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Perinatal Period and Pregnancy: Intervals of High Risk for Chemical Carcinogens

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Experiments in rodents indicate that during the post-embryonic period of prenatal development, the fetus is more sensitive than the adult to certain carcinogens, by several decimal orders of magnitude. Most such agents are direct-acting and independent of metabolism. To other substances, often those which require enzyme-mediated metabolic conversion to a chemically reactive derivative in order to effect carcinogenesis, the fetus may be less vulnerable than the adult. The neonate is also more susceptible than adults to some carcinogens, and may be more susceptible than the fetus to certain agents. Both rodent and primate studies indicate that gravid females are also at elevated risk for carcinogenesis, in part because of the presence in the placenta of trophoblastic tissue which may become malignant. The contributions of rapid growth rate, changing metabolic competence, and tissue differentiation to elevated perinatal susceptibility to carcinogens in rodents and primates are discussed, together with the implications of these findings for human beings subjected to industrial or environmental exposures to such chemicals.

Introduction

The birth in Japan of many infants whose normal physical and mental development was grotesquely and permanently distorted by organomercurial poisoning has clearly and tragically illustrated the vulnerability of human beings to toxic agents during early life. The methylmercury responsible for this disaster originated from the discharge of industrial wastes into Minamata Bay, and demonstration of the linkage between the industrial discharge and the human syndrome known as Minamata Disease—a form of cerebral palsy—has further established that pollution of the ecosystem by man can have unforeseen and catastrophic effects on human health (*1*).

Carcinogens, like methylmercury and many other toxic agents, can also affect the very young, and their effects are likewise irreversible and potentially lethal. Both transplacental and early postnatal exposures to many different kinds of carcinogenic substances have been shown in rodents to result in more severe carcinogenic effects than are elicited in adults by comparable treatment (*2–6*). It has recently been shown that this is not a phenomenon limited to rodents. Transplacental carcinogenesis by diethylstilbestrol (DES) in the human female reproductive tract has confirmed the significance for human beings of prenatal exposure to carcinogens (*7*). Furthermore, experimental findings in nonhuman primates have confirmed that also in these animals, as in rodents, the fetus is quantitatively more susceptible to nonhormonal, direct-acting carcinogens than adults (*8*). Exposure of pregnant women or of women of childbearing age to environments either within or outside the workplace where exposure to carcinogens may occur has therefore increasingly become a matter of concern, generally expressed exclusively in terms of possible prenatal hazard to their offspring. Less extensively documented but convincing evidence is now accumulating, however, that the pregnant female is herself at higher risk to at least some carcinogens than nonpregnant adults of comparable age. Accordingly the fetus, the infant, and the pregnant female are all reviewed in this report as individuals in transitory states of heightened susceptibility to carcinogenesis.

Transplacental Carcinogenesis

Organic compounds of low molecular weight which are nonionic readily cross the placenta, and those which are carcinogenic can induce inapparent

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but permanent neoplastic change in fetal tissues. The potential neoplastic cells which result may only proliferate to generate grossly apparent tumors long after birth. Transplacental carcinogenesis in rodents has been extensively reviewed and summarized (*2–6*), and only the principal conclusions from these summaries will be given here.

As many chemical carcinogens require enzyme-mediated metabolism to a chemically reactive derivative, or ultimate carcinogen, in order to effect neoplastic transformation (*9*), and since the enzyme systems required for these transformations are present at low levels or not at all in fetal rodent tissues until shortly before birth (*10*), the efficiency of a compound as a transplacental carcinogen will be largely determined by whether or not it is dependent on metabolism. The most effective transplacental carcinogens are enzyme-independent, i.e., direct-acting, such as the alkylating agents (alkylnitrosamides, alkyl alkylsulfonates, etc.). For an enzyme-dependent agent to be a transplacental carcinogen, one of two conditions must be met: the ultimate carcinogenic metabolite must be formed in maternal or placental tissues and must be sufficiently stable to reach the fetus by subsequent passage through maternal and fetal circulations; or it must be formed within the fetal target tissues. Agents which are potent carcinogens in adults, but which are poorly metabolized in fetal tissues and yield highly unstable (short-lived) reactive metabolites, are generally less effective transplacentally, e.g., dimethylnitrosamine (*11*).

