONATE**

Medications should be administered at the time of feeding in order to limit the number of times the infant is disturbed. When vomiting is a problem, oral drugs may be administered 30 minutes before a feeding. After a stabilizing dose is attained, the drug dose should be maintained so that the infant sleeps well, eats effectively, and gains weight for a period of three to five days; then the dose may be tapered. The physician may be hesitant to taper the dose of medication; this hesitancy may result in prolonging the infant’s hospitalization and drug therapy. The abstinence scoring sheet and changes in weight may be used to determine objectively the rapidity with which drug therapy should be tapered. Irritability and tremors should not be used as a criteria for continued drug administration as subacute symptoms of irritability, tremors, and poor sleeping patterns may last until age 6 months.

**FOLLOW-UP CARE**

Optimal treatment of the infant requires a team approach by a physician who is knowledgeable of the symptoms and therapy of neonatal withdrawal and who communicates with the parents; a nursing staff willing to tolerate the symptoms of the infant and willing to incorporate the parents into the total care of the infant; and a social service worker who can win the confidence of the parents and thus determine the parents’ ability to care for the infant after discharge from the hospital.

The period of treatment in the hospital is the time when both parents learn to help care for their infant. The infant who is withdrawing from a drug is a very difficult infant with whom to bond and with whom to live on a 24-hour basis; the caretakers should be provided constant emotional support. Participation of the parents in the care of their infant in the hospital assists them in gaining confidence in interpreting the infant’s symptoms and decreases the demands for medication sought for subacute symptoms of withdrawal once the infant is discharged from the hospital. No infant born to a known drug abuser should be discharged home on drugs as the parents may sympathetically use the drug for a longer period of time than is indicated or they may use the drug to supply their own need for drug replacement. Parents of infants who are withdrawing from drugs prescribed to the mother for medical purposes have strong guilt feelings and tend to overreact to the symptoms demonstrated by the infant.

Recurrence of withdrawal symptoms in the infant may develop after discharge from the hospital. It is essential that the hospital staff establish rapport with the parents so that they will return the infant to the hospital for treatment in this event. Sudden infant death syndrome (SIDS) and acquired immunodeficiency syndrome (AIDS) have been observed in infants born to methadone and heroin users. In one study, the incidence of SIDS was correlated with the severity of the infants’ withdrawal symptoms while in the nursery.

There should be a long-term follow-up of the physical and mental development of any infant who is withdrawing from maternal drugs.

**AGENTS PRODUCING SYMPTOMS SIMILAR TO THOSE OF NARCOTIC WITHDRAWAL**

Other maternal medications may produce in the infant a symptom complex similar to that of narcotic withdrawal (Table 1). The symptoms observed in the infant may represent withdrawal or intoxication and may last for variable periods of time (days to months).

In general, infants who demonstrate intoxication from maternal drugs require mostly supportive care during the period of excretion of the drug rather than administration of additional pharmacologic agents that the infant must metabolize and excrete. In cases of severe symptomatology, drug therapy may be indicated for patient comfort.

