OBSTETRICS

Saving lives and changing family histories: appropriate counseling of pregnant women and men and women of reproductive age, concerning the risk of diagnostic radiation exposures during and before pregnancy

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Over the past 50 years, our laboratory has provided consultations dealing with the risks of various environmental toxicant exposures during pregnancy. These contacts were primarily by telephone or written communications. Since the year 2000, the primary source of consultations has been via the internet. In 2007, the pregnancy website of the Health Physics Society received 1,299,672 visits. The contacts who downloaded information totaled 620,035. After reading the website information, 1442 individuals who were still concerned contacted me directly. Unfortunately, we have learned that many physicians and other counselors are not prepared to counsel patients concerning radiation risks. Approximately, 8% of the website contacts, who had consulted a professional, were provided inaccurate information that could have resulted in an unnecessary interruption of a wanted pregnancy.

Research from our and other investigators' laboratories has provided radiation risk data that are the basis for properly counseling contacts with radiation exposures. Mammalian animal research has been an important source of information that improves the quality and accuracy of estimating the reproductive and developmental risks of ionizing radiation in humans.

What are the reproductive and developmental risks of in utero ionizing radiation exposure?

1. Birth defects, mental retardation, and other neurobehavioral effects, growth retardation, and embryonic death are deterministic effects (threshold effects). This indicates that these effects have a no adverse effect level (NOAEL). Almost all diagnostic radiological procedures provide exposures that are below the NOAEL for these developmental effects.

2. For the embryo to be deleteriously affected by ionizing radiation when the mother is exposed to a diagnostic study, the embryo has to be exposed above the NOAEL to increase the risk of deterministic effects. This rarely happens when the pregnant women have x-ray studies of the head, neck, chest or extremities.

3. During the preimplantation and preorganogenesis stages of embryonic development, the embryo is least likely to be malformed by the effects of ionizing radiation because the cells of the very young embryo are omnipotential and can replace adjacent cells that have been deleteriously affected. This early period of development has been designated as "the all-or-none period."

4. Protraction and fractionation of exposures of ionizing radiation to the embryo decrease the magnitude of the deleterious effects of deterministic effects.

5. The increased risk of cancer following high exposures to ionizing radiation exposure to adult populations has been demonstrated in the atomic bomb survivor population. Radiation-induced carcinogenesis is assumed to be a stochastic effect (nonthreshold effect) so that there is theoretically a risk at low exposures. Whereas there is no question that high exposures of ionizing radiation can increase the risk of cancer, the magnitude of the risk of cancer from embryonic exposures following diagnostic radiological procedures is very controversial. Recent publications and analyses indicate that the risk is lower for the irradiated embryo than the irradiated child, which surprised many scientists interested in this subject, and that there may be no increased carcinogenic risk from diagnostic radiological studies.

Examples of appropriate and inappropriate counseling will be presented to demonstrate how counseling can save lives and change family histories. The reader is referred to the Health Physics Society website to obtain many examples of the answers to questions posed by women and men who have been exposed to radiation (www.hps.org). Then click on ATE (ask the expert).

Key words: cancer, congenital malformations, ionizing radiation risk, pregnancy risks

There have been many publications concerning the effects of radiation on the developing embryo. The subject includes the effects of ionizing radiation (x-rays, gamma rays, internal and external radionuclides, neutrons) and nonionizing radiation (ie, electromagnetic fields of various frequencies, microwave radiation, communication band radiation, diathermy, lasers, and ultrasound). Exposures to ionizing radiation will be emphasized in this publication. For further details the reader is referred to comprehensive reviews concerning the effects of various forms of radiation on the developing embryo and fetus.[1-17]

When attempting to evaluate the nature and magnitude of the effects of an environmental toxicant like radiation, it is important to utilize all the available approaches and methodologies. The process that our laboratory utilizes in evaluating reproductive and developmental risks is as follows.

Method of evaluating allegations of environmental developmental toxicity[11]

Epidemiologic studies

At what exposures do controlled epidemiologic studies consistently demon-

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strate or not demonstrate an increased risk of birth defects, pregnancy loss, or other developmental effects in exposed human populations?

Secular trend data

Do secular trends demonstrate a relationship between the incidence of various developmental effects and a quantitative change in the population exposure? This type of ecological analysis can be performed only if a large portion of the population is involved and the actual exposures are available.

Animal developmental toxicity studies

Does an animal model mimic the human developmental effect at clinically comparable exposures? Developmental toxicity studies are indicative of a potential hazard in general and may or may not indicate the potential for a specific effect on the human embryo or fetus.

Dose-response relationship

Does the incidence and severity of developmental toxicity increase with dose? Does the developmental toxicity in animals occur at a dose that is equivalent to the human dose? This is characteristic for ionizing radiation effects more than for all other environmental toxicants.

Biological plausibility

Are the mechanisms of developmental toxicity understood and/or are the results biologically plausible?

It is important to emphasize 3 important points about this method of evaluating developmental risks.

First, quality epidemiological studies are the foundation for determining human risks. It is rare that in vitro studies or animal studies can refute either negative or positive findings in epidemiological studies if an adequate and well-performed number of epidemiological studies are available.

Second, animal studies involving the radiation of pregnant mammals (mice, rats, and rabbits) are more predictive of human risks than similar studies attempting to determine the toxic effects of drugs and chemicals. Drugs and chemicals, whether injected or ingested, have to be absorbed, metabolized by the liver, and transported by the placenta, whereas ionizing radiation produces its effects by directly affecting the embryo. There are numerous examples of differences in metabolism, absorption and placental transport of drugs that make risk assessment of human risks problematic. That is not true for ionizing radiation.

Third, biological plausibility is a powerful tool in evaluating environmentally produced developmental effects. Figure 1 is a photograph of a young boy with a congenital limb reduction defect (LRD). This unilateral LRD most likely is due to vascular disruption, amniotic band syndrome, or a placental embolus to the limb at midgestation. A similar malformation, not in this child, was alleged to have resulted from an in utero ionizing radiation exposure. Besides the fact that there had been no radiation exposure, this unilateral malformation in a child who had a normal birthweight had normal intellect, and a normal head circumference is unlikely to have resulted from a teratogenic exposure to ionizing radiation.[18] The 3 key features of radiation teratogenesis are missing, and it would be most unlikely that radiation exposure to an embryo would result in a severe malformation in 1 arm, leaving the other arm unaffected. It is simply not biologically possible.

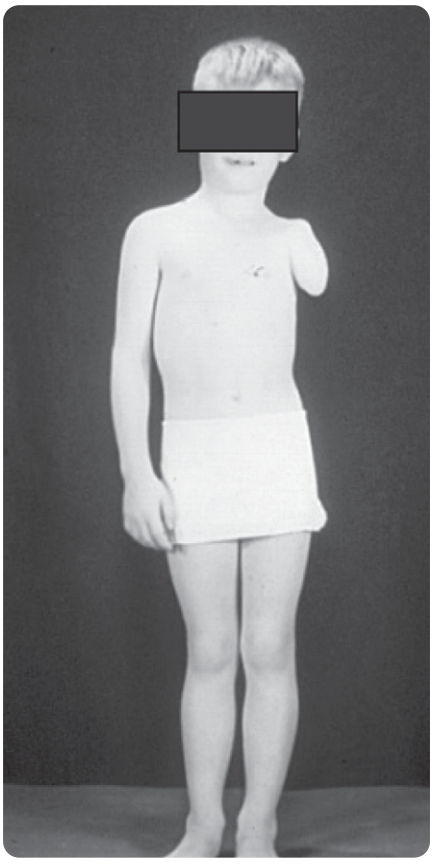
Pathologic effects of exposing the embryo to ionizing radiation

The risks associated with exposure to environmental toxicants during pregnancy, including ionizing radiation, can result in the following effects; there is no question that all of the threshold effects mentioned below have been observed in human populations if the exposure is high enough (Table 1).

1. Pregnancy loss (abortion, stillbirths, threshold phenomena).
2. Congenital malformations (anatomical defects; threshold phenomenon).
3. Neurobehavioral abnormalities (ie, mental retardation) (threshold phenomenon).
4. Fetal growth retardation (reversible and irreversible) (threshold phenomenon).
5. Cancer (stochastic phenomenon, nonthreshold phenomenon, based on the linear no threshold hypothesis for mutagenic agents).

Four of the 5 developmental effects of irradiation are threshold phenomena (deterministic effects). That means that below the threshold exposure, the risk is

FIGURE 1
Child with a congenital amputation



The most likely causes include an embolus from placental tissue during development, vascular spasms, or other interference of blood flow to the developing arm or the amniotic band syndrome. A similar child was involved in a negligence lawsuit alleging that radiation caused a unilateral congenital malformation of a limb. On the basis of biological plausibility, a clinical teratologist or geneticist would be able to determine that this child's malformation could not have been due to radiation exposure. As an infant he was normal weight at birth and had normal head size and normal mentality. Therefore, he had none of the features associated with radiation teratogenesis.

