DRUGS AND BEHAVIORAL DEVELOPMENT

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INTRODUCTION

Drugs are used during pregnancy and lactation by mothers who suffer from depression, hypertension, epilepsy, asthma, insomnia, phobia, and other neurological and psychiatric disorders. These drugs include imipramine, α-methyldopa, clonidine, reserpine, diazepam, phenobarbital, haloperidol, etc. Moreover, drugs are used to treat conditions that threaten the pregnancy, e.g., sex steroids (progesterone) are presumed to prevent spontaneous abortion. In addition, there is much self-medication including alcohol and opiates. Nearly all these drugs can enter the fetal circulation, following maternal administration, either through the placenta or via the mother’s milk. The absence of a blood-brain barrier and the higher accumulation of these chemicals in brain cells make the fetal (and neonatal) brain a major target of its mother’s medication. The use of most of these drugs is only discouraged by physicians (and by the companies that make them) during the first trimester of gestation. However, rapid growth of the brain and emergence of behavioral states in both man and other mammals (e.g., the rat) take place during the second half of gestation and the neonatal period. During this period the brain appears to be very sensitive to the effects of centrally acting drugs, resulting in the functional deficits that are studied in behavioral teratogenicity. Behavioral teratogenicity is the study of subtle neurobehavioral changes that can be induced in the developing child by a variety of environmental factors including drugs. However, the enormous variation in what is called “normal” behavior often makes it very difficult to demonstrate subtle effects of drugs. Neurobehavioral impairments such as short attention span, attentional distractibility, perceptual motor disturbances, sleep disturbances, and subtle and specific disabilities in certain types of learning tasks are, as Hutchinson emphasizes, so prevalent and nonspecific that they may obscure etiological identification, but they are, in fact, the cleft lip and cleft palate of behavior.

The behavioral teratogenicity of many centrally acting drugs that are commonly used during pregnancy has mainly been investigated by monitoring the behavioral repertoire of experimental animals after termination of the treatment. These tests have been carried out either when the animals were still young or when they were adults. Parallel human epidemiological studies have also been carried out to supplement the animal results. One of the difficulties that is encountered is that the influence of drugs on behavior must be rather strong to be detected by conventional tests after terminating the drug treatment. In addition, the drug does not necessarily have the same effect on behavior during chronic exposure as it does after exposure, i.e., long-lasting behavioral consequences. If we test an animal in a complex learning paradigm, the results of its performance may be very difficult to interpret, since we do not know at what level (motor, sensory, affective, learning, etc.) the effect is. Thus, it is very important in behavioral teratogenicity experiments to use a battery of tests in which many aspects of animal behavior can be tested.

Several facets of behavioral teratogenicity — including test paradigms, experimental design, and behavioral outcomes — have been discussed in previous reviews. The present review attempts to describe developmental aspects of behavior in the rat, an animal commonly used in experimental studies, with emphasis on the fact that many of the behavioral tests are good indicators of the central effects of the drugs and might help in understanding the mechanisms by which later behavioral abnormalities take place. In the second part of this paper we will review the effects of a few centrally acting drugs on the development of human behavior. Particular attention has been paid, in this review, to the development of the
behavioral states, since they influence the outcome of the other behavioral measures, yet they have been neglected so far in behavioral teratogenicity.

We will describe the influence of a few centrally acting drugs and will attempt to introduce this developmental approach rather than to review the effect of every drug. Emphasis is put on the fact that an immature unborn or newborn brain is more vulnerable than that of the adult, and that the fetal or neonatal brain is influenced chronically, during the treatment, in ways that are not necessarily comparable to the effects on the mother. It is generally claimed that behavioral influences in immature animals are not stable and reproducible measures, so that they have often been neglected in conventional teratological screening tests. However, this point of view has been challenged in a recent symposium and workshop sponsored by the National Center for Toxicological Research and the National Institute of Occupational Safety and Health (September 3 to 6, 1985; Cincinnati, Ohio). We will show that spontaneously generated behavior in the immature rat can be measured systematically and can reveal severe effects of treatments at doses below those inducing teratological effects.

