Oncogenic sensitivity of children to environmental toxicants (Brent), 6-18-08

Robert L. Brent MD. Ph.D

The topic of oncogenic risks from exposures to mutagenic and other environmental toxicants is the relatively complex for several reasons. There are multiple causes of cancer and many of the animal and human studies only focus on one of the causes or one of the mechanisms. In humans, both in adults and children, cancer can be caused by the following etiologies or mechanisms of action (MOA) and these mechanisms may interact to increase or decrease the risks.

1. Spontaneous mutations (Chromosomal abnormalities, point mutations at the molecular level.)
2. Genetic predisposition. Inherited "cancer" genes. Polymorphism
3. Increased accumulation of mutations in populations of cells with increased rate of proliferation as the result of inflammatory processes (**Cohen et al 1995, 1998**) or in the aged population.
4. Genotoxic and mutagenic drugs, chemicals and physical agents
5. Endocrine receptor agonists and antagonists. Other receptor agonists and antagonists.
6. Increased mutations in harmartomas and other forms of displaced tissues (i.e. columnar epithelium in the lining of the vagina from intrauterine DES exposure).
7. Immunological suppression from genetic diseases, or environmental exposures to immunosuppressive toxicants.

Cancer is a leading cause of death in childhood and adolescence **(Napier, 2003)**. In the age group of 1 to 4 years, cancer is the third highest cause of death. From ages of 5 to 9 and 10 to 14, cancer is the second highest cause of death and from age 15 to 19, cancer is the fourth

highest cause of death and during adulthood, cancer is the second highest cost of death. Environmental oncogenic exposures can occur during preconception gametocyte development, pregnancy, childhood, adolescence and adulthood. While here are many causes of cancer, including environmental toxicants, there is uncertainty with regard to the magnitude of the contribution of environmental toxicant exposure (chemicals and drugs) to the overall incidence of cancer in children and adults. It is common knowledge that tobacco smoking and the ingestion of alcohol significantly increased the risk of certain cancers.

What is the impact of chemicals and drugs on the prevalence of cancer in these age groups? There is a truism in toxicology that indicates that children are at greater risk from exposure to environmental toxicants. If the toxicant's effect is deterministic and therefore has a threshold, then the threshold for children may be lower. Investigators as a group, are not supportive of this generalization that infants and children may be more sensitive, since there is data that indicates that developing organisms may be less sensitive or equally sensitive to a many environmental toxicants **(Done, 1964; Brent et al., 2004, Brent and Weitzman, 2004. Sheuplein et al., 2002).** stated, "The newborns metabolic activity rapidly matures, and by about 6 months of age, children are usually not more sensitive to chemical toxicity than adults. By then most metabolic systems are relatively mature, becoming almost completely capable by one year of age. In many instances children are less sensitive than adults. Whether children are at greater risk from chemical exposures is another question".

If the toxicant has a mutagenic effect and has the potential for the induction of cancer, then the effect is considered to be stochastic and theoretically there may not be a threshold. However, there is not unanimity of opinion concerning the universal application of the linear-no-threshold hypothesis for risk assessment of mutagenic oncogenic agents. There is a significant

group of scientists that support the concept of “hormesis” which subscribes to the concept that toxicants, that are harmful at high exposures, may be without effects or even beneficial at very low exposures (Luckye 1980, 1994). This concept has not been generally accepted by the scientific community.

Children are believed to be more sensitive to the oncogenic effects of mutagenic agents. The magnitude of the increased risk varies considerably with the oncogenic agent and the life-stage when the exposure occurs. The following life stages have to be considered.

1. Preconception exposure to environmental toxicants

The risk of mutagenic exposures to the gametocytes of adults and the risk of mutations in the ova or sperm that would increase the risk of cancer in the F-1 offspring has been studied in animal models and large human populations exposed to environmental toxicants. High exposures of some cytotoxic drugs and chemicals can produce sterility in animal models as well as an increase in the incidence of pregnancy loss from unbalanced chromosome abnormalities. However, the frequency of chromosome abnormalities in the offspring that are viable is very low. The incidence of cancer in the viable offspring is not measurably increased in these human population studies. In humans this is a low risk phenomenon as indicated by numerous human epidemiology studies. (**Ames and Gold, 1990; Boice JD et al., 2003; Brent 1994, 1999, 2007, Brent et al., 2004; Byrne, 1999; Mulvihill et al 1987, Neel, 1999; Neel and Lewis, 1990; Nygaard et al., 1991a and b; Winther et al., 2004**). There are some researchers who are of the opinion that methylation mutations produced by preconception pesticide exposures in animal models has been demonstrated to be inherited and these investigations are ongoing in some laboratories (**Anway.et al 2005)**.