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TABLE 1
Radiation effects at different stages of gestation

Stage, gestation, wks	Effect
First and second weeks after first missed menstrual period (prior to conception)	First 2 weeks after first missed menstrual period. This is preconception radiation. Mother has not yet ovulated.
Third and fourth week of gestation (first 2 wks p.c.)	Minimum human acute lethal dose (from animal studies). Approximately 0.10 to 0.20 Gy. Most sensitive period for the induction of embryonic death.
Fourth to eighth week of gestation (second to sixth week p.c.)	Minimum lethal dose (from animal studies). At 18 days p.c. = 0.25 Gy (25 rad) After 50 days p.c., greater than 0.50 Gy (50 rad) Embryo is predisposed to the induction of major malformations and growth retardation. Minimum dose for growth retardation. At 18-36 days = 0.20 to 0.50 Gy (20 rad-50 rad) At 36-110 days = 250-500 mGy (25-50 rad). But the induced growth retardation during this period is not as severe as during midgestation from similar exposures.
Eighth to fifteenth week of gestation	Most sensitive period for irreversible whole-body growth retardation, microcephaly, and severe mental retardation. Threshold for severe metal retardation is 0.35 to 0.50 Gy (35-50 rad). Decrease in IQ can occur at lower exposures.
Sixteenth week to term of gestation	Higher exposures can produce growth retardation and decreased brain size and intellect, although the effects are not as severe as occurs from similar exposures during midgestation. No documented risk for major anatomical malformations. Minimum lethal dose threshold (from animal studies). At 15 weeks to term, greater than 1.5 Gy (150 rad). Minimum dose for severe mental retardation. At 15 weeks to term, greater than 1.50 Gy, but decrease in IQ can occur at lower exposures.

P.C., preconception.
This shows radiation exposure and risk at different gestational phases. There is no evidence that radiation exposure in the diagnostic ranges (less than 0.10 Gy, less than 10 rad) is associated with measurably increased incidence of congenital malformation, stillbirth, miscarriage, growth, and mental retardation.

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no longer present. Another way of referring to the fact that a threshold exists is by determining the no-adverse-effect level (NOAEL). That means that the effect involves many cells (a multicellular effect), and, as the exposure is increased, both the incidence and the severity of the effect increases (Table 2).

Stochastic effects primarily describe the effects of mutagenic agents that theoretically do not have a threshold and relate to the risks of cancer and genetic effects. Mutagenic agent effects have an increased risk as the exposure increases; however, the magnitude or severity of the effect remains the same. Leukemia resulting from a high exposure to radiation is not more severe than a spontaneously occurring leukemia. As the radiation exposure increases, the risk increases; however, the severity of the effect remains the same (Table 2). The risks of mutagenic agents are so small at very low expo-

TABLE 2
Stochastic and threshold dose-response relationships of diseases produced by environmental agents

Phenomenon	Pathology	Site	Diseases	Risk	Definition
Stochastic	Damage to a single cell may result in disease	DNA	Cancer, germ cell mutation	Some risk exists at all dosages; at low doses, risk may be less than spontaneous risk.	The incidence of the disease increases, but the severity and nature of the disease remains the same.
Threshold	Multicellular injury	Multiple, variable etiology, affecting many cell and organ processes	Malformation, growth retardation, death, toxicity, etc	No increased risk below the threshold dose.	Both the severity and incidence of the disease increase with dose.

Adapted from Brent RL. The effect of embryonic and fetal exposure to x-ray microwaves and ultrasound: counseling the pregnant and nonpregnant patient about these risks. Sem Oncol 1989;16:347-69[9] and Brent RL. Utilization of developmental basic science principles in the evaluation of reproductive risks from pre- and postconception environmental radiation exposures. Teratology 1999;59:182-204.

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sures that it is frequently impossible to demonstrate the risk in human studies.

When counseling women and families of reproductive age, it is important to inform them about the background risks of reproductive and developmental effects for which all healthy women are at risk.[8,10,11,19-23] It is much simpler to counsel families concerning the deterministic risks because if the exposure is below the NOAEL, it is appropriate to inform the family that their risks are not increased. For the oncogenic or mutagenic risks, you can inform the family that their risk is very, very small.

If the mother is healthy and has no personal or family history (including the father) of reproductive or developmental problems, she must be told the following:

> "You began this pregnancy with a 3% risk for birth defects and at the time that you recognized that you were pregnant, you had a 15% risk of miscarriage. Those are average background risks that we cannot change at this time."

If the woman is not yet pregnant and she intends to become pregnant, she should be informed to start taking 400 μg of folic acid each day and 6 μg of vitamin B-12 because of the beneficial effects of folic acid in reducing the risk of neural tube defects if taken preconceptually and during pregnancy.

What do we know about the qualitative and quantitative effects of ionizing radiation on the developing embryo?[8,11] Radiation effects may be manifested acutely and result in cell death, embryonic death, growth retardation, and teratogenesis. Cell death, alterations of the mitotic index, and cell migration can alter the growth of the embryo and the development of the central nervous system. Other effects may not be immediately obvious and can be measured or ascertained only in the postpartum or adult period. For instance, neuronal depletion, neurobehavioral abnormalities, infertility, tissue hypoplasia, neoplasia, or shortening of the lifespan are phenomena that can be evaluated only in the postpartum or adult organism.[8,10-12,24-30]

TABLE 3
First-day x-irradiation in the rat

Dose, Gy	Litters	Embryos	Resorptions, %	Fetal weight, g
0.00	77	902	4.77	5.264
0.05	58	699	6.49	5.199
0.10	76	944	7.75	5.207
0.20	71	851	11.41	5.148
0.30	43	490	18.57	5.015

Because the spontaneous resorption rate ranges from 4-8% in the rat, it is necessary to utilize large numbers of pregnant animals to determine at what radiation exposure the resorption rate is increased from x-irradiation exposures on the first postconception day. Statistical tests indicated that the resorption rate is increased with exposures between 0.1 and 0.2 Gy, although the 0.2 Gy exposure is the first exposure that is statistically significant. Note that there was no growth retardation in the surviving embryos, which is true, even when the exposure is 1 Gy and there is significant mortality.

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Congenital malformations and growth retardation

Studies involving irradiation of the human fetus from diagnostic exposures has not been observed to cause congenital malformations or growth retardation[32-35]; however, not all such clinical studies are negative.[36] These are extremely difficult studies to perform, and it appears that the animal data support the contention that gross anatomical congenital malformations will not be increased in a human pregnant population exposed to less than 0.2 Gy (20,000 mrad, 20 rad) acute exposures. The NOAEL for congenital malformations is greater than 0.2 Gy (greater than 20 rad) at the most sensitive stage of development (9 days p.c. [postconception] in the rat) (22 days p.c. in the human). Although we cannot be certain of the human NOAEL, animal data indicate that the NOAEL for birth defects is much higher at later stages of pregnancy[6,10,36,37] (Table 1).

Radiation exposure during preorganogenesis has a NOAEL for lethality if the exposure is less than 0.15 to 0.2 Gy; however, the embryos that survive to term are not growth retarded nor do they have a higher incidence of malformations (Tables 1 and 3).[1,10-11,38-46] The threshold for growth retardation is higher than for birth defects during early organogenesis (0.25-0.4 Gy, 25-40 rads) and continues to rise throughout pregnancy.

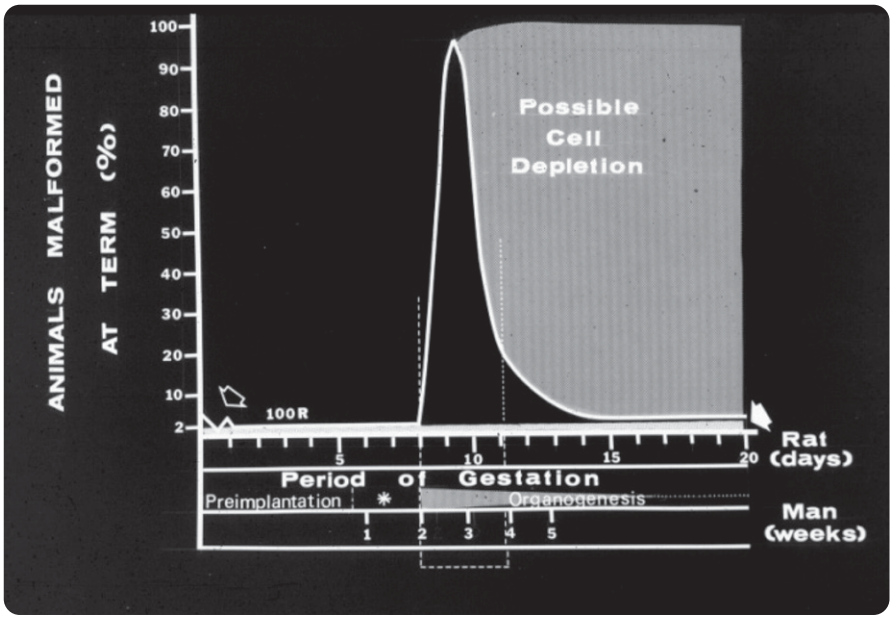
Embryonic death

The NOAEL for the lethal effects of radiation is lowest during the preimplantation, preorganogenesis stages in the rat and is approximately 0.15-0.20 Gy (15-20 rad) (0-8 days p.c.). Table 3 demonstrates the lethal effects of irradiating the embryo on the first postconception day. Note that the threshold exposure is around 0.2 Gy, but the risk of growth retardation is not increased in any of the surviving embryos receiving .20 Gy or less.