DEVELOPMENT OF BEHAVIOR

Developmental Aspects of Behavioral States in the Rat: Influence of Drugs

The rat is an altricial mammal, i.e., it is born very immature. The gestational period of the rat is 21 days. A newborn rat is comparable to a 7-month-old human fetus from various structural and functional aspects of brain development. A brief observation of a newborn rat leaves one wondering at the rapid alteration of the different behavioral states, i.e., wakefulness (W), quiet sleep (QS), and rapid eye movement sleep (REM). The behavioral states are generated within the brain and may influence the outcome of behavioral tests dramatically. Unfortunately, in most of the conventional teratological studies, behavioral states are not taken into consideration. During neurological examination of newborn and young children, however, much attention has been paid to the behavioral states, although not in relation to behavioral teratology.

Developmental aspects of the behavioral states have been studied in various mammals including the human. Behavioral states are a constellation of different physiological and behavioral variables which are stable over time and recur repeatedly, not only in the same subject, but also in a similar way in others. Considering all the different criteria used by different investigators, one can define the three different behavioral states as follows:

- **W** — characterized by the presence of high postural muscle (neck or chin) tonus, presence of different types of more or less coordinated and presumably goal-directed behavior, such as head flexion and dorsiflexion, head raising, head shaking, nipple searching, rhythmic fore- and hind-paw movements, or locomotion. Eye movements are also present during this state. The open eyes is another W criterion which obviously can only be used after eye opening (around day 14 postnatal). Respiration rate is rapid, regular (sometimes irregular during movement). Electroencephalogram (EEG) shows dominant power peak in higher EEG frequency band (the so-called low amplitude, fast EEG activity). In our experience EEG can only be used reliably as a state criterion in the rat after day 14 of postnatal life.
- **QS** — defined on the basis of a moderately low level of postural muscle tonus, absence of gross movements (although startles can be present), absence of eye movement, regular respiration. Eyes closed, EEG showing dominant power peak in lower EEG frequency band (the so-called high amplitude, slow wave EEG).
- **REM** — characterized by the absence of tonus in postural neck muscles, presence of eye movements, myoclonic jerks and twitches of the extremities, pinna movement, lack of gross coordinated body movement, eyes closed, rapid-irregular and shallow
breathing. Heart beat variation is used as a state criterion in human fetus and neonate, but is not useful in the definition of the behavioral states in rats. Other parameters which are not exclusive to a particular behavioral state and are not consistently present during the state are the so-called state-concomitants such as mouthing (or sucking). Since behavioral states are exclusively generated in the brain, they can be used as a good indicator of hazards to the developing brain. Different state criteria develop at different stages of development. Moreover, neuronal mechanisms responsible for coherence among the different state criteria only develop at later stages of development, thereby generating true behavioral states. These considerations should be taken into account when using behavioral states as a screening test for behavioral teratogenicity.

In the rat the first behavioral state criterion which can be recorded is gross and jerky movements. These movements appear around day 16 to 17 of gestation. In the 16- to 17-day-old fetus little activity occurs, with long intervals of inactivity. The frequency of activity increases greatly, reaching a peak at 18 days, whereupon it declines to a lower level until term. Three types of movements can be distinguished: generalized body movement (all parts of the body participate), regional movement (one region of the body is engaged such as head and fore limbs), and local movement (only one part moves).

In the human fetus the first movements appear at 7.5 weeks postmenstrual age, by 9.5 weeks fetal motility occurs quite frequently, and by 15 weeks all the different types of movement patterns can be distinguished such as general body movement, startle, hiccup, breathing, isolated arm and/or leg movement, retroflexion, rotation and anteroflexion of the head, jaw movements, sucking and swallowing, hand-face contact, stretch, yawn, and rotations. These movements closely resemble those observed in preterm and full-term newborn infants. Eye movements appear at 16 weeks gestation and become more frequent at 24 weeks. It seems that although separate criteria of the behavioral states are present at a very early age, the mechanisms which are responsible for coherence of these characteristic criteria develop much later. In humans, true behavioral states can be distinguished by 32 weeks of postmenstrual age. Unfortunately, only body movements have been recorded so far in rat fetuses, so that no reliable information is present on behavioral states. However, since movements appear rather late (16 to 17 days gestation), there is probably very little, if any, organization of behavioral states in the rat before birth.