What questions have been raised with regard to preconception exposures of children that may or may not be applicable to other populations? In Nygaard's studies of almost 1000 leukemic children who were successfully treated for leukemia there was a much higher incidence of infertility in the males than in the females; a significant gender difference in infertility. If the surviving patients became pregnant or fathered a child successfully, the incidence of developmental problems in the offspring was not increased (Nygaard et al 1991 a and b). Whether this gender difference in susceptibility can be applied to adult populations has not been definitively answered. While infertility has been observed in the offspring of adults who were treated for cancer as children or adolescents, there does not appear to be an increase in cancer in the F-1 generation, but the numbers of F-1 children in these studies are small.

2. <u>Oncogenic risks from *in utero* exposures to environmental toxicants</u>

There are publications that indicate that *in utero* embryonic or fetal exposures to environmental toxicants can increase the risk of cancer in the offspring. Two widely studied intrauterine toxicants are diethylstilbestrol (DES) and ionizing radiation. A research group at the "Boston Lying-in Hospital" published their report on the benefits of DES administration during problem pregnancies for "preventing late pregnancy accidents" **(Smith 1948; Smith et al. 1946; Smith and Van S. Smith 1949)**. The alleged benefits of DES were accepted by a large group of practitioners for the treatment of recurrent abortion, pregnant diabetics, threatened abortion, pregnancy bleeding, hypertension and other pregnancy problems **(Marselos and Tomatis 1993; Noller and Fish 1974).**

In 1971 the FDA removed its approval of the use of DES for use in pregnant women (**FDA Drug Bulletin 1971**). This was the same year that **Herbst et al. (1971**) reported the cluster of cases of clear-cell adenocarcinoma of the vagina (CCACV) in young women whose

mothers had been administered DES during pregnancy. It was Herbst's effort to create the registry that permitted the accumulation of cases of clear cell adenocarcinoma of the vagina (CCAV) and to estimate the incidence between 1:1000 and 1:10,000 exposures of DES during pregnancy.

Studies of the exposure of ionizing radiation to pregnant animals and to pregnant women have **not** resulted in consistent results with regard to the risk of cancer in the offspring. Stewart and colleagues reported that the embryo was much more sensitive to the oncogenic effects of ionizing radiation than the child or adult **(Stewart, 1970; Stewart et al., 1958; Stewart and Kneale, 1973).** In 1999 Boice and Miller published their interpretation of the data pertaining to the oncogenic risks of intrauterine radiation. They noted, "Evidence for a causal association derives almost exclusively from case-control studies, whereas practically all cohort studies find no association, most notably the series of atomic bomb survivors exposed in utero." The most recent report from Radiation Effects Research Foundation (RERF) supports the conclusions of **Boice and Miller (1999). Preston et al (2008**) compared the oncogenic effect of in utero and childhood radiation exposure and concluded that "the lifetime risks following in utero exposure may be considerably lower than following childhood exposure", which is in marked disagreement with Stewart's conclusions about the marked increase in risk following in utero radiation.

During the final preparation of this manuscript the long-awaited results of the in-utero radiation carcinogenic effects were published in March 2008 in the Journal of the National Cancer Institute by Preston et al (2008). The data is summarized in Tables 1 and 2
The authors concluded,

> "Lifetime risks following in utero exposure may be considerably lower than for early childhood exposure, but further follow-up is needed. There was no statistical increase in the oncogenic risks of in utero exposed individuals with exposures <0.2 Sv (,20 rads) (Table 1). The in utero exposed population was much less sensitive to the oncogenic effects of radiation than the children that were exposed to the A-bomb[144] (Tables 2 and 3).

It is interesting that the research of Rugh et al. (1966) and Brent and Bolden (1961) indicated that the embryonic mouse was less sensitive to the oncogenic effects of ionizing radiation than the postnatal mouse. However, both Rugh and Brent were reluctant to refute Stewart's conclusion that the radiation induced oncogenic risk of the human embryo was two orders of magnitude greater than the postnatal human based on the mouse radiation studies alone.

Preston et al. (2008) concluded that the embryo is actually less sensitive to the oncogenic effects of ionizing radiation than the young child (Tables 1 and 2). In fact these authors concluded that below 0.2 Sv (20 rad) there was no statistically increased incidence of cancer in the in utero population. This is in marked contradiction to the studies of Stewart in the 1950's to the 1970's that copncluded that the fetus was markedly more sensitive to the oncogenic effects of ionizing radiation that the child or adult.