There are no human studies available during this stage of pregnancy; however, the equivalent period of development in the human would be from 0-16 days postconception (Figures 2 and 3). The NOAEL for increased risk of embryonic death increases throughout gestation and is similar to the mother's risk in late gestation.

The example of the hysteria that can occur following low-dose ionizing radiation exposure to pregnant women is represented by the results of the Chernobyl nuclear power plant explosion that occurred in 1986. There were reports of an increase in the frequency of medical abortions in Russia following the disaster. This was not the case in northern and central Europe because the exposures to the population were extremely low at great distances from the Chernobyl nuclear power plant, and there was no increase in any reproductive effect studied, including congenital malformations, stillbirths, and sponta-

FIGURE 2
A cartoon demonstrating the effects of radiation during gestation for the rat and the human



The experimental data following 1 Gy exposure to the pregnant rat on each day of gestations in separate experiments are depicted in this figure. You will note that the embryo in the first 2 weeks of human gestation and the first 8 days of rat gestation does not exhibit an increased risk for viable malformations at term. The very sensitive period for major organ malformations following radiation is present for approximately 2.5 to 3 weeks in the human from the 18th to the 40th day p.c. and 4-5 days in the rat. Interestingly, severe effects can occur after the period when major anatomical malformations cannot be produced because of irreparable cell depletion that may occur in important organs in the latter part of pregnancy (ie, the central nervous system and the gonads).

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neous abortions in Norway, Sweden, Finland, and Austria.[47-52] Yet in many countries in southeastern Europe and the Ukraine, pregnant women were inappropriately encouraged to interrupt their pregnancies.

If these data regarding the risks of developmental effects are the best estimates of the risk of irradiation during pregnancy, why did the National Council on Radiation Protection (NCRP) Handbook 54[53] establish .05 Gy (5 rad) as the embryonic exposure not to exceed when exposing pregnant women? The 0.05 Gy exposure was selected because it provided a reasonable "margin of safety" from the exposures that may represent a developmental risk. In 1977 almost 100% of diagnostic studies had exposures below 0.05 Gy. With the advent of computed tomography (CT) scans and the expansion of the use of radionuclides it is more likely that 0.05 Gy exposures will be exceeded. This can promote concern in many patients and some health care professionals. However, the threshold for birth defects, growth retardation, neurobehavioral effects, and growth retardation are above the level of diagnostic radiological exposures and the threshold increases as pregnancy progresses.

The all-or-none phenomenon

Irradiation of rats and mice with 1.5 to 2.0 Gy during the preimplantation and preorganogenesis stages increases the risk of embryo lethality; however, malformation rates in the surviving fetuses at term are similar to the controls, not because malformations cannot be produced at this stage (Figure 2). However, at this early stage of pregnancy, high exposures induce cell loss or chromosome abnormalities that most likely result in zygote death or malformations that are lethal. Our laboratory has published numerous articles on the rat and mouse that confirm the all-or-none principle.[1,10,11,38-43,54-56] Many other investigators have confirmed these findings including a recent report in the medical literature.[57]

A number of investigators have reported studies that demonstrated that high exposures of the ethylnitrosourea, retinoic acid, ethylene oxide, and high-dose radiation early in gestation resulted in lethality and a small increase in incidence of malformations.[44,45,58-68] Nagao et al[67] in 1986 performed an interesting group of experiments demonstrating, at least in their studies, that when mitomycin C was administered on the second or third postconception day, many embryos died early and late, and some were obviously malformed. When the treated embryos were transferred to untreated dams or normal embryos were transferred to treated dams, the investigators observed that the malformations were due to the effect of mitomycin C on the mother, indicating that the malformations were due to a maternal toxic effect. Rutledge[68] wrote a commentary on the publications by Nagao et al[67] and concluded that the observations of Nagao et al[67] indicated that the malformations were due to a maternal toxic effect. However, Rutledge concluded that the malformations produced in his studies were more likely because of a direct effect on the embryo.

In some instances, the results that refuted the all-or-none phenomenon were in error. As an example, Rugh[69-72] irradiated pregnant CF-1 mice on the first day of pregnancy and reported an increase in the incidence of exencephaly. In Rugh's studies, there was no dose-response relationship. The Argonne laboratories reported that the incidence of exencephaly in 1000 consecutive CF-1 litters was similar to the incidence in Rugh's radiated litters. This is what happens when you utilize too few pregnant animals in a study and the animals have a particular malformation that occurs in a 1% incidence, as in the CF-1 mouse. Rugh should have been suspicious of his results when he observed that there was no dose-response relationship. Fortunately, Rugh recognized this problem and

revised his conclusion to indicate that the results were not biologically plausible.[72]

During the 1980s and 1990s, Streffer and Pamfer and colleagues[45,59,60,73] published their excellent research that indicated that the all-or-none phenomenon might not be correct. These investigators utilized the Heiligenberger Stamm strain, referred to as the HLG/Zte strain in their radiation studies. It is a strain with a 1-4% spontaneous incidence of gastroschisis. Irradiation of this strain on the first day of pregnancy with high exposures results in an increase in embryonic mortality and a moderate but statically increased incidence of gastroschisis. C57Bl mice or HLGxC57Bl hybrids in their laboratory, when irradiated, have an increase in mortality but no increase in congenital malformations. Streffer and his colleagues stated:

> "The fact that malformations can be induced after exposure to a single cell, the zygote, contradicts the long-standing dogma of teratology that developmental defects are inducible only when the conceptus is exposed during organogenesis."

Dr Streffer is an excellent scientist, and although he was gently critical of the importance of the all-or-none phenomenon, we are colleagues and friends. More recently, he has summarized his research dealing with preimplantation exposures to radiation and concluded:

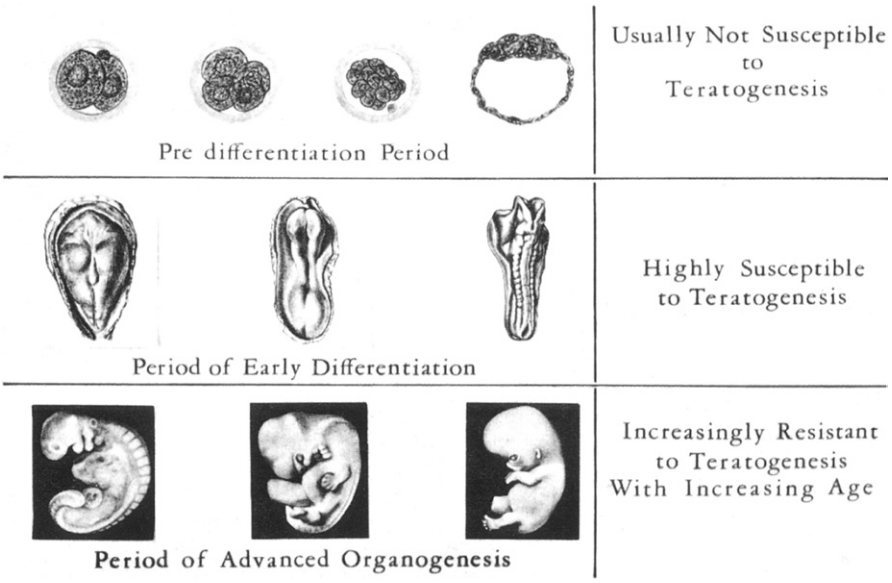
> "During the preimplantation period, radiation exposures can cause death of the embryo after radiation doses of 0.2 Gy and higher. Malformations are only observed in very rare cases when genetic predisposition exists."[74]

The all-or-none phenomenon concept indicates that the predominant effect of embryotoxic exposures during the preimplantation period is embryonic death. It also indicates that even in susceptible mouse strains, the risk for malformations is very low, even at high doses, and, most important, there are no increased developmental risks below 0.2 Gy, even in the genetically susceptible strains. The biologic basis to explain the all-or-none phenomenon is depicted in Figure 3.[37,38] Until differentiation is initiated, each omnipotential cell has the potential for forming an embryo. Whereas induced cell death can result in malformations during early organogenesis, cell death during preorganogenesis can result in embryonic death. If enough omnipotential cells survive, they can reorganize and result in normal development (Figure 3). In 1953, our laboratory referred to these cells as omnipotential cells.[38] Today they are referred to as stem cells.