In the newborn rat we could demonstrate two distinct behavioral states which can be distinguished on the basis of neck muscle tonus, eye movements, and gross coordinated or jerky body movements (Figures 1 and 2). Although not all state characteristic criteria can be fulfilled at this stage of development, one can rather confidently identify these two types of spontaneous behaviors (W and REM) by observation and by monitoring them physio-
logically. During the lst week of life rats spend very little time in W under optimal environmental condition, and are mostly in REM sleep. There are also periods, of course, during which the behavioral state cannot be differentiated. During the 2nd week of life the number/duration of quiet periods during sleep increases. By 14 days of age three different behavioral states (W, QS, and REM) can be defined. At this moment there is also a sharp decline in the amount of time spent in REM and an increase in W and QS.

Unfortunately, only the effects of a few drugs on behavioral states have been tested during development.26

Our own studies have shown clear disturbances of sleep-wake patterns following administration of antidepressant drugs (such as clomipramine20 or antihypertensives (such as clonidine or α-methyldopa27-28). In the developing rat these drugs dramatically reduce the amount of time spent in REM as well as the density of eye movements during sleep. The only comparable/similar data available in man are from heroin- and methadone-addicted mothers: both drugs suppress REM in adults. So far the postnatal studies that have been carried out show the effects of drug withdrawal. These babies showed a rebound phenomenon similar to that occurring after termination of REM deprivation in adults, i.e., an increased amount of REM and behavioral-state inconsistency.29 Another explanation for the observed data can be the retardation in development, since we know that premature babies also show a higher amount of REM and behavioral-state inconsistency. Although not directly studied in fetal and neonatal offspring of mothers exposed to drugs, it is known from adult studies that the majority of centrally acting drugs suppress REM sleep and disturb the sleep-wake rhythm20 by affecting different neurotransmitters such as noradrenaline (e.g., α-methyldopa and clonidine), serotonin (e.g., imipramine and clomipramine), GABA (e.g., diazepam), acetylcholine (e.g., atropine or scopolamine), and drugs which suppress reticular formation activity (e.g., phenobarbital).

Since behavioral states determine the level at which the central nervous system (CNS) functions, the REM suppressant effect is a good indicator for the effects of drugs on brain function. The potency of centrally acting drugs in suppressing REM varies from total suppression by a variety of antidepressant and antihypertensive drugs to partial suppression by sleeping pills and tranquilizers. More studies are required to evaluate the influence of chronic drug exposure during development on animals and man.

Other Behavioral Tests during Early Development in the Rat: Influence of Drugs

In addition to monitoring the behavioral states, when testing behavioral teratogenicity one must include both several tests of cognitive, affective, and arousal behavior and general developmental parameters. These tests may include: growth parameters, hormonal determination, thermoregulation, reflexes, motor function, sensation, learning and problem solving, memory, activity, exploration, circadian rhythm, responsiveness to stress, aggregation, and other social interactions.
Physical Growth and Maturation

Physical growth and maturation includes maternal body weight, offspring body weight, time of upper and lower incisor eruption, eye opening, ear opening, testicular descent, and vaginal opening. The dose commonly used of central acting drugs does not severely affect the physical maturation, except for a reduction in body weight that may lag 1 day behind the controls.