Infants who manifest adverse reaction to maternal psychotropic agents and who require pharma-
<table>
<thead>
<tr>
<th>Drug</th>
<th>Symptoms</th>
<th>Duration of Symptoms</th>
<th>W/I</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Hyperactivity, crying, irritability; poor suck, tremors, convulsions, onsets of symptoms at birth, poor sleeping patterns, hyperphagia, diaphoresis</td>
<td>18 mo</td>
<td>W</td>
<td>42–44</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Tremors, poor sleeping patterns, feeding difficulty, abdominal pain</td>
<td>9 mo</td>
<td>I</td>
<td>45</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Irritability, severe tremors, hyperacusis, excessive crying, vasomotor instability, diarrhea, restlessness, ↑ tone, hyperphagia, vomiting, disturbed sleep; onset 1st 24 h of life or at 10–14 d of age</td>
<td>4–6 mo Rx</td>
<td>W</td>
<td>46–49</td>
</tr>
<tr>
<td>Bromide</td>
<td>Lethargy, dilated pupils, hypotonia, hyperpnea, high-pitched cry, feeding difficulty, ↓ reflexes</td>
<td>2½ mo, 5 d Rx</td>
<td>I</td>
<td>50,51</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Irritability, tremors; symptoms may start at 21 d</td>
<td>9 mo, 1½ mo Rx</td>
<td>W</td>
<td>52</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Extrapyramidal dysfunction, intention tremor, opisthotonos, mask-like faces; onset 1st 24–36 h</td>
<td>9 mo, 12wk Rx</td>
<td>I</td>
<td>41,53</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Hypothermia, cyanosis, tremors; onset 12 h of age</td>
<td>4 d Rx</td>
<td>W</td>
<td>54</td>
</tr>
<tr>
<td>Desmethylinipramine</td>
<td>Breathelessness, cyanosis, ↑ HR, ↑ RR, diaphoresis, irritability, feeding difficulty, weight loss</td>
<td>10–30 d</td>
<td>I</td>
<td>55</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Hypotonia, poor suck, hypothermia, apnea, ↑ hyporeflexia, tremors, vomiting, hyperactivity, tachypnea, (mother multiple drug therapy)</td>
<td>8 mo, 10–66 d Rx</td>
<td>I</td>
<td>56,57</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Tremulousness, diaphoresis. Onset 5 d of age</td>
<td>9 d Rx</td>
<td>I</td>
<td>58</td>
</tr>
<tr>
<td>Ethchlorvynol</td>
<td>↑Lethargy, jitteriness, hyperphagia, irritability, poor suck, hypotonia, (mother receiving multiple-drug therapy)</td>
<td>? 10 d Rx</td>
<td>I and W</td>
<td>59</td>
</tr>
<tr>
<td>Glutethimide</td>
<td>↑ tone, tremors, opisthotonos, high-pitched cry, hyperactive, irritable, &quot;colic&quot;</td>
<td>6 mo</td>
<td>W</td>
<td>60</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Tremors, irritability, hyperactivity, jitteriness, shrill cry, myoclonic jerks, hypotonia, ↑ RR, ↑ HR, feeding problem, clonic movements (Mother receiving multiple therapy)</td>
<td>5 wk Rx</td>
<td>W</td>
<td>61</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Cyanosis, respiratory distress, vasomotor instability, irritability, hypokinesia, convulsions, jerky movements, ↑ RR, autonomic dysfunction, hyperactivity, belly dance movements of abdomen before voiding</td>
<td>? 6 d</td>
<td>I</td>
<td>62</td>
</tr>
<tr>
<td>Lithium</td>
<td>Respiratory distress, lethargy, cyanosis, poor suck, hypotonia</td>
<td>10 d</td>
<td>I</td>
<td>63,64</td>
</tr>
<tr>
<td>Local anesthesia</td>
<td>Acidosis, convulsions, ↓ HR, opisthotonos, neurologic depression, apnea, spontaneous movement, ↓ responsiveness, ↑ reflexes, abnormal oculomotor reflexes, death, hypotonia, fixed pupils</td>
<td>Related to Rx, excreted 1st 24 h</td>
<td>I</td>
<td>65–69</td>
</tr>
<tr>
<td>Magnesium sulphate</td>
<td>Respiratory depression, hypotonia, convulsions, death</td>
<td>Depends on Rx</td>
<td>I</td>
<td>70,71</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Irritability, tremors, poor sleep patterns, abdominal pain</td>
<td>9 mo, 3 mo Rx</td>
<td>W</td>
<td>45</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>Jitteriness, hypotonia, vomiting, lethargy, vertical nystagmus</td>
<td>18 d + Rx, 8 da + Rx</td>
<td>I</td>
<td>72,73</td>
</tr>
<tr>
<td>Theophylline</td>
<td>↑ HR, gagging, vomiting, jitteriness, opisthotonos</td>
<td>2 d</td>
<td>I</td>
<td>74</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>? Late-onset, extrapyramidal dysfunction</td>
<td>9 mo, 2–3 d Rx</td>
<td>I</td>
<td>53,57</td>
</tr>
</tbody>
</table>