How should risk managers and counselors interpret and utilize the mouse data? The fact that the reported malformations are specific for susceptible strains of mice indicates that these are genetically susceptible strains (epigenetic effect), resulting in an increase in the specific malformation from many forms of stress. In some experiments, cross-transfer has indicated that radiation of the uterus has been responsible for the epigenetic effect. Induced genetic changes in the 1-cell embryo would not result in an increase in only 1 type of abnormality, such as gastroschisis or exencephaly. Ionizing radiation's mutagenic effect is not site directed. It produces mutations randomly. There would be no biologic basis to conclude that the radiation would raise the incidence of only 1 genetically determined malformation from a radiation-induced mutation.

Therefore, it is important to realize that these unusual instances of malformations surviving to term following radiation exposures of mice on the first day of pregnancy have little applicability to

FIGURE 3
Demonstration of the 3 important phases of embryonic development with regard to the sensitivity to radiation (Wilson[37])



The period during predifferentiation, sometimes referred to as the all-or-none period, is due to the fact that these cells are omnipotential. Using today's language, we would refer to them as stem cells. They are very susceptible to the lethal effects of radiation, but the survivors do not appear to have an increased risk for anatomical malformations at delivery. The second group of embryos are 3 embryos in the very early stages of organogenesis from the beginning of differentiation on the 18th day p.c. This sensitive stage for the production of anatomical malformations lasts about 2.5 weeks. From the 40th day of gestation until delivery, the fetuses' sensitivity to radiation gradually decreases, although significant, serious effects of the central nervous system and developing gonads can result if the exposure is high enough.

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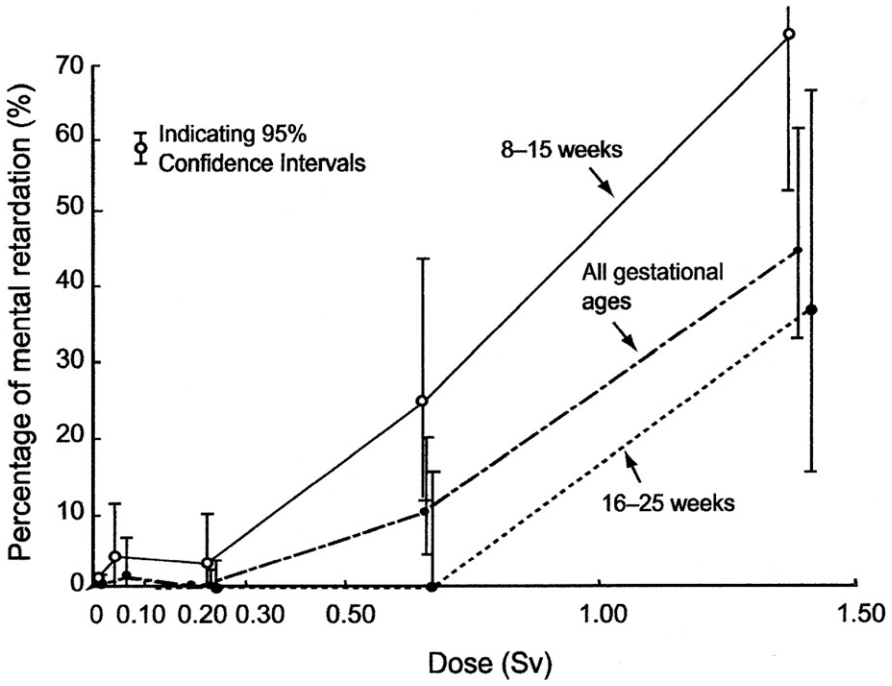
FIGURE 4
Risks of mental retardation from various exposures to radiation



Approximately 40% of the children will be seriously retarded following 1 Gy of radiation during the stages of the 8th-15th weeks of human gestation. After 15 weeks of gestation, the fetuses are less sensitive to the effects of radiation to the central nervous system. The controversy raised by these data was whether there was a threshold. In the original publication, Otake and Schull[77] indicated that they believed that there was no threshold for radiation induced mental retardation.

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the human situation. The exposure utilized by Streffer et al was not in the diagnostic range and the malformation that was present in the mouse had a high background incidence.

Most inadvertent radiation exposures of pregnant women during this early period of gestation are the result of diagnostic radiological studies that involve very low exposures. Therefore the all-or-none phenomenon can be very helpful in evaluating the developmental risks of exposures during the first 2 weeks of human pregnancy. When the exposure is in the diagnostic range and the pregnancy stage is in the first 2 weeks, there is minimal likelihood that the developmental risks of surviving embryos will be measurably increased. Our pregnancy website had 59 consultations in 2007 of women who had CT scans during the first week of pregnancy when the pregnancy test was negative. Knowledge and appropriate utilization of the all-or-none phenomenon is very helpful in this situation.

Neurobehavioral effects

There is no doubt that high doses (1-2 Gy) of ionizing radiation to the developing human fetus can produce mental retardation and microcephaly.[75-83] The most sensitive stage for the induction of mental retardation and severe microcephaly is reported to be from the 8th-15th week of human gestation.

During early organogenesis 1 Gy (100 rad) can produce a high incidence of malformations: 41% of brain malformations and 90% of eye malformations on the ninth day after conception in the rat.[36,37,39] During midgestation the brain can be depleted of neurons; when these cells are killed at this stage, they are not replaced. That is why mental retardation and microcephaly are more readily induced from the 8th-15th week of gestation. There is little disagreement about the sensitivity of the brain during organogenesis and fetogenesis. Although most radiation embryologists assumed that the exposure to diagnostic radiation was too small to produce mental retardation, there were few data in the human to confirm or refute any definitive conclusion.

In 1984, Otake and Schull[77] reanalyzed the data of the children who were irradiated in utero in Hiroshima and Nagasaki (Radiation Effects Research Foundation). They concluded that the most sensitive period for the induction of mental retardation was from the 8th-15th week of gestation and that 40% of the offspring that received 1 Gy were mentally retarded (IQ $<$ 70) (Figure 4). They also indicated that from 15 weeks until term, much higher exposures were required to produce mental retardation and the incidence was lower.

Their evaluations also concluded that mental retardation could be produced below 0.1 Gy and that radiation-induced mental retardation was a stochastic effect; in other words, it did not have a threshold. Several other investigators and even some official publications repeated the conclusions of Otake and Schull that mental retardation was an effect without a threshold.[84]

Shortly after the publication of Otake and Schull's paper,[77] a group of scientists was convened in Washington, DC, by the president of the NCRP at the NCRP office in Bethesda, MD, to discuss this issue. Drs J. Schull, R. Miller, R. Brent, R. Monson, and M. Winick discussed the idea that radiation induced mental retardation was a stochastic effect. Drs Miller, Monson, Brent, and Winick did not support this concept that in utero radiation induced mental retardation was a stochastic effect. S. Jablon, who was a statistician, did not support this "new" concept in his presentation of the Taylor lecture.[85] In Jablon's Taylor address, he said, "Somatic effects, such as the developing fetal brain, are not at all well understood, and I will say only that it is most unlikely that mental retardation following fetal radiation is a stochastic effect; the magnitude of the deficit that is

induced surely increases with the dose" (Table 2).

Without examining the human epidemiological data, there are reasons to argue against Otake and Schull's conclusion (Table 2). It is not biologically plausible that radiation of the brain at midgestation that resulted in mental retardation would be a stochastic (nonthreshold) effect. The 2 major disease categories that theoretically have no threshold from radiation exposure are oncogenesis and mutagenesis. Both these pathological effects can be manifested from an alteration of the genome of 1 cell. There is no way that a genetic alteration in 1 cell could pathologically result in mental retardation at midgestation.[10,11]

In 1999, Schull and Otake[94] reevaluated their original position expressed in 1984 and stated that "no threshold can be unequivocally demonstrated statistically in the occurrence of clinically identified mental retardation among those survivors exposed at 8-15 weeks after ovulation." They even calculated a 95% confidence interval for the threshold for mental retardation. However, in their conclusion, the authors comment as follows: "Where does this leave us?" First, it seems most unlikely that the epidemiological data will ever provide a compelling answer to the question of whether a threshold does or does not exist. The data are simply too limited to expect more than has been described. Unfortunately, in 1984, with fewer data, these authors were able to conclude that there was no threshold (Otake and Schull[77]). If we examine all the basic science data, it will be evident that radiation-induced mental retardation is a deterministic or threshold effect.