Thermoregulation

Body temperature can be recorded by removing the pup from the nest and measuring body temperature after 30 sec. In addition, the ability of the pup to regulate its temperature can be tested by putting the pup in a box filled with home shaving wood at room temperature and measuring its body temperature after 40 min of isolation.31

Reflexes

Righting reflex — The pup is placed on its back on a flat Formica® table and released. The time until all four paws return to the surface is recorded.32

Grasping reflex — This can be tested in two ways: the first is to stroke the ventral surface of a forepaw with a 3-mm-diameter glass rod. Positive response is recorded when the pup flexes the foot to grasp the rod. The second is to lift the pup up to a horizontal rod and note whether or not the pup grasps the rod and how long it hangs on to the rod before dropping (20 mm) to a soft pad.32

Rooting reflex — The pup is stimulated bilaterally in the face region by stroking the muzzle with a finger. The pup crawling forward, pushing the head in a rooting fashion is recorded as a positive response.32

Auditory startle reflex — In this test the animal is put over an accelerometer, and startle response to a loud noise (toy cricket) is measured by the accelerometer.

Sucking

Using an anesthetized lactating mother, the time the pup attaches to the nipple, the duration of sucking, the strength of sucking (using electromyogram [EMG] recording), and the number of times the rat pup shifts from one nipple to another can be measured.

Swimming

The ability of the pup to keep its head and nose above water, the parallel position of the body with respect to the surface of the water, and forelimb activity are measured. One-week-old pups cannot swim. In an early swimming pattern (day 7 to 15), animals perform rapid contralateral flexor-extensor movements of their forelimbs during swimming. By day 12 the rat is able to keep its head above water. By day 22, the pup swims like an adult rat33 with its forelimbs extended.

Olfactory Discrimination Task

The pup is put in a box with familiar shaving wood on one side and an unfamiliar olfactory cue on the other side. The time that passes until the pup chooses one side of the box as well as the side chosen is recorded.

Activity and Circadian Rhythmicity

The general spontaneous activity of the animal can be tested using an accelerometer and a photocell activity meter. This can be done in individual boxes filled with home shaving wood. The activity can also be measured in an open field. Since the activity pattern shows circadian rhythmicity by 3 to 4 weeks of age, 48-hr recordings will be useful in determining this endogenous phenomenon, presumably generated in the suprachiasmatic nuclei of the
hypothalamus. Circadian rhythmicity can also be seen in food and water intake and in sleep-wakefulness.

Learning

**Auditory stimulus discrimination** — Campbell and Haroutunian developed a technique to measure the development of perception, using the heart rate orientation response (marked cardiac deceleration to novel stimuli). Animals are habituated to a 1600-Hz tone in 15 trials. On trial 16, the stimulus frequency is changed into one of seven tones distributed on either side of the habituated frequency. Rats that are 20 days old respond to this experimental paradigm, while 16-day-old rats do not.

**Mazes** — Water mazes are those in which the subject has to swim to find a safe platform in the correct alley, the latter being indicated by light. Another type of maze is the running maze in which food-deprived rats have to run into one of the two alleys in which the food is placed.

**Active and passive avoidance** — These tests are similar to the ones used for adult rats, but they use a simpler paradigm.

**Taste aversion learning** — In this test the pup is conditioned by injection of either saline or lithium chloride immediately after the infusion of a novel saccharin solution into the oral cavity. Testing takes place 12 hr after conditioning. Animals are again infused with saccharin to assess changes in intake, without any injection. Pups that are 15 days old already show a reduction of saccharin intake as a function of lithium chloride experience.

**IMPLICATIONS OF BEHAVIORAL TERATOGENICITY IN HUMAN**

As evident from the previous section, our means of measuring behavior in fetal and neonatal animals is growing rapidly. However, these means have not yet been fully employed for determining the hazards of drugs on behavior (see Table 1). A few exceptions to this are reviewed in the Proceedings of NCTR collaborative studies. Even less epidemiological data are available on humans. Most human data have been obtained shortly after terminating drug treatment. Although such data may indicate lasting consequences of drugs, they are difficult to interpret, since they might simply be the acute effects of drug withdrawal. Following a new approach in developmental psychobiology which Oppenheim calls ‘ontogenetic adaptations’, the behavior of the developing animal is considered not as an inadequate antecedent of adult behavior, but rather as perfectly organized behavior, adapted to the age of the animal. According to this point of view, in behavioral teratogenicity in which we are interested in defining subtle behavioral changes (which is usually the case after a clinical dose of drugs), we should study the spontaneous and elicited behavior of the animal both in relation to its age and in its exchange with the social environment.

