The Influence of Chemicals and Environment on Brain Development; “Behavioral Teratology”

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INTRODUCTION

We are exposed to tens of thousands of chemical substances in our environment throughout life, while annually more than a thousand new chemicals are synthetized. The magnitude of the contribution of chemical compounds to “functional” developmental defects is unknown, but these compounds will most probably lead much more frequently to disturbances than is reported for the classical gross morphological “teratological” defects, which may thus be considered as the “tip of an iceberg.”

Such chemicals may 1) be present in food, water, or air as industrial or laboratory chemicals, household products, agricultural chemicals, food and fuel additives, 2) be taken at the mother’s own initiative (e.g., self-medication, alcohol, smoking, addiction), 3) be prescribed to the mother as a medicine during pregnancy (a prospective survey disclosed that in the USA women take on the average 11 different drugs in the course of pregnancy!), 4) reach the newborn via the mother’s milk (medicines, environmental chemicals such as insecticides, alcohol, nicotine, marijuana), or 5) be prescribed directly to the child. Many of the chemicals are of a type that can easily cross the placenta. Since the blood-brain barrier at the early stages of development is not yet capable of preventing passage, the chemicals may readily reach the fetal brain. Such compounds may alter the intricate structure or chemical composition of fetal brain tissue to such an extent that permanent behavioral deviations develop later. This field is known as "behavioral teratology," which is the subject of the present short communication.

Only relatively few chemical substances have been shown definitively to cause permanent developmental disturbances, either by producing catastro-
phies (methylmercury, thalidomide, polychlorinated biphenyls [PCBs]) or by behavioral changes defined via clinical and psychological observations (alcohol, smoking, diethylstilboestrol— which has recently turned out to be supplied by Dutch mail order as a sex-stimulating compound!). There are, however, good reasons (from animal experiments and from a few human studies) for suspecting numerous other chemicals to have similar effects. The influence of chemicals on the developing child, therefore, seems to be an important public health problem, particularly in view of the enormous psychological and economic burden which mental retardation or disturbed behaviour may impose on the parents, the affected children themselves, and on society.

**SUBSTANCES AFFECTING BRAIN DEVELOPMENT**

Those chemical compounds which are of importance for adult brain function appear generally to be involved in brain development as well. At present this is established for the following three groups of chemicals:

1) Environmental chemicals, that may impair brain development are a) industrial chemicals like mercury (causing the Minamata disease, which occurred later also in New Mexico and Iran), lead, PCBs; b) agricultural chemicals like herbicides, pesticides (DDT), and fungicides; c) food additives; and d) chemicals used for warfare (the 2,4,5-T defoliant).

2) Substances taken at the mother's initiative: a) cigarettes (50% of the pregnant mothers smoke) may affect mental development, learning and behavioral characteristics of children; and b) alcohol (85% of the mothers drink some alcohol; this is probably the major chemical cause of mental retardation). In addition, alcohol has been used to prevent premature delivery; c) heroin and methadon were also found to impair brain development.

3) Neuroactive medicines which can be subdivided into: a) sex hormones, which in normal development seem to constitute the biological basis for sex-related brain differences in animals as well as in humans. It is therefore a matter of considerable concern that progestatives and oestrogens are still frequently prescribed to pregnant women in the mistaken belief that they prevent impending miscarriages. Their use by the mother induces permanent personality disorders, an increased percentage of infertility, and interference with sexual function and psychosexual development in the child. b) Corticosteroids are used to promote lung development in the child in cases of imminent prematurity. In quite a number of patients this treatment does not seem to have the expected effect. In addition, animal experiments and observations in humans indicate that prenatal exposure to corticosteroids can retard brain development and psychomotor performance. c) Thyroid hormones have been injected directly into the amniotic fluid in order to enhance
fetal lung maturation. No follow-up investigation of these children has been carried out to our knowledge, although it is known from animal experiments that such treatment may hamper brain development. d) Recent research indicates also that neurotransmitters of the four groups mentioned below are essential for normal brain development.

i. Acetylcholine. Nicotine (an acetylcholine receptor agonist) enhances cell death in the rat fetal brain stem.

ii. Biogenic amines. Smoking might affect brain development by interfering with noradrenaline or dopamine metabolism. Amphetamine (which increases the release of catecholamines) is commonly used as a dieting aid but is also given to children in cases of enuresis nocturna or "minimal brain dysfunction." Offspring of pregnant rats treated with such a drug showed in adulthood an inability to adapt to new surroundings. α-Methyl dopa (a false transmitter precursor for noradrenaline) and propranolol (a β-adrenergic blocker), when taken prenatally by the mother, result in a reduced head circumference in the neonate. The use of neuroleptics such as phenothiazines (a dopamine antagonist) during pregnancy has been reported to result in extrapyramidal disturbances in the newborn child and, in animal experiments, impaired learning ability. Barbiturates, which also stimulate dopamine receptors, are commonly used as hypnotics, sedatives, and for preventing neonatal jaundice. They may induce a long-term withdrawal syndrome lasting as long as three months. In animal studies, prenatal exposure to barbiturate has been shown to impair maze-learning ability by the offspring.