There have been many studies that have examined the neuropathology of the brains of humans and experimental animals that have been exposed to ionizing radiation. In adult humans and rats that were exposed in utero, heterotopia (Figure 5) has been demonstrated in the most severely affected individuals. This is a failure of migration of the ependymal cells that differentiate into migrating neurons to reach their proper position in the outer layers of the cortex. This phenomenon is never seen in the very low exposures. Following 2 Gy in utero exposure on the 17th day p.c. in the rat, the outer layer of the cortex demonstrates abnormal neuronal organization and areas of heterotopia.

This type of disorganization is never observed at low exposures in experimental animals, nor do you observe heterotopia at very low exposures. The irradiated fetal brain demonstrates minimal reduction of cortical neurons following 0.3 Gy exposures. It is most important to note that when you examine similar brains that were exposed to 0.01-0.1 Gy, the irradiated brains cannot be differentiated from the controls.

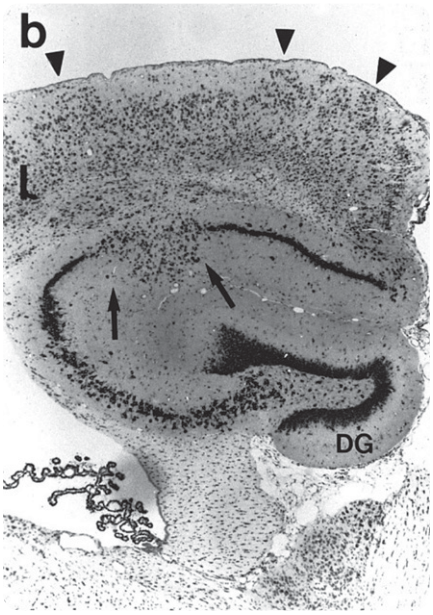
To attempt to resolve the controversy introduced by the Otake and Schull publication,[77] we began a series of experiments dealing with the neurobehavioral effects of in utero ionizing radiation using the rat.[10,86-92] Nine developmental and behavioral parameters were evaluated.[86,87] Radiation was carried out late in rat gestation when it was known that the neurological effects were the most sensitive and severe. The research of Hicks and D'Amato[93] demonstrated that the central nervous system had a broad range of serious effects that resulted following late gestation radiation in the rat. Severe hypoplasia of the cerebral cortex can be produced by administering 1.5 Gy on the 17th-20th day p.c. in the pregnant rat that is tantamount to human microcephaly.

Neurobehavioral studies were performed on the offspring of pregnant animals exposed on the ninth day p.c. and 17th day p.c. Adult offspring that were irradiated on the ninth day p.c. with 0.1-0.6 Gy did not exhibit any growth retardation, developmental effects, or neurobehavioral effects when they reached sexual maturity. This is of interest because although there was only a small number of individuals that survived the in utero A-bomb radiation during early pregnancy, Otake and Schull[77] reported there was no increase in severe mental retardation or microcephaly in this group of human survivors.

This observation in humans and the negative results in the animals irradiated early in pregnancy are supported by the known resiliency of the central nervous system early in pregnancy. At low exposures, below the threshold for the production of major malformations, the central nervous system cortical neuronal primordial cells are readily replaced. This does not happen in the human in midgestation or in the rat in late gestation. Irradiation of the rat during late gestation does result in developmental effects at low exposures with thresholds for growth and development at 0.4 Gy and for 1 reflex at 0.2 Gy.

Besides Otake and Shull, there have been a number of investigators that have evaluated the data pertaining to the population of individuals exposed in utero in Hiroshima and Nagasaki.[81-83] The discussion of the issue of radiation-induced mental retardation by Miller[79] indicated that when the exposure is less than 0.5 Gy, the risk

FIGURE 5
Rat brain after 1 Gy radiation on the 17th day p.c.



Arrows are pointing toward neuronal cells that failed to migrate to their proper location. This is referred to as heterotopia. It is found in human brains in retarded individuals following high doses of radiation (Jensh et al[86,87]).

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of severe mental retardation is similar to the unexposed population.

Mental retardation is not an uncommon occurrence, with a prevalence of approximately 1 per 100 births. Miller's recalculation of the risk of mental retardation estimates the threshold to be 0.57 Gy (95% confidence interval, 0.35-0.66 Gy). In a more recent publication, Schull and Otake[94] now agree that there is a threshold for radiation produced mental retardation. These authors also reported that on the average, 1 Gy exposure during pregnancy reduced the IQ 30 points. Therefore, even if mental retardation were a stochastic effect, the loss of IQ at 0.01 Gy would only be 0.3 IQ points, which could not be responsible for mental retardation.

To summarize the controversy about the relationship of ionizing radiation and mental retardation and whether 0.01 Gy can increase the risk of mental retardation, the data indicate that it is not a stochastic effect, which is supported by the following findings.

- Teratogenic effects are primarily threshold phenomena.
- In utero exposure to ionizing radiation indicates that there is approximately a 30 point IQ loss per Gy (100 rad) during the most sensitive period of human brain development, indicating that severe mental retardation would not occur, even if there were not a threshold, because a linear relationship to exposure would predict a 0.3 IQ loss at .01 Gy (1 rad).
- Animal studies indicate that at 0.01 Gy, there are no observable histologic effects in the developing brain that could account for severe central nervous system effects.
- Neurobehavioral evaluations of animals exposed in utero demonstrate a threshold for behavioral effects at the same dose as for other teratologic effects (0.2 Gy).

Whereas Schull and Otake[94] are concerned that the epidemiological data are not consistent and robust enough to answer the question as to whether mental retardation is a stochastic or a deterministic effect, the basic science of neurological development and neuropathology can readily answer the question. It is true that epidemiology is the foundation of determining human risks; however, occasionally basic science and animal studies can fill the void left by insufficient epidemiological data. Radiation induced mental retardation is a deterministic effect.[10,11,79]

The importance of dose rate, fractionation, and protraction in determining the risks of ionizing radiation on the developing embryo

Many diagnostic radiological studies occur over a period of hours or days, and it is important to consider the modifying biological effect of the protraction or fractionation when estimating the reproductive and developmental risks. This concept is strengthened further by the fact that most human exposures to extensive diagnostic radiation studies are fractionated or protracted. Protracted exposures are less likely to produce deterministic developmental effects than is an acute exposure of low linear energy transfer (LET) radiation.[95-109]

Brizzee and Brannon[97] irradiated rats with 1.5 Gy (150 rad) on the 12th day of gestation with an acute exposure and various fractionated exposures over a period of 12 hours. The brains of the adult rats were examined histologically. The acute exposure reduced the volume of the outer layers of the cerebral cortex by almost 50%. It was obvious that the number of neurons were markedly depleted. The animals that received 1.5 Gy in 9 fractions over a period of 12 hours were not statistically different from the unirradiated controls, although there was a slight visible reduction in the thickness of the cerebral cortex. Thus, the fractionation of radiation reduced the severity of the neuropathological effect of the exposure, even when it occurs only over a period of 12 hours.

Coppenger and Brown[98] and Stadler and Gowen[107] exposed rats and mice, respectively, over a period of 10 and 11 generations. They utilized a ^{60}Co source that could be lowered for 1 hour each day to permit personnel to water, feed, and observe the animals. At 0.02 Gy (2 rad) per day continuous radiation exposure, these investigators did not observe any reproductive or developmental effects. They did observe effects at 0.05 Gy (5 rad) per day. Russell et al[105] utilized continuous exposure from an x-ray machine during the day to pregnant mice for the entire gestational period. She and her colleagues did not observe any effects following 0.125 Gy per day except that the female mice had a reduced number of litters during their reproductive life.

Our own laboratory irradiated rats on the ninth day p.c. with 1.5 Gy (150 rad). Four different dose rates were utilized: 0.005, 0.012, 0.34, and 1.0 Gy per minute.[96] The results demonstrated the marked ameliorative effect of protracted irradiation over a 5-hour period. The acute exposure of 1.5 Gy delivered in 1.5 minutes resulted in 30.3% anencephaly at term. The exposure that delivered the 1.5 Gy over a period of 5 hours resulted in 0% anencephaly. Of course, there were deleterious effects in the group of animals that had received the protracted radiation; however, the effects were less severe.

Although these animal results cannot be directly applied to developing human embryos and fetuses, the impact of protraction and fractionation should be considered when counseling pregnant women who have been exposed to the following: (1) multiple procedures over a period of days, (2) radionuclides with long half-lives, and (3) background radiation from flying at high altitudes or occupational exposures.

The indirect effect of irradiation on embryonic development: does maternal radiation exposure without directly exposing the embryo increase the risk of developmental effects?