Table 1				
Number of patients with solid cancers				
In utero exposure from the Atomic bomb				
Dose in Sv (rads)	No. of patients	No. of Cancers	Person years	% of Cancers
<0.005 (<0.5)	1547	54	49,326	3.5
0.005-<0.1 (0.5 to 10)	435	16	14,005	**3.7**
0.1 to <0.2 (10 to <20)	168	6	5041	**3.6**
0.2 to <0.5 (20 to <50)	172	8	5496	**4.6**
0.5 to <1.0 (50 to <100)	92	7	2771	**7.6**
>1.o	48	3	1404	**6.2**
Total	2452	94	94	**3.5**

Table 2				
Number of patients with solid cancers				
Early childhood exposure from the Atomic bomb				
Dose in Sv (rads)	No. of patients	No. of Cancers	Person years	% of Cancers
<0.005 (<0.5)	8549	318	247,744	**3.7**
0.005-<0.1 (0.5 to 10)	4528	173	134,621	**3.8**
0.1 to <0.2 (10 to <20)	853	38	25,802	**4.4**
0.2 to <0.5 (20 to <50)	859	51	25,722	**5.9**
0.5 to <1.0 (50 to <100)	325	21	9522	**6.5**
>1.o	274	48	7620	**17.5**

Total	15388	649	451,031	**4.2**

One of the mechanisms hypothesized to explain the increased risk of cancer in offspring that were irradiated in utero is the increased prevalence of chromosome abnormalities in the cells of the in utero irradiated offspring. Nakano et al, (2007) irradiated mice in utero with 1 or 2 Gy of x-rays and 6 week-old mice with the same exposures. The mice irradiated at 6 weeks of age had a 5% incidence of translocations while the mice that were irradiated in utero had a 0.8% incidence of translocations. The authors found that the embryos were sensitive to the induction of chromosome aberrations, but that the aberrant cells do not persist because fetal stem cells tend to be free of aberrations and their progeny replace the pre-existing cell populations during the postnatal growth of the animals.

For 50 years the predominant view has been that the embryo is much more sensitive to the oncogenic risk of ionizing radiation than the child or the adult. This view prevailed in spite of the fact that many cohort studies were negative and the case control studies were not consistent. The most recent data provided by outstanding and objective scholars is that the embryo is less sensitive to the oncogenic effects of ionizing radiation and that there may even be a threshold for the oncogenic effects.

These results raise a number of issues.

1. Is there a threshold or no effect exposure for the oncogenic effects of some chemicals or drugs, not only for the embryo, but for the child and adult as well?
2. Because there are multiple mechanisms and exposures that increase oncogenic risks it is difficult to establish generalizations regarding exposures and oncogenic risks. In fact oncogenic risks that result from the production of congenital malformations or displaced tissues (DES) have less of a role in increasing cancer risks from exposures to children and adults.

3. Oncogenic risks from environmental toxicant exposures in children and adolescents

An increase in carcinogenic risks has been demonstrated for children exposed to high doses of ionizing radiation, and for exposures to radioactive ^{131}. A number of authors and agencies have suggested that children may be 10 times more sensitive to the oncogenic effects of ionizing radiation. In Hall's 2002 publication he writes, "It is clear that children are ten times

more sensitive than adults to the induction of cancer" **(Hall, 2002) (Figure 1)**. Figure 1 is a simplification of Figure 3 in Hall's 2002 publication. This graph is not a chart of the relative sensitivity of different aged individuals to the oncogenic effect of radiation, but a chart of the decreasing ability of older individuals to manifest the full extent of the oncogenic risks and the greater risk that the older population will die from non-radiation causes. It takes 40 to 50 years to manifest the full extent of the risk of whole-body ionizing **radiation.** There are reports that indicate that low exposures to radiation, below 0.2 Gy (20 rad) do not increase the risk of cancer. The scientists from the Hospital for Sick Children reported on the incidence of cancer in infants who had cardiac catheterization from 1946 to 1968 at a time when image amplification was not utilized and therefore exposures could be as high as 0.3 Gy (30 rad). Yet, there was no increase in any type of cancer in this population (almost 5000 patients in the original exposed population involved in the study) reported in 1983 and 1993. **(Spengler et al., 1983, McLaughlan et al., 1993)**.

Most agents that have been demonstrated to be carcinogenic in humans will produce cancer in some laboratory animals, but not all laboratory animals. But the converse is not true; namely, that all agents that have been demonstrated to be carcinogenic in animals are carcinogenic in humans. Animal studies have revealed marked differences among species with regard to the oncogenic susceptibility to environmental chemicals and drugs as exemplified by the phthalates. Animal carcinogenicity studies utilizing the phthalates and other chemicals that stimulate the peroxisome proliferation response may not be appropriate models to determine human cancer risks (**Koop et al., 1999**).