iii. The amino acids. The effect of alcohol and lead on brain development might be mediated via GABA receptors. Prenatal or early postnatal treatment of rats with the often used tranquilizer diazepam (which acts upon GABA receptors) produces long-lasting effects on brain enzymes, thereby resulting in behavioral disturbances such as hyperactivity and lack of acoustic startle reflexes. Diazepam administration during pregnancy in humans results in low Apgar scores, depressed respiration, and impaired suckling. Long-term follow-ups of such children are lacking.

iv. The peptides. Little is known about the possible long-term effects on brain development of this recently discovered group of neurotransmitters. It will probably take gynaecologists some time to get used to the idea that even oxytocin can be considered as a neurotransmitter, and thus as a "psychotropic drug" that may be detrimental to the child via a direct action on the developing brain. Oxytocin may pass the placenta and cause fetal distress, including a rise in core temperature; also, retarded motor and speech development have been suggested to be due to this peptide, while a long-term effect on water metabolism was recently established in the rat. Vasopressin, which can permanently alter osmoregulation following prenatal administration, and its an-
alogues have been applied to mentally retarded children. Naloxone, an opiate antagonist, is administered clinically in order to normalize fetal heart rate. Animal experiments have implicated naloxone as the cause of a permanent impairment of sensitivity to thermal stimuli and of maze-learning ability. β-Endorphin, used during delivery in order to provide analgesia, induces similar disturbances.

MECHANISMS OF ACTION OF MEDICINES ON THE DEVELOPING BRAIN

Chemicals may impair the developing child's brain in different ways. 1) In the first place this action may be indirect, as in the case of aspirin, which, when taken by the pregnant mother, results in a higher incidence of intracranial bleeding and perinatal mortality. Over-the-counter drugs are consequently not safe for the unborn child! 2) Drugs may affect brain development by interacting directly with one of the fundamental cellular processes, e.g. cell division, cell death, cell migration, and the formation of neurites, synapses, receptors and cell metabolism. Most, if not all, medicines, in fact, appear to affect several of these processes simultaneously.

Cell division is reported to be slowed down by a number of chemicals, i.e., by barbiturates, corticosteroids, chlorpromazine, alcohol, reserpine, and thyroid hormones. Indirect evidence for decreased brain cell division is provided by the smaller head circumferences which have been found at birth following treatment of the mother with sex hormones, α-methyl dopa, propanolol, diphenylhydantoin, or by the use of alcohol during human pregnancy.

Cell death is augmented by nicotine and by alcohol exposure prior to birth. Cell migration is disturbed by alcohol, while the formation of neurites and synapses is known to be affected by sex hormones, corticosteroids, morphine, methadone, anticonvulsive agents, and alcohol.

Another direct effect of chemicals is upon the glial cells. Neuroleptic drugs inhibit glial adenylate cyclase activity, while corticosteroids probably affect glial cell proliferation. Clonidine interacts with glial cells to decrease the level of their cyclic AMP.

3) The third mechanism involves effects of chemicals on the interaction of brain and behaviour during development. In man and other mammals "active" sleep (AS or REM sleep) occupies a large proportion of time in utero and in the early postnatal period. This led to the question whether or not AS plays an important role in brain maturation. Experimental suppression
of AS during early postnatal life by means of clomipramine (Anafranil) or clonidine (Catapresan) (drugs that are used for treating depression, hypertension, migraine, nocturnal enuresis, withdrawal, “minimal brain dysfunction”) revealed a clearcut reduction of cortical size, higher level of open-field activity, deficient masculine sexual behaviour, and disturbed sleep pattern in rats in adulthood. An interaction was found on brain development between the stimulating effects of rearing in “enriched” environments and the enhanced amount of AS in this condition. Concomitant AS-deprivation by means of clonidine neutralizes the stimulating effect which environmental enrichment normally exerts upon cortical growth.

A higher level of activity in the open-field test was found in adulthood in AS-deprived animals. This test is believed to measure the level of “emotionality” or “fearfulness.” Hyperactivity and emotional liability have also been described in children (eg, in “minimal brain dysfunction”; although its etiology is largely unknown, prenatal complications (eg smoking) are believed to increase the chance that such abnormalities will occur). It might not be premature, therefore, to express a word of caution about exposure of infants to smoking, drugs, or other chemicals affecting sleep (particularly AS) which, from animal experiments, are known to cause a comparable syndrome. A wide variety of chemical compounds having comparable effects upon monoamine systems and/or AS are currently in clinical use. It is both surprising and a source of concern that practically no follow-up studies appear to have been carried out on the possible long-lasting functional consequences of such treatments in humans. In addition, humans are generally more sensitive than animals to the teratogenicity of drugs. Taken together, the literature on this subject points to a potential health hazard not only during the first trimester of pregnancy (as is now generally accepted) but also throughout the entire period of gestation, and even during lactation. Adequate information to the public on the dangers of environmental chemicals, smoking, drinking, and medicines seems essential. In addition, the medical profession should be made aware that the immediate beneficial effects of many drugs may be offset by the induction of permanent behavioral and psychological defects of the developing child.

REFERENCES