In the 1950s and 1960s, our embryology unit at the University of Rochester, Rochester, NY and the Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA received numerous consultations from obstetricians, genetic counselors, general physicians, and patients. Pregnant patients had been exposed to ionizing radiation from various diagnostic procedures. The number of calls that were initiated by pregnant women who were concerned about the fetal effects of a chest x-ray or an x-ray of

their extremities, head, or neck was surprising. Initially we reassured the patients that there was no increased risk because it was not biologically plausible to conclude that the embryo or fetus would be harmed by a low exposure of radiation to other parts of the body when the embryo would not be exposed. On the other hand, we had no scientific data to support that conclusion. So we initiated a series of animal experiments using the pregnant rat.

The first animal experiments dealing with the indirect effect of radiation on embryonic development were reported in the 1960s.[110-114] Pregnant rats were anesthetized on the ninth day p.c. The abdomen was opened and the 2 uterine horns containing the embryos were placed in a U-shaped lead shield. Another lead shield was place over the embryos (Figure 6).

Microdosimeters were used to measure the exposure inside the lead shields. The exposure was insignificant, being less than 0.01 Gy (1 rad), even when very high exposures were administered to the pregnant rat. The pregnant rat was given 4 Gy (400 rads) of whole-body irradiation. There were shielded unirradiated controls and rat embryos that received 4 Gy. All the embryos that received 4 Gy did not survive to term. There was no increase in the incidence of congenital malformations or growth retardation in the unirradiated, shielded embryos, in spite of the fact that the pregnant rat received 4 Gy (400 rad) of whole-body radiation. Malformations were not increased, even when the pregnant rat received higher exposures; however, the mothers exhibited radiation sickness at 10 and 14 Gy, resulting in an increase in embryonic death and growth retardation but not an increase in malformations.

Brent and McLaughlin[113] transilluminated the embryonic sites on the 12th day p.c. so that the placenta and embryo's location could be identified. Then a series of experiments were performed while shielding the placenta or embryo. The results indicated that the placenta was very resistant to 4 Gy and the shielded embryos survived. When the placenta was shielded and the embryo was irradiated, the embryos were seriously affected.

The final series of experiments were performed on the day of conception and a lead shield was fabricated so that it was attached to a hemostat. The hemostat could be closed over the fallopian tube and ovary, or just the fallopian tube, without compromising the blood supply to the uterus and fallopian tube. On the first day of pregnancy, the pregnant rats received whole-body radiation with the fallopian tube shielded, the ovary shielded, or both the ovary and fallopian tube shielded. At this stage the fertilized ova or 2-cell zygotes are within the fallopian tube.

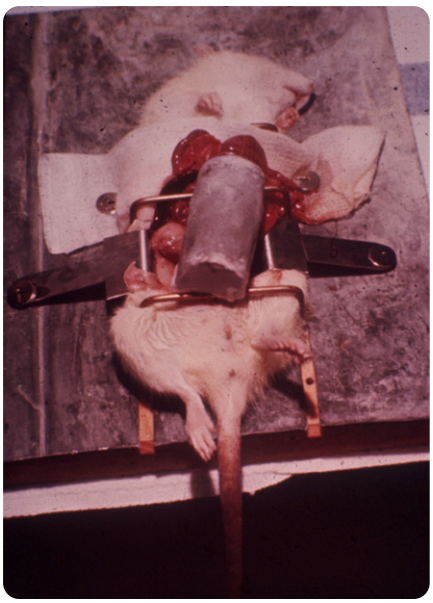
In other experiments the mother was shielded and the fallopian tube and or ovary was irradiated. The exposure was 1 Gy (100 rads) in all instances, and the results indicated that the embryos were not affected when the embryos in the fallopian tube were shielded.[42,43,114] In other words, if the maternal organism and the uterus received whole-body radiation and the fallopian tube was shielded, the 1- or 2-cell embryo was not affected.

These experiments demonstrated that when the pregnant mother has diagnostic radiological studies of the head, neck, chest, or extremities, the embryo is not exposed to radiation doses that will increase the risk of embryonic death (miscarriage), growth retardation, or congenital malformations. These negative experiments were carried out during preorganogenesis, early organogenesis, and the early fetal period. On the other hand, when the exposures are in the range of radiation therapy (> 1000 rads), growth retardation and embryonic death in the rat occurred because the pregnant rats exhibited signs of radiation sickness.[110]

Besides the above-mentioned studies that specifically analyzed the indirect effect of irradiation during pregnancy, there are scores of animal experiments indicating that the NOAEL for congenital malformations, fetal growth retardation, and embryonic loss are greater than 0.20 Gy whole-body irradiation, even when the embryo is also exposed. In the rat, embryonic death may occur in the preimplantation period at 0.15 to 0.2 Gy, although there are no human data that are informative about the NOAEL for embryonic death during the preimplantation stages.

In spite of all these studies, Hujoel et al[115] published a report in the Journal of the American Medical Association indicating that dental x-rays averaging 0.4 mGy (40 mrad) in pregnant women may be responsible for babies being born with low birthweight because of the irradiation of the maternal thyroid and/or pituitary. Whereas the conclusion and the hypothesis to explain the results were naive, poor quality research results do appear in the scientific literature. The problem with this paper is that the pregnancy website of the Health Physics Society received many e-mails indicating concern about the article by Hujoel et

FIGURE 6
Indirect effect of radiation on the developing embryo



A photograph from experiments that were performed to study the indirect effect of radiation on the developing embryo, which is irradiation of the mother or parts of the mother when the embryo is shielded. The photograph demonstrates the shielding technique that was used to prevent the pregnant uterus from being exposed while the mother received high doses of ionizing radiation.

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al.[115] The contacts wanted to know whether they should refrain from visiting the dentist while they were pregnant.

A commentary from our laboratory responded to the article by Hujoel et al[115] as follows[22]:

1. Epidemiological studies indicate that the threshold exposure for growth retardation for direct radiation of the fetus is 200- to 300-fold higher than the exposure from dental radiography.
2. Epidemiological studies that involve diagnostic radiation to the thyroid, pituitary, and head do not find that fetal growth retardation is a result of these exposures.
3. Numerous animal studies indicate that the embryo must be directly radiated to produce fetal growth retardation.[42,43,110-114] When the whole pregnant animal is irradiated, which includes the embryo, maternal thyroid, and pituitary, the threshold dose for growth retardation is 500-fold higher than dental radiography exposures to the mother's neck and head in the study by Hujoel et al.[115]
4. The suggestion that low-dose radiation to the pituitary and thyroid of the mother could produce fetal growth retardation is itself biologically and medically naive. Hujoel et al could have read any basic pediatric or pediatric endocrinology textbook, and they would have discovered that growth hormone does not influence human growth until several months after the infant is born. So neither maternal growth hormone nor fetal growth hormone plays a role in fetal growth. The mother's thyroid function will not be affected by the level of radiation absorbed from dental x-rays. Maternal thyroid function is irrelevant to the fetus's growth unless the mother is severely hypothyroid. Even the hypothesis of Hujoel et al is biologically incorrect.

This information should be helpful to radiologists, dentists, obstetricians, health physicists, teratology counselors, and radiation biologists to counsel pregnant patients about their concerns of visiting dentist. It can be definitively stated that dental radiography is not a risk for any fetal effects, including fetal growth retardation.

The risk of leukemia and cancer in children and adults who were exposed to ionizing radiation during their in utero development

Stewart et al[116-120] suggested that the human embryo was more sensitive than the child or adult to the leukemogenic effects of radiation, and in later publications they concluded that other cancers also occur more frequently in persons exposed in utero to diagnostic radiological procedures (primarily pelvimetry). Stewart's estimate is that 0.01 to 0.02 Gy (1-2 rads) in utero radiation exposure increases the chance of leukemia developing in the offspring by a factor of 1.5 to 2.0 over the natural incidence. This incidence is considerably greater than the increase resulting from 0.02 Gy delivered to an adult. In fact, a dose of 0.02 Gy delivered to an adult population would not make a perceptible change in the incidence of leukemia, even for large population groups.[121-123]

Lilienfeld[123] reviewed the epidemiologic considerations with respect to leukemogenesis. The results of Lilienfeld,[123] McMahon,[124] McMahon and Hutchison,[125] Graham et al,[126] Polhemus and Koch,[127] Yamazaki et al,[128] Ager et al,[129] and Ford and Patterson[130] support the thesis that diagnostic radiation absorbed in utero is associated with an increased risk of leukemia. Six of 9 studies summarized in the paper by Lilienfeld[123] indicated an increase in leukemia risk of 1.3- to 1.8-fold following diagnostic radiation exposure in utero. Lilienfeld states: "When one considers the variety of control groups used and the sampling variability, the results are remarkably consistent in showing an excess frequency of leukemia among children of radiation-exposed pregnant mothers.[123]

Diamond et al[131] have extended the studies of Lilienfeld and corroborated their early finding of a higher incidence of leukemia (3-fold) in children exposed to diagnostic radiation in utero. They also reported that this effect did not occur in the black population.

