Behavioral Teratology: Birth Defects of the Mind

The effects of most drugs on human fetuses are unknown. Sometimes—the case of thalidomide is an outstanding example—investigators can link drugs to physical deformities. But birth defects can be covert as well as overt; they can affect behavior as well as anatomy. To many people, the idea that children may have lower intelligence or impaired behavior because they were exposed in the womb to certain drugs or foreign substances is at least as disturbing as the idea that they may be physically deformed.

The belief that drugs can cause behavioral birth defects is not new. Nevertheless, the actual testing of drugs for behavioral defects has, until recently, been something that everyone talked about but no one did, according to Patricia Rodier of the University of Virginia. This dearth of research stems from the fact that psychologists, who know how to test behavior, were unfamiliar with teratology, and teratologists, who know how to test for agents that produce birth defects, were unfamiliar with behavioral techniques.

Within the past few years this lack of communication has begun to be remedied. A number of investigators have applied the tools and expertise of behavioral psychology to detect behavioral birth defects and to implicate certain drugs as the causes of these defects, thereby establishing the new field of behavioral teratology.

As is so often true when a new field is established, behavioral teratology is still in need of guidelines and accepted procedures. Behavioral teratologists are looking for subtle and common defects—shorter attention span, lower intelligence, or hyperactivity, for example. The nature of these defects makes it difficult to pinpoint their causes in the human population.

Although researchers have now shown that a number of substances are behavioral teratogens in animals, they have so far only been able to detect a few behavioral teratogens in humans. They have reached no consensus on what behavioral tests to use in animal studies, how far to generalize from the animal studies to humans, and what behavioral tests could be designated as a standard test battery.

Each of the human behavioral teratogens that has been identified is a special case—for specific reasons it was easy to detect children exposed prenatally to these substances. The most firmly established human behavioral teratogens are drugs that also cause physical deformities of fetuses. Children who are born with these physical deformities are tagged; if their behavior or intelligence is abnormal, the drug that produced the physical deformities is immediately suspect. In this way, researchers recently established that children are more likely to be mentally retarded if their mothers were alcoholic or took thalidomide or the anticonvulsant drugs hydantoin or trimethadione during pregnancy.

Another class of drugs that seems to cause long-lasting effects on children's behavior is obstetric medications, which are drugs given to women during labor and delivery. The implication of obstetric medications as behavioral teratogens may have far-reaching consequences because these drugs are so commonly used. In a recent colloquium, Yvonne Brackbill of the University of Florida estimated that women are given medications in 95 percent of all labors and deliveries in this country.

Evidence that obstetric medications affect children's behavior comes from data from a large-scale prospective study being analyzed by Brackbill and Sarah Broman of the National Institute of Neurological and Communicative Disorders and Stroke. Brackbill and Broman are psychologists specializing in the development of infants and children.

Brackbill and Broman examined data on 3500 healthy full-term babies born to women who participated in the Collaborative Perinatal Project, a longitudinal study of more than 50,000 babies, which was overseen by the National Institutes of Health in the 1950's. These investigators studied only the healthiest women with the most uncomplicated pregnancies, labors, and deliveries and the healthiest babies. Thus they tried to rule out the possibility that the women in their sample who had medicated labors and deliveries also had more complicated pregnancies and births; had that been so, any less-healthy babies might have been a consequence of the complications rather than the drugs. In this select group, Brackbill and Broman find that obstetric medication affected the children's behavior at least through 7 years of age. According to Brackbill, these results are generally consistent with results of 35 smaller-scale cross-sectional studies conducted by other researchers.

Of particular significance, Brackbill says, is the finding, common to these studies, that the effects of obstetric medication are dose-related. The greatest effects are seen in children of women who received the strongest drugs (inhalant anesthetics) or the highest total doses of drugs. These effects are most pronounced in selected areas of cognitive function and gross motor ability. When the babies in these studies were tested at 4 months, 8 months, and 12 months of age, those whose mothers were heavily medicated lagged in their development of the ability to sit, stand, and move about. They were also deficient in developing inhibitory abilities, such as the ability to stop responding to redundant signals, to stop crying when comforted, and to stop responding to distracting stimuli. As they grew older, their development of language and cognitive skills lagged or was impaired.