Among the better-studied agents which are known from epidemiological evidence to produce structural malformations and/or neurobehavioral deficits in humans are alcohol, anticonvulsants (including hydantoin, barbiturates, and benzodiazepines), and opiates. In fetal alcohol syndrome, the characteristic defects produced by chronic maternal alcoholism include growth deficiency, mental retardation, dysmorphic craniofacial features, microcephaly, variable joint anomalies, cardiac defects, and poor motor coordination. Fetal hydantoin syndrome, described by Hanson and Smith, includes craniofacial malformation and hand anomalies in infants born to mothers who received phenytoin during gestation. Functional neurobehavioral changes include pre- and postnatal growth deficiency and mental retardation. Moreover, Stoops and Hart reported that children with epilepsy who were attending normal school had significantly lower reading skills if they had received phenytoin for at least 2 years, as compared to other anticonvulsants. When phenobarbital has been
Table 1
BEHAVIORAL TERATOGENICITY OF DRUGS AND ALCOHOL DURING EARLY DEVELOPMENT IN RAT

<table>
<thead>
<tr>
<th>Physical growth and maturation</th>
<th>Antihypertensives (clonidine, α-methyldopa)</th>
<th>Antidepressants (imipramine)</th>
<th>Antiepileptics and sedatives (diazepam and phenobarbital)</th>
<th>Opiates (heroin and methadon)</th>
<th>Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermoregulation</td>
<td>Delayed</td>
<td>Delayed</td>
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<td>Sucking</td>
<td>Impaired</td>
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<td>Impaired</td>
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<td>Behavioral states</td>
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<tr>
<td>% REM sleep</td>
<td>Reduced</td>
<td>Reduced</td>
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<tr>
<td>Number of eye movements</td>
<td>Reduced</td>
<td>Reduced</td>
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<td>Reflexes</td>
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<td>Righting, grasping, rooting</td>
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<td>Auditory startle reflex</td>
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<td>Swimming ability</td>
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<td>Olfactory discrimination</td>
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<td>Activity</td>
<td>Hyperactivity</td>
<td>Hyperactivity</td>
<td>Hyperactivity</td>
<td>Hyperactivity</td>
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<tr>
<td>Circadian rhythmicity (activity, drinking, sleep-wake)</td>
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<td>Learning</td>
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<td>Auditory stimulus discrimination</td>
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<td>Mazes</td>
<td>Impaired</td>
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<td>Active and passive avoidance</td>
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<td>Taste aversion learning</td>
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Part C: Factors Influencing Brain Development

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taken during pregnancy the neonates may suffer withdrawal symptoms. Desmond et al. reported that babies born to mothers who received phenobarbital during pregnancy may be irritable and overexcitable for months later. Although phenobarbital was given on a large scale in the late 1960s and early 1970s (also to newborn babies with jaundice), the possible neurological effects of its use in this age group have not been explored. In early childhood excitement, irritability, fearfulness, and aggression appear to be specific effects of barbiturates, since they are not seen with other anticonvulsants (reviewed in Reference 41).

The floppy infant syndrome has been described in babies born to women treated chronically with diazepam during pregnancy. This syndrome includes the following characteristics: failure to start breathing, shallow inadequate respiration, periodic cessation of respiration, floppiness, hypotonia, hyporeflexia, subnormal temperature, poor sucking. Doses larger than 30 mg given to the mother during labor were shown to result in low Apgar scores at birth, apneic spells, hypotonia, reluctance to feed, and an impaired metabolic response to cold stress. In the fetus, diazepam causes reduction of the beat-to-beat heart rate variability. In some infants withdrawal symptoms were described after prolonged intrauterine exposure to diazepam. These include tremor, hyperactivity, hypertonicity, and irritability. These symptoms lasted 10 days to 6 weeks in infants whose mothers received diazepam therapy during 3 to 5 months of pregnancy.