*Abbreviations used are: HR, heart rate; RR, respiratory rate; Rx, refers to infant treated with pharmacologic agents and the natural course of the symptoms may have been shortened.
### TABLE 2. Pharmacologically Active Excipients in Products Used to Treat Neonatal Withdrawal*

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anise oil</td>
<td>Tincture of paregoric (po)</td>
</tr>
<tr>
<td>Benzoic acid and sodium benzoate</td>
<td>Diazepam (P)</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>Chlorpromazine (P)</td>
</tr>
<tr>
<td>Camphor</td>
<td>Diazepam (P)</td>
</tr>
<tr>
<td>Chlorobutanol</td>
<td>Methadone (P)</td>
</tr>
<tr>
<td>Ethyl alcohol</td>
<td>Methadone (po)</td>
</tr>
<tr>
<td>Opium alkaloids</td>
<td>Opiate tincture (po)</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Diazepam (P)</td>
</tr>
<tr>
<td>Sodium bisulfite and sulfate</td>
<td>Chlorpromazine (P)</td>
</tr>
</tbody>
</table>

* Abbreviations used are: P, parenteral; po, per os (by mouth).

Pharmacologic therapy are best treated with phenobarbital as it produces fewer adverse effects than the use of neuroleptic agents in the neonate. Diphenhydramine has been used in one infant thought to be having an adverse reaction to a phenothiazine agent.41

Infants who are withdrawing from maternally acquired barbiturates should be administered phenobarbital if pharmacologic treatment is necessary. The therapeutic plasma level necessary to treat barbiturate withdrawal is not known. The calculated loading dose (10 to 15 mg/kg/24 h) of phenobarbital should be given in divided doses over a 24-hour period and followed by a maintenance dose of 3 to 5 mg/kg/24 h. Blood levels should be monitored to prevent intoxication. Infants rarely require phenobarbital administration for longer than 6 to 8 weeks.

### SUMMARY

The Committee on Drugs of the American Academy of Pediatrics recommends that thoughtful consideration be given to the need for administration of pharmacologic agents to newborn infants who have symptoms of drug withdrawal. Supportive care should be the first line of therapy, and objective methods such as an abstinence scoring sheet should be used to determine the need for instituting and then discontinuing pharmacologic treatment. When appropriate, specific drug therapy should be used for treatment of withdrawal symptoms (ie, phenobarbital for phenobarbital withdrawal and opiate for opiate withdrawal). Attention should be given to potential adverse effects in the infant resulting from excipients present in many of the drugs (Table 2).

The information provided herein should serve as a guide for the physician in providing supportive care and pharmacologic treatment of the infant suffering from drug withdrawal.

**REFERENCES**

23. Deleted in proof
61. Prenner BM: Neonatal withdrawal syndrome associated


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### A DIFFERENCE IN THE FAMILY

Sometimes outsiders accept [a disabled] child but expect unreasonable sacrifices of his parents. Lucy Forrest described...the ways that neighbors and strangers helped her and her husband implement a demanding treatment plan for Christopher. Volunteers came in daily to 'pattern' the little boy; contributions helped the family finance bimonthly trips to a distant clinic. But this support given freely during the early months when the Forrests devoted every minute to their baby, almost evaporated when they started to pick up the threads of their previous life. Specifically, when Lucy began to repaper their new house, some of the volunteers acted shocked and even hostile. The reaction wounded the young couple; they felt the world exacted a heavy price for its sympathy, asking that they devote their entire lives to their hurt son and give up the pleasures others take for granted.

Submitted by Student

### Neonatal Drug Withdrawal

_Pediatrics_ 1983;72;895

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