In rodents, the fetus is susceptible to chemical carcinogens, but the embryo generally is not. In the rat and mouse, major organ systems become vulnerable to direct-acting carcinogens after the definitive organ rudiments have formed, at approximately day 11 of gestation, and susceptibility increases rapidly thereafter, becoming maximal a few days prior to birth. At the time of maximal susceptibility, vulnerable organ systems may be as much as two decimal orders of magnitude more susceptible in the fetus than in the adult. In the rat for example, a single intravenous exposure to ethylnitrosourea (ENU) at a dosage of 160 mg/kg body weight produced tumors of the nervous system in 50% of treated adults; the offspring of rats given ENU on day 15 of gestation developed a comparable incidence of neurogenic tumors at a dose (to the dams) of only 3.2 mg/kg (*12*). To agents dependent on fetal oxidative enzyme systems, susceptibility may be confined to the last few days before birth, as only then are the necessary enzymes present in significant quantity (*11*). Many enzyme-dependent carcinogens are nonetheless extremely effective transplacentally, suggesting an important role for maternal metabolism in the activation of these compounds.

A given carcinogen will usually induce tumors of different organ systems in different species. This is true for both direct-acting and enzyme-dependent carcinogens. ENU, for example, under comparable conditions of transplacental exposure, induces almost exclusively tumors of the nervous system in rats, but in mice yields epithelial tumors, principally of the lungs and liver. The overwhelming majority of transplacentally induced tumors in rodents, irrespective of the organ system in which they develop, are of adult morphology, although the carcinogenic exposure which initiated their development occurred while morphogenetic differentiation was still in progress. On the basis of morphology, therefore, it is not possible in experimental animal systems to distinguish tumors induced by prenatal exposure to a carcinogen from those originating after birth.

No agent is known which is carcinogenic exclusively during prenatal life in all systems. The literature on transplacental carcinogenesis has developed by testing compounds known from studies in adults to be carcinogenic in the test species. The wide variety of compounds already shown to be carcinogenic transplacentally suggests that most carcinogens will to some extent affect the offspring when given during pregnancy.

Recent studies in nonhuman primates have confirmed the greater susceptibility of the fetus to a representative direct-acting carcinogen, ENU (*8*). An important difference is that in the patas monkey (*Erythrocebus patas*), and presumably in other primates, fetal susceptibility is maximal during the first third of the gestation period, corresponding to the first trimester of human pregnancy. In fact, the stages of development of the mouse and rat between days 11 and 20 of gestation and of the monkey between days 30 and 60, are roughly comparable. The practical consequence is however, that if human prenatal susceptibility is like that of the lower primate, the human fetus may be most susceptible to at least some transplacental carcinogens before the mother may know she is pregnant.

Carcinogenesis During Early Postnatal Life

The neonatal mouse and to a lesser extent, the neonatal rat and occasionally other species, have also been shown to exhibit greater ssusceptibility than adults to many, but not all, chemical carcinogens. Studies on neonates have been carried out chiefly in the context of bioassay of suspected carcinogens, and the results have been critically re-

viewed (*13*). In some instances, the enhanced susceptibility of the newborn is very pronounced, as in the case of aflatoxin B_1 in the infant mouse (*14*). The results in rodents have been sufficiently striking that subsequent investigators studying primates have introduced neonatal exposure as a standard protocol to evaluate nonhuman primate responses to a wide variety of carcinogens (*15*). The available evidence is sufficiently convincing to warrant consideration of early postnatal life as a period of generally enhanced susceptibility.

Enhanced Susceptibility of Adult Females During Pregnancy

The possibility of a transitory state of increased susceptibility to carcinogens during pregnancy has not been systematically studied, and individual reports in the literature have attracted little notice. Ivankovic (*16*) reported that rats given ENU during pregnancy frequently died subsequently to malignant tumors of the ovaries, uterus, and vagina, and that these sites were rarely involved in nonpregnant rats given this carcinogen. Alexandrov (*17*) reported similar findings in pregnant rats given either ENU or its methyl homolog, and observed mammary tumors in addition to those of the reproductive system. While a few of the uterine tumors were of Schwann cell origin and can be interpreted as a manifestation of the pronounced susceptibility of the rat nervous system to alkylnitrosoureas, the great majority of neoplasms in the uterus and all those of ovary, mammary glands, and vagina were of epithelial or mesenchymal origin. As these are hormone-responsive tissues and the female endocrine system undergoes major functional changes during pregnancy, it is reasonable to infer a hormonal component in the pathogenesis of these tumors.