Although the influence of classical teratogens on human development is easy to establish, as in the cases of thalidomide, fetal alcohol syndrome, and Minamata syndrome (induced by methylmercury), this is not so easy for drugs used in the clinical dose range which include subtle behavioral defects. Although the Apgar score is routinely used in neonatology, it is not a sensitive test to detect subtle changes at the behavioral level. Many investigators are now using the Brazelton Neonatal Assessment Scale, Prechtli's neurological examination of the full-term infant, and Bayley Scales of Mental Development.

In the Brazelton Neonatal Assessment Scale (reviewed in Reference 49), several important items are considered which reflect: (1) the newborn's organization in response to state control, including habituation, peak of excitement, lability of state, rapidity of build-up, irritability, and self-quieting; (2) the newborn's motoric organization, including tonus, pull to sit, motor maturity, defensive movement, hand to mouth, and general activity; (3) the newborn's physiological stability in response to stress, including tremor, color change, and startle; and (4) the newborn's interactive capacities, including orientation to animate visual or auditory stimuli, orientation to animate visual (face) or auditory (voice) stimuli, orientation to animate visual and auditory (face and voice) alertness, cuddliness, and consolability. A good example of this new development in assessment of the neurobehavioral consequences of drugs on human development is the result of investigation in offspring of opiate-addicted mothers. Davis and Shanks reported that opioid-dependent infants exhibit hyperexcitability, irritability, tremors, hypertonicity, impaired nutritive sucking, severe sleep deficit, and hyperthermia. Two characteristics of these infants are (1) lability of "state" with frequent shifts through the various stages of sleep and wakefulness and (2) hyperactivity, including jerky movements and a purposeless "en masse" type of activity. These babies are less alert, have a lower capacity to attend and react to noxious stimuli, and also habituate less to disturbing events. They are less cuddly, having less smooth or mature types of movements.

In both animals and human studies, prenatal exposure to opiates produces effects that occur in two phases. An acute phase consists of neonatal abstinence, hyperactivity, disturbed sleep, and increased lability of state. This early phase can be very prolonged: 20 to 25 days in rats, 3 to 6 months in human. The second phase includes impaired organizational and perceptual abilities, poor self-adjustment, and in situations requiring motor inhibition, heightened activity. An example of a more subtle influence of prenatal drug exposure on human behavior comes from a recent study on the influence of prenatal anesthetic exposure. Two types of behavioral differences between control and anesthetic-exposed infants were
observed. First, exposed infants had total looking times at visual patterns nearly 50% larger than unexposed infants. Second, there were significant differences in preferences for some pairs of visual stimuli between the two groups.

One of the important aspects of the Brazelton Neonatal Assessment Scale and that of Prechtl is that these tests consider the behavioral state. We have emphasized the importance of examining behavioral states in animal studies in the previous section of this review. Several investigators have also examined behavioral states of passively dependent human infants. Schulman and Dinges et al. have found a significant decrease in QS and increased REM sleep in opioid-exposed neonates, a profile shared by many newborns at high risk for CNS impairment. Sisson et al. also found a decrease in both QS and REM sleep. Sisson concluded that since protein synthesis occurs during REM sleep, neuronal treatment of withdrawal is essential not only to relieve symptoms, but also to promote normal and necessary sleep patterns required for brain development. In support of the predictive values of the behavioral states, Becker and Thomas have recently shown a significant negative correlation between rate and intensity of REM ("REM storms") during REM sleep in 6-month-old infants and Bayley Scales of Mental Development at 1 year of age. They concluded that REM storms express dysfunction or delay in the development of central inhibitory feedback controls for sleep organization and phasic sleep-related events.