The second agent that received much attention is saccharin, which produced bladder cancer when high doses of saccharin were administered to rodents. At high doses, precipitates of

saccharin accumulate in the rodent bladder producing inflammation and proliferation that ultimately results in bladder tumors. Other experiments indicated that human exposures of saccharin would never result in the situation that occurred in the rodent (**Cohen et al., 1995; 1998, 2006; Dominick et al., 2006; Wei et al., 2005**)

We really do not have enough data pertaining to each mutagenic agent to be able to estimate the risk of its mutagenic effect. Many of these studies are ecological studies, in which the exposure is estimated or even hypothesized. No measurements are made on the exposed populations. The exposure is assumed because of the location of the population being studied. That risk estimates based on an assumption of the exposure, may be erroneous. Many of these exposures are mixtures and we are still attempting to solve the problem of estimating the toxic effect of mixtures.

While there is no question that the developing embryo, child and adolescent are more susceptible to oncogenic effects of mutagens there is very little discussion in the available publications about the dose response curve of the mutagenic agents and whether there is a threshold for mutagenic effects at low exposures which frequently occur with exposures to environmental chemical agents and whether the NOAEL is the same or lower for developing humans.

Many of the animal studies utilized very large doses of the mutagens and most investigators did not determine a NOAEL. In many of the human industrial exposure studies or air pollution studies the content of the contaminated environment is not quantitatively determined. None of the studies evaluated the immunological status of the animals to determine whether the immune system was suppressed by the genotoxic agent. We know that when the immune system is suppressed the risk of cancer is increased. This happens clinically when

patients are administered large doses of cortisone, are treated with chemotherapeutic drugs or develop immune deficiency diseases. Genetic effects in the F-1 generation cannot be determined in preliminary one-generation or multigenerational studies, because you would need very large populations of animals to perform studies that would estimate human risks for genetic disease in the offspring of exposed adult animals prior to conception, except for the Rodent Dominant Lethal Assay (**Environmental Protection Agency, EPA 1998 a-d**)

Most publications refer to the variable risk of cancer in the fetus, child and adolescence as the result of variable sensitivity. In other words, the infant is more sensitive to a mutagenic agent and therefore has an increased risk of cancer following an exposure. Actually there are two other explanations for the increased life-long cancer risk that infants may manifest. A developing organism has a greater proportion of its cells undergoing division and therefore the cells may not be more sensitive, but the proportion of susceptible cells is greater. More important is the fact that the child that is exposed has a lifetime to manifest the genotoxic effect in a clinical malignancy (waiting for that second mutation to occur).

The difficulties that we face in determining the oncogenic risk of environmental toxicants are that most of the animal studies utilize exposures above the typical population exposures. We do not know whether there is a NOAEL for the induction of cancer from chemicals, drugs or even physical agents... We do not know whether the NOAEL is lower or higher in developing organisms. Many of the publications that estimate oncogenic risks are in disagreement and we do not know which is correct or whether any of the risk estimates are correct. Even the concept that the developing organism is more “sensitive” has to be evaluated. Are the cells more sensitive; are there more cells in the sensitive stage (proliferating) or is the organism more “sensitive” because it has a longer period of time to manifest the toxic effects? Obviously, there are important

problems to solve for the scientists working in the field of the oncogenic effects of environmental toxicants.

Conclusions:

1. Since children are still developing during childhood and adolescence it is believed that children are more sensitive to the effects of environmental toxicants and that they may be more susceptible to the oncogenic and mutagenic effects of oncogenic exposures. What we do not know is whether there is a threshold for chemically induced oncogenensis and if there is a threshold, is the threshold lower, higher for children than adults or the same.

2. The studies dealing with the survivors of childhood leukemia indicate that boys who receive chemotherapy are four times more likely to be infertile than the girl survivors. We do not know the extent of infertility of males in adult populations treated with chemotherapy when compared to females similarly exposed..

3. In the past it was believed that the embryo was the most sensitive to the oncogenic effects of environmental toxicant, but the recent publication of Preston et al (2008) indicated that the embryo was less sensitive than children and that there was a threshold below which the risk was not increased.

4. Immunological suppression is a mechanism responsible for an increased risk of cancer. This phenomenon occurs in both children and adults. It is not known whether the increased incidence in these immunosuppressed populations is due to the inability to monitor spontaneously occurring new cancer clusters or because the oncogenic mutations are increased in the population exposed to immunosuppressants.

5. While animal studies are useful for studying the toxic effect of chemicals, the problem with the risk of cancer in humans from oncogenic exposures is the long latency period. The long

latency period differentiates human cancer development and animal cancer development following oncogenic exposures.

All these factors make it extremely difficult to transpose investigations in animals and humans at one stage to other human stages for determining both qualitative and quantitative risks for cancer.

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