It might be argued that the women who took no medication during labor and delivery were somehow different from those who did. Perhaps their labors were shorter and easier, for example, so their babies were in better condition when they were born. But implicit in this argument is the assumption that women and their doctors choose obstetric medications according to the women's individual needs.

A number of social scientists believe, however, that obstetric medication is usually chosen by doctors and hospitals as a routine procedure, somewhat independent of the women's requirements. For example, doctors in private hospitals commonly issue standing orders for obstetric medications. These are orders for drugs to be given in the physician's absence and are, by definition, orders based on a general condition or illness rather than individual needs. Moreover, results from the Collaborative Perinatal Project indicate that hospitals differ widely in the obstetric medications used in them. One hospital will tend to use inhalent anesthetics for cesarean sections, for example, whereas another will use local anesthetics. "These differences mean the decisions about what drugs to use are made by the hospitals," says Brackbill.

Brackbill points out that it is not surprising that obstetric medications have

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long-lasting behavioral effects on children. Important areas of the newborn's brain, particularly the hippocampus and the cerebellum, are not fully developed at birth and so are particularly vulnerable to damage. Obstetrical medication crosses the placenta rapidly, easily reaches the fetus's brain because the blood-brain barrier is immature, and is only slowly cleared from the newborn's body because the baby's liver and kidneys are functioning immaturely at birth.

Another class of human behavioral teratogens is the narcotics, including methadone and heroin. Although neither methadone nor heroin causes gross physical abnormalities in human fetuses, children exposed prenatally to these drugs have severely altered behavior.

That these narcotics are behavioral teratogens has significant consequences. Donald Hutchings of the New York State Psychiatric Institute cites estimates that 3000 babies are born each year to addicted women in New York City alone. This is one-third the number exposed to thalidomide worldwide. Because most of these addicted women are unable to care for their babies, they are placed in foster homes. The babies are difficult to live with, however, because their behavior is disturbed. Thus, says Hutchings, "no foster parents can tolerate these babies and they bounce from one foster home to the next."

Since babies born to addicted mothers are behaviorally disturbed from birth, researchers have suspected for some time that heroin and methadone are behavioral teratogens. The newborn babies of addicts exhibit what is called a neonatal abstinence syndrome, characterized by unusually strong reflex responses, tremors, irritability, excessive and high-pitched crying, disturbed sleep, and a voracious appetite accompanied by failure to gain weight. Later the children tend to be hyperactive and to have short attention spans.

Despite their suspicions that prenatal exposure to heroin or methadone permanently alters children's behavior, investigators have found it difficult to prove that these narcotics are behavioral teratogens. The problem, explains Hutchings, is that there are other confounding variables. Mothers addicted to these narcotics typically have poor diets, are heavy smokers, and often abuse other drugs, such as amphetamines, barbiturates, tranquilizers, and alcohol, as well. Moreover, babies born to these mothers are treated for days or weeks with barbiturates, phenothiazines, or hypnotics in order to alleviate their withdrawal symptoms.

To separate the effects of heroin or methadone from the effects of other drugs on the babies of addicts, investigators turned to animal studies. Sonya Sobrian of Howard University, for example, has found that rats exposed prenatally to morphine were hyperactive during the third and fourth postnatal weeks. This hyperactivity disappeared when the animals were 30 days old. Hutchings found that rats exposed prenatally to methadone behaved similarly and, in addition, he found their sleep cycles to be impaired. When Hutchings and his associates tested adult rats exposed prenatally to methadone, the rats overreacted on certain learning tasks. The results of the animal studies, in conjunction with the observations of the behavior of children, implicate these nar-

Teratogens Acting Through Males

Pregnant women and women who wish to become pregnant are usually warned not to smoke cigarettes, consume large amounts of alcohol, or take any drugs. Their husbands, on the other hand, are rarely, if ever, admonished to avoid known teratogens. Nevertheless, evidence is slowly accumulating that if males are exposed to teratogens before their offspring are conceived, the incidence of birth defects among those offspring may increase.