There are a number of interesting associations in these data that should be pointed out. In the studies of Stewart and Kneale,[120] there was a higher incidence of previous miscarriage in the mothers receiving pelvimetry, and the children in the pelvimetry group had a higher incidence of upper respiratory infections prior to the development of leukemia.[120] Others have reported that infants from families with a strong family history of allergy are also more susceptible to radiation-induced leukemia when exposed to diagnostic radiation in utero.[122]

The problem with these data is that in some instances patients with an allergic history and no preconception radiation had a higher frequency of leukemia than did some groups that had received irradiation in utero. Tabuchi[33] reported no increase in leukemia following diagnostic radiological procedures.

In some of the studies that did not report an increased risk of leukemia, the number of patients was small. Of the 86 persons exposed in utero to high exposures from the atomic bomb, none developed leukemia.[132] These persons received considerably higher doses of radiation than did those patients in the previous studies. Kato[133] studied 1300 people, some of whom were exposed to the atomic bomb while in utero, and observed no increased evidence of malignancy in the first 24 years of follow-up, although there was an increased mortality in the first year of life and after 10 years of age.

It is of interest that Graham et al[126] reported an increased risk of leukemia that was identical whether a mother had received radiation from diagnostic procedures shortly before or after conception. Hoshino et al[132] reported no increase in leukemia in a study of 17,000 children of parents who had received radiation before conception from the atomic bomb.

The question arises as to what extent the same biases that contribute to the increased risk of leukemia in the cases of radiation exposure before conception also affect the in utero radiation cases. Graham et al[126] pointed out that children of mothers with a history of abortion or stillbirth also had children with a higher risk of leukemia. Neutel and Buck[134] found that childhood malig-

TABLE 4
Risk of leukemia

Group	Risk	Latency
Identical twin of a leukemic twin	1:5	Weeks to months
Radiation induced polycythemia	1:6	10-15 y
Bloom's syndrome	1:8	< 10 y of age
Hiroshima survivors < 1000 m hypocenter	1:60	3-12 y
Down's syndrome	1:95	Weeks to months
Radiation rx of ankylosing spondylitis	1:270	15 y
Siblings of a leukemic child	1:720	10 y
Combined background risk of leukemia plus radiation risk from Stewart[117-121]	1:2000	10 y
Additional risk of in utero diagnostic radiation studies (Stewart[118])	1:6000	10 y
In utero diagnostic radiation (RERF) data and other cohort studies	Risk the same for exposure during childhood but actual risk is uncertain (Miller[79]; Brent[10])	Lifetime
US Caucasian < 15 years of age	1:3000	10 y

RERF, Radiation Effects Research Foundation; *rx*, treatment.

Adapted from Miller RW. Epidemiological conclusions from radiation toxicity studies. In: Fry RJM, Grahn D, Griem ML, et al, eds. Late effects of radiation. London: Taylor & Francis; 1970. p. 245-56.

Brent. Saving lives and changing family histories. Am J Obstet Gynecol 2009.

nancy occurred more often in the offspring of mothers who smoked. Fasal et al[135] reported that infants who were heavier at birth were more likely to get leukemia. It appears that whenever one looks for the association of an event with the occurrence of leukemia, it may be found.

At present it is not clear whether radiation exposure from diagnostic radiological procedures during the preconception or postconception period is a causative or associative factor in the increased incidence of leukemia. Miller[136] and others[122,137-140] dissent from the conclusions of Stewart et al and all the reports that support their hypothesis. Miller[136] writes:

> Minimal doses of x-rays are equally oncogenic whether exposure occurred before conception or during pregnancy, whether the neoplasm studies were leukemia or any other major cancer of childhood, and whether the study was based on interviews that may be biased, or on hospital records. Taken in aggregate, the similarity of results, in the absence of a dose-response effect or of supporting data from animal experimentation, raises a question about biologic plausibility of a causal relationship.

Furthermore, Miller points out that siblings of children with leukemia have an incidence of leukemia of 1 in 720 per 10 years, which is greater than the 1:2000 risk of leukemia following pelvimetry exposure and the 1:3000 probability of leukemia in the general population of children followed up for 10 years (Table 4). The publication of Stewart and Kneale[120] on this subject reinforces the contention that radiation may not be the etiologic factor responsible for the induction of malignancy because unirradiated siblings of the irradiated patient population had a higher incidence than control siblings and control patients. This observation would indicate that genetic or other environmental factors might be of importance in the production of leukemia as well as prenatal diagnostic radiation.

Rugh et al[141] irradiated mice with 1.0 Gy on each day of gestation and observed the incidence of tumors in the offspring. There was no statistical increase in the incidence of tumors in adult animals from irradiation in utero on any day. Brent and Bolden[114] exposed pregnant mice to doses of 0.30, 0.60, and 0.90 Gy after 0.5, 7.5, 8.5, 12.5, and 16.5 days of gestation. They also did not observe an increase in the incidence of tumors. However, the presexually mature mouse was more sensitive than the adult mouse to the leukemogenic effect of radiation. The difficulty with animal data is that although it is interesting, it cannot be utilized to definitively refute human epidemiology data or biologically valid hypotheses.

At present, a number of investigators believe that in utero exposure to small amounts of radiation increases the risk of leukemia and other malignancies, whereas other investigators seriously question that the embryo is markedly more sensitive to the leukemogenic effects of irradiation when compared with the child or adult. Until the mechanism is understood, there will be doubt concerning the magnitude of the role of in utero radiation in leukemia induction.

The increased incidence of cancer in children exposed in utero to diagnostic radiation has to be clarified in view of the fact that higher doses of radiation to an-

TABLE 5
Number of patients with solid cancers

In utero exposure from the atomic bomb

Dose in Sv (rads)	Patients, n	Cancers, n	Person-years	Cancers, %
< 0.005 (< 0.5)	1547	54	49,326	3.5
0.005 to < 0.1 (0.5-10)	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
> 1.0	48	3	1404	6.2
Total	2452	94	94	3.5

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imal embryos and to the children exposed in utero at Hiroshima and Nagasaki, Japan have not resulted in a marked increase in the incidence of cancers from high doses of radiation, which one would expect, if the embryo were as sensitive to the carcinogenic effects of radiation as Stewart and colleagues suggest.[116-120]

One cannot overemphasize either the importance of the multiplicity of factors involved or the difficulties in their identification and control. Even laboratory experiments concerned with tumor production are difficult to interpret. For example, Ross and Bras[142] reported that the incidence of spontaneous tumors varied with the diet and weight of the animals. Heavier animals on high-protein diets had a higher incidence of tumors than did the lighter rats on low-protein diets. Hence, there are many unanswered questions concerning the relationship between in utero radiation exposure and the occurrence of leukemia and solid cancer tumors.

Recently published results of the occurrence of cancer in adults who were irradiated in utero in Hiroshima and Nagasaki indicate that there is an increase in the incidence of cancers in the exposed population.[143] The long-term study in Hiroshima and Nagasaki does not support the marked increased incidence in childhood malignancies suggested by Stewart and colleagues, and the incidence of cancer in the adults does not support the markedly increased sensitivity of the fetus to radiation-induced cancer as suggested by Stewart et al.[116-120] There is little disagreement with the concept that low doses of radiation to the embryo represent a theoretical carcinogenic risk and that there may be different risks following the same exposure at different stages of development. The concept that is difficult to explain from a basic science viewpoint is why would proliferating embryonic cells be 2 orders of magnitude more sensitive to radiation than a child's or adult's proliferating cells?

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.[143] The data are summarized in Tables 5 and 6. 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 less than 0.2 Sv (20 rads) (Table 5). 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[143] (Table 6).

It is interesting that the research of Rugh et al[141] and Brent and Bolden[114] indicated that the embryonic mouse was less sensitive to the oncogenic effects of ionizing radiation than the postnatal mouse. However, both Rugh and Brent and Bolden were reluctant to refute Stewart's conclusion that the radiation induced oncogenic risk of the human embryo was 2 orders of magnitude greater than the postnatal human on the basis of the mouse radiation studies alone.

Although a dose of less than 0.1 Gy to the implanted embryo does not result in a significant increase in the incidence of congenital malformations, growth retardation, or fetal death, we cannot yet categorically dismiss low-risk oncogenic effects at exposures below 0.1 Gy (10 rad). Even if one believed that the increased oncogenic risks of low-level radiation were real, let us examine how difficult it would be to use this information in counseling a patient whose embryo has received a dose of perhaps 0.02 Gy (2 rad) during her pregnancy. According to Stewart et al[116-120] the risk of leukemia following this exposure in utero is 1:2000 vs 1:3000 in unexposed controls over a 10 year period (Table 4). If one were inclined to recommend therapeutic abortion for this embryo because the probability of developing leukemia is 50% greater than controls, one would perform abortions in 1999 exposed that would not develop leukemia for every leukemic subject saved.