Despite growing literature in the field of human behavioral teratogenicity, it is very difficult to be certain about a causal relationship between pre- or perinatal drug exposure and behavioral outcomes. The major difficulty in studying subtle changes in human behavior is the presence of an enormous range of so-called "normal" behavior. Other factors such as the lack of comparable controls, social and economical state of the child, genetic and educational background, etc. further complicate the study of drug teratogenicity in human. However, in animal experimental studies many of these factors can be controlled, and although the implication of animal results to human health is questioned, empirical evidence is in favor of such an implicability. In our own studies on the significance of sleep and central monoamine neurotransmission during early development, we have found that chronic exposure of developing rats to antidepressant (clomipramine) or antihypertensive (clonidine) drugs results in disturbed adult sleep patterns (including an increased number of myoclonic jerks during REM sleep) and reduced sexual behavior in males. Comparable sleep disturbances have recently been reported in children born to hypertensive mothers treated with clonidine or α-methyldopa. Several other psychoactive drugs (including reserpine, pargyline, barbiturates, diazepam, and haloperidol) have been shown to impair reproductive function and sexual behavior in rats. Some of these agents may exert their demasculinizing effects by reducing the concentration of perinatal testosterone or disturbances of monoamines. Human studies of effects of these drugs on sexual behavior are lacking. However, another example of hazards of medicines found in animal studies that was confirmed in human is exposure to diethylstilbestrol (DES). Pre- or perinatal DES alters features of sexually dimorphic infantile social play in female rats, increases masculine mounting behavior, and decreases feminine lordosis (for review see Reference 62). Recent studies in 30 women aged 17 to 30 with documented prenatal exposure to DES showed increased bisexuality and homosexuality compared to control groups, although 75% of these DES women were still exclusively heterosexual.

In addition, prenatally estrogen-progesterone-exposed children have been found at the age of 4 to 21 years to be generally less self-confident, less sensitive, and more dependent and group oriented than normal children. An increased infertility and interference with sexual function were also found following prenatal estrogen injections. It is probable that as a consequence of prenatal drug or hormonal exposure, not only the sexual behavior, but also sexually dimorphic aspects of the brain are being affected. No study has addressed this possibility so far. However, a recent study in male rats, in which prenatal stress indicated
a reduction in the size of the sexually dimorphic nucleus (SDN) of the preoptic area to the extent that sexual differences diminished (normally the SDN is larger in males), suggests that this possibility is not far fetched.

CONCLUDING REMARKS

1. Centrally acting drugs are commonly used during pregnancy and lactation.
2. These substances pass the placenta; there is no blood-brain barrier to them and they accumulate to a larger extent in fetal brain than in maternal plasma.
3. Depending upon the stage of fetal development, these drugs may induce different defects. Behavioral teratogenicity is common following the use of these drugs, particularly if they are used during the last trimester of gestation in human or during the last few days of prenatal and the first 2 weeks of postnatal life in the rat.
4. It is now well established that behavioral tests can be sensitive and reproducible enough to be used for experiments on behavioral teratogenicity.
5. The rat is less susceptible to the influence of these drugs on behavior than the human both during the treatment and in regard to long-lasting consequences.
6. More appropriate animal models (such as the monkey) for behavioral teratogenicity of drugs used during prenatal life in human (which is quite different from the prenatal developmental period in rat) are required.
7. Use of ultrasound techniques for observing the behavioral states of the fetus during the last trimester, as well as complete neurological and behavioral examination of infants and young children, will improve our knowledge of behavioral teratogenicity of medicines in human.
8. In neurological examination of children, their perinatal medical history should be considered, particularly with regard to drugs used by their mothers.
9. In prescribing drugs to the pregnant mother during the last trimester, the beneficial influence of these chemicals on the mother should be evaluated against possible hazards to the child’s behavior.
10. Collaborative studies with the government drug regulatory agency, obstetricians, pediatricians, basic researchers, and pharmaceutical companies are required to help improve early diagnosis and prevent drug hazards on the development of behavior in human.
11. The rapid increase in the use of self-medication cases should be prevented by public educational programs.
12. The concept of behavioral continuity brought by Prechtl emphasizes the significance of any environmental (e.g., stress) or chemical (e.g., drugs, lead, methylmercury) factor that may disturb this continuity and result in abnormal or maladaptive behavior.
13. In evaluating the influences of drugs on behavior, attention should be paid to discriminate the effects of chronic exposure from those of acute withdrawal and long-lasting sequelae.

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