The first hint that teratogens administered to males may cause birth defects came 15 years ago in the wake of the thalidomide tragedy. Cecelia Lutwak-Mann of Cambridge University gave thalidomide to male rabbits before breeding them and found significantly higher death rates, presumably caused by congenital defects, among fetal and neonatal offspring.

In the years since Lutwak-Mann's study, researchers have found that a diverse group of animal teratogens cause birth defects when administered to male animals only. These teratogens include lead, narcotics, alcohol, and caffeine. For example, Justin Joffe and Lester Soyka of the University of Vermont report that methadone is a teratogen when administered to male rats only. The offspring of methadone-treated male rats are more likely to die before weaning, have lower birth weights, and to perform abnormally on at least one test of behavior. Moreover, the litter sizes of females mated to methadone-treated males are smaller than normal.

It is far more difficult to study teratogenicity in humans than in other animals. Nonetheless, men who are exposed to certain drugs may run an increased risk of fathering babies with birth defects. The best evidence comes from a 1974 study of operating-room personnel exposed to anesthetic gases. The wives of these men had significantly increased rates of spontaneous abortions, and their babies were more likely to have congenital defects than the offspring of unexposed men.

So far no one is certain how substances administered to males can cause birth defects. Joffe and Soyka list three possibilities. First, the drugs could damage the sperm itself, perhaps by impairing spermatogenesis or the maturation of sperm.

A second possibility is that the drugs act through the semen. A number of drugs are excreted in semen, including thalidomide, narcotics, and anticonvulsants. These drugs in semen enter the female circulation by passing through the vaginal walls and could possibly enter the circulation of the developing embryo at the placenta. They could also affect the embryo by some local action on the uterus.

The third possibility is that drug effects could be produced indirectly as a result of the action of drugs on the male. For example, methadone decreases plasma testosterone levels and sexual activity in men and laboratory animals. These effects of the drug, at least in animals, could alter the female's response to the males and thereby adversely affect the uterine environment at the time of implantation.

Although no one believes that drugs taken by males are a major contributor to birth defects, many investigators are now concluding that these drugs could cause at least a clinically significant number of birth defects. The phenomenon of drugs causing birth defects through their action in males alone is unexpected and peculiar. But it promises to be increasingly studied in the future.—G.B.K.

cotics as causes of childhood hyperactivity, Hutchings says.

Synthetic sex hormones also seem to be human behavioral teratogens, but in this case, the behavioral effects that have been detected are not necessarily detrimental. Until recently, obstetricians often prescribed synthetic estrogens (such as diethylstilbestrol), progestins, or a combination of the two for women whose pregnancies were at risk. Two years ago, the Federal Drug Administration tried to put a stop to this practice since the hormones were found not only to be ineffective in maintaining pregnancies but to cause increased incidences of congenital heart defects as well (*Science*, 26 November 1976, p. 926).

June Machover Reinisch of Rutgers University finds that prenatal exposure to sex hormones affects children's personalities but not their intelligence quotients (IQ's). Children exposed prenatally to progestins, which act like male sex hormones, were significantly more independent, individualistic, self-assured, and self-sufficient than their siblings who were not so exposed. Children exposed prenatally to estrogens were significantly less individualistic and less self-sufficient than their unexposed siblings.

Reinisch reached her conclusions by studying personality and IQ test results of 75 children whose mothers had taken synthetic estrogens and progestins during pregnancy. She and others suspected that the hormones might affect the children's behavior because prenatal exposure of laboratory animals to the hormones affects a wide range of behaviors, including activity level, social interactions, curiosity, emotionality, dominance, and aggression. Moreover, it was known that central nervous system tissue in human and animal fetuses is permanently altered by the presence or absence of sex hormones during critical periods of development.