Recent observations in this laboratory in the course of studies on transplacental carcinogenesis in the patas monkey indicate both a confirmation of heightened maternal susceptibility in this nonhuman primate and an additional dimension to carcinogenic risk during pregnancy. The latter consists of highly malignant tumors apparently of trophoblastic origin which are rapidly fatal. A typical case of the five so far observed is illustrated in Figures 1 and 2. The animal illustrated had received ENU during the early months of pregnancy, delivered a live infant 17 weeks after the first injection, and died suddenly and unexpectedly 5 weeks later from exsanguinating pulmonary hemorrhage. No obvious primary tumor was found, but multiple tumor nodules were apparent in several of the viscera, especially the lungs. Tumor cells in these cases have often been found microscopically in the uterine endometrial stroma and myometrium. The disease resembles human choriocarcinoma both clinically and histologically, and is one of the most rapidly progressive chemically induced neoplasms ever reported in a primate. No similar tumors have

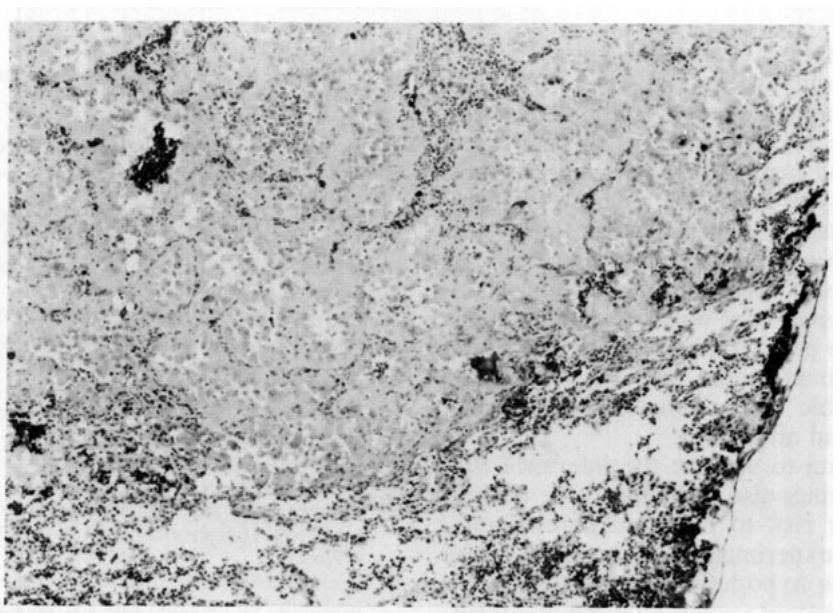

FIGURE 1. Low-power view of one of many pulmonary metastases in a female patas monkey which died of sudden exsanguinating pulmonary hemorrhage 5 weeks post partum. The animal had received ENU during pregnancy. Masses of tumor cells line ill-defined spaces divided by connective tissue septae. H & E, ×80.

FIGURE 2. Higher magnification illustrates detail of large cells resembling cytotrophoblast, some in mitosis. H & E, ×430.

been seen in nongravid females given the same regimen of ENU for the same or longer periods and observed for much longer times.

The evidence from both rat and primate studies, although limited, thus suggests that the pregnant female is at higher risk to at least certain carcinogens than nongravid females or males of comparable age.

Discussion

The empirical nature of current knowledge of perinatal susceptibility to carcinogenesis dictates caution in extrapolating beyond specific data, especially between species. The reasons for increased susceptibility during early life are not clear, beyond the fact that rapidly proliferating tissues are intrinsically at higher risk to carcinogenesis than those with lower rates of cell division. The fact that empirical observations of heightened perinatal susceptibility have been made not only in several rodent species, but also in primates, however, justifies the inference that humans must also be considered especially vulnerable to carcinogens during early life, both before and after birth.

There are no data to support the inference that pregnant human beings also resemble lower animals in being at higher risk to chemical carcinogens. Even though the experimental data are less well established for this hypothesis, the consequences are potentially important enough to warrant consideration, and re-emphasize the importance of recognizing and avoiding exposure to carcinogens during pregnancy.

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