It is one thing to avoid radiation because of a potential or conjectured hazard, but it is another matter to recommend therapeutic abortion on this basis. If a physician were inclined to accept this increased probability (1:2000) as a risk

TABLE 6
Number of patients with solid cancers

Early childhood exposure from the atomic bomb

Dose in Sv (rads)	Patients, n	Cancers, n	Person-years	Cancers, %
< 0.005 (< 0.5)	8549	318	247,744	3.7
0.005 to < 0.1 (0.5-10)	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
> 1.0	274	48	7620	17.5
Total	15,388	649	451,031	4.2

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great enough to recommend therapeutic abortion, he or she would be placed in a serious dilemma because there are other epidemiologic situations in which the risk of leukemia is greater. In fact, the hypothetical incremental risk for 0.02 Gy of in utero radiation is 1:6000 over a 10-year period. It is the combination of the control risk plus the incremental radiation risk that results in a 1:2000 risk for these patients. If one examines Table 4, it is obvious that the risk of leukemia is greater in unirradiated siblings of children with leukemia (1:720) than in patients subjected to diagnostic radiation (1:6000) according to the data of Stewart and colleagues.[116-120]

Certainly the position that all future pregnancies of parents with 1 child with leukemia should be aborted would be untenable. One can carry this argument to its ridiculous extreme by advocating that all pregnancies should be aborted because the risk of malformation is approximately 30-60 per 1000 deliveries, and this does not include the probability of postnatal diseases occurring in these offspring. Some may interpret this as a facetious discussion, but the clinician and the patient must recognize that "spontaneous" developmental risks of pregnancy are 2 orders of magnitude greater than the theoretical risks of oncogenesis following in utero diagnostic radiation exposures.

In 1999, Boice and Miller[144] published their interpretation of the data pertaining to the oncogenic risks of low-level 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." Learned debate continues as to the causal nature of low-level intrauterine radiation exposure and subsequent cancer risk. The association is not questioned, but the etiologic significance is. Different scientists interpreting the same data have different opinions as to the causal nature of the association and the possible level of risk.[138,143-149]

The most recent conclusions from the Radiation Effects Research Foundation website[143] with regard to the oncogenic effects of in utero radiation in the atomic bomb survivors is stated as follows: 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[143] (Tables 5 and 6).

After reading the multiple opinions concerning the leukemogenic and oncogenic risks of low-level radiation exposures that occur from diagnostic radiological procedures, the physician can be placed in the untenable position of having to counsel a pregnant woman who asks the following question: "I am 2 months pregnant and had a CT scan of my abdomen. What is my child's risk of developing cancer?"

Although there are a few ways of explaining the risk of cancer to a mother of a child that has been exposed to diagnostic irradiation during childhood or pregnancy, we do not know the exact risk at these low exposures. There may not even be a measurably increased risk at exposures in the diagnostic radiological range, according to the most recent publication by Preston et al.[143]

We do know the following facts:

1. Approximately 18% of the population will develop a malignancy. That means that 18,000 of every 100,000 persons will develop cancer. You can be optimistic and indicate that the cure rate for cancers is increasing every year, and you can point out that the greatest improvement in cure rates has occurred in the childhood cancers.
2. You can indicate that the data from Hiroshima and Nagasaki has not recorded a single case of childhood leukemia in the population that was exposed to radiation in utero.
3. You can report that the latest publication from the data obtained from studying the cancer rate in the population exposed in utero following the atomic bomb indicates that there is a threshold for oncogenic effects at less than 0.2 Sv (less than 20 rad)[143] (Table 5). That means that there may not be a risk for the oncogenic effects of ionizing radiation from diagnostic radiological exposures

The language that is used to explain the risks can decrease or promote concern. Your patient reads in the newspaper or on the internet that a CT scan exposure has a 1 in 5000 risk of resulting in cancer, keeping in mind that the information is most likely incorrect. How

would you communicate the risk to your patient? There are 3 possibilities:

1. you have a 1 in 5000 risk of developing cancer from this x-ray study;
2. you have a 4999 in 5000 probability of not developing cancer from this x-ray study; or
3. would you just say, I do not know the risk, but it is very, very small or not increased at all.

It is important to understand that many lay individuals are not trained in interpreting risks. Many individuals will travel to a casino or buy tickets for the state lottery with a 1 in 5 million chance of winning. However, if the individual was told that he/she had a 4,999,999 probability of not winning, it would dampen enthusiasm for gambling. Keep that in mind when you are counseling patients concerning their oncogenic risks.

Counseling pregnant women and men and women of reproductive age with regard to the reproductive and developmental risks from radiation exposures

Experience with thousands of consultations in the clinic, on the telephone, by letter, and, most recently, via the Internet has taught us many lessons about the misinformation that patients receive concerning the reproductive and developmental risks of radiation exposures that have been provided by physicians, nurses, doctors in training, other health care professionals, friends of the patient, the news media, and the Internet. Unfortunately, we have learned that many physicians and other counselors are not prepared to counsel patients concerning radiation risks. Approximately 8% of the website contacts, who had consulted a professional, were provided inaccurate information that could have resulted in an unnecessary interruption of a wanted pregnancy.

Too frequently, advice is provided to the patient without performing an adequate evaluation that is necessary to determine whether there is a measurably increased risk to the mother and/or her developing embryo.[11,16,19-22,53,115,150-153]

Whereas the individual contacting a counselor or physician may be the patient, the husband, a relative, or a friend, the counselor needs to have the following information:

1. Is the contact pregnant, possibly pregnant, or planning to become pregnant?
2. If the contact is pregnant, does she know the date she became pregnant? Does she know the date of the first day of her last menstrual period?
3. Does she know the date of conception from other sources: an ultrasound that timed the pregnancy or a date when intercourse took place that is consistent with other information about timing?
4. Are there historical pregnancy risks for the mother or the family? For example, a history of miscarriages, birth defects, infertility, or serious illnesses in the contact, parents, or siblings.
5. What was the type of radiation exposure? Lay individuals confuse ionizing radiation with nonionizing radiation and microwave antennas with microwave receivers (dishes).
6. If the contact is concerned about ionizing radiation, has the exposure to the embryo been estimated by a qualified health physicist? Was the exposure an acute, protracted, or fractionated exposure?
7. Has the contact sought advice from another counselor about the developmental risks of this exposure?
8. Was this a planned or wanted pregnancy? What are their concerns and thoughts about the pregnancy?

An evaluation should be made with both patient and counselor arriving at a decision. The counselor should record this information, noting that the patient has been informed that every pregnancy has a significant risk of problems, and that the decision to continue the pregnancy does not mean that the counselor is guaranteeing the outcome of the pregnancy. The use of amniocentesis and ultrasound to evaluate the fetus is a decision that would have to be determined for each contact.

Many other issues may occur during this interaction with the contact. In e-mail interactions, it may take as many as 10 interactions before a reasonable risk estimate can be provided to the contact. Because many of the contacts are concerned, anxious, or distraught, it is sometimes possible to give a presumptive risk analysis to the patient while waiting for more information (ie, the actual radiation exposure). Rarely, there is not enough information to provide a definitive risk analysis to the contact.

Table 1 summarizes the estimated developmental risks that can be utilized by counselors when evaluating ionizing radiation exposures to the embryo.

An overview of these risks is as follows:

- The risks of the vast majority of most diagnostic radiological procedures do not represent significant reproductive risks and do not warrant the interruption of wanted pregnancies.
- Therapeutic radiation and therapeutic radionuclide procedures do represent potential developmental risks; however, each case has to be evaluated because not infrequently, the risks are also not increased, depending on the part of the body being irradiated and the calculated exposure to the fetus.
- Evaluation of the allegation of radiation-induced malformations necessitates detailed analysis and cannot be performed superficially.
- There is not always enough information to draw definitive conclusions about whether there is an increased risk for developmental or reproductive effects. It is difficult for a physician and scientist to say, "I do not know the answer to your question."

It is most important that a counselor understand that his/her task is primarily to provide an accurate, scientifically based risk analysis. It is not the counselor's responsibility to tell the patient what to do, although it is appropriate to discuss all options that are within the law.

A summary of interaction on the health physics pregnancy website, ask the expert (ATE)[154,155]

The pregnancy website is the largest component of the Health Physic's Society's (HPS.org) ATE website. The pregnancy section of the Ask the Expert website is the most frequently contacted section. In 2007 the pregnancy website of the Health Phys-

ics Society (HPS) received 1,299,672 visits. The contacts who downloaded information totaled 620,035.

It would be impossible to provide the answers to the numerous types of questions that are received on the pregnancy website. However, the website lists scores of questions and the answers that have been provided. Go to HPS.org and click on the section Ask the Expert. Then click on Pregnancy.

This publication has concentrated on the developmental risk of embryonic exposures. Approximately 20% of the questions are concerned with radiation exposure to the testicles and ovary and the effect on fertility and the genetic