During the course of her research on the sex hormones, Reinisch came across a curious phenomenon that illustrates a difficulty in conducting retrospective studies. She found that women often did not remember, or did not admit to remembering, taking sex hormones during their pregnancies, even though, according to their medical records, many had received as many as two intramuscular injections each week. Yet these women insisted they had taken no medication during their pregnancies except vitamins.

Although researchers are, of course, interested in detecting more human behavioral teratogens among commonly used drugs, they would ultimately like to use animal studies to assess the risk that new drugs are behavioral teratogens. Japan and the United Kingdom already require that new drugs be tested for behavioral teratogenicity in animals, but neither country specifies what tests should be used or what animal species should be tested. Rodier comments "The danger is that anyone who knows what he's doing can choose a series of 20 behavioral tests that would show no effect, even in animals with severe brain damage."

The appropriate choice of behavioral tests is crucial because animals with severe central nervous system defects may perform normally on certain behavioral tests. For example, Raef Haddad of the New York State Institute for Basic Research in Mental Retardation finds that ferrets missing half of their cerebral cortexes still performed normally on operant conditioning tests, which are popular tests of learning. These ferrets did poorly on certain maze learning tests, however.

Despite the difficulties in establishing tests for behavioral teratogenicity, researchers believe that eventually animal behavioral tests will be an accepted aspect of drug screening in this country. They admit that studies of behavioral teratology are only now gaining momentum, but they point out that there are at least a few general principles that apply to this new discipline. As Richard Butcher of the Children's Hospital Research Foundation in Cincinnati explains, it is now clear that behavioral defects can occur in the absence of physical malformations. Moreover, the fetus is vulnerable to brain damage throughout gestation—there is no safe period. Finally, drugs that in high doses produce physical malformations often produce behavioral defects in lower doses.

The ramifications of behavioral teratology have only begun to be sensed. Drugs that seemed safe because they were given late in gestation or because they seemed to cause no physical malformations may have to be reevaluated. It may well be that, as Hutchings speculates, possibly women have already been exposed to a behavioral teratogen comparable to thalidomide in its potency. But, unlike thalidomide, the effects of such a behavioral teratogen would have gone unnoticed in the general population.—GINA BARI KOLATA

The New Physics: Quarks, Leptons, and Quantum Field Theories

Two electron-positron colliding beam storage rings, one recently completed at the Deutsches Elektronen-Synchrotron (DESY) laboratory in Hamburg, West Germany, and the other a year away from being turned on at the Stanford Linear Accelerator Center (SLAC), are the first of a new generation of accelerators that physicists expect to answer some of the basic questions about what makes elementary particles tick (*Science*, 10 November, p. 608). In short, the experimental agenda for the new storage rings includes searches for new particles and information that can show whether the current theoretical notions as to how particles interact are correct (or, if not, where they have gone wrong).

This is the second of two Research News articles on electron-positron storage rings and elementary particle physics.

Elementary particles fall into one of three general categories. The first of these, the leptons, are by many criteria the most "elementary" of the elementary particles. They behave as pointlike entities with no spatial extent and there are only six of them (so far)—the electron, the muon, the recently found tau particle, and their respective neutrinos.

The second class of elementary particles comprises the hadrons, including the proton, neutron, and pi meson. But there are well over a hundred species of hadrons known, giving rise to the term elementary particle "zoo," as well as to considerable doubt as to whether there is anything elementary about them at all. Order was restored to the particle zoo 15 years ago when Murray Gell-Mann and George Zweig of the California Institute of Technology showed, independently, that the pattern of hadron masses, electric charges, spin angular momenta, and other characteristics made sense if the hadrons were composed of still more elementary entities that came to be called quarks. Quarks are distinguished by a new property with the whimsical name flavor. Gell-Mann and Zweig postulated three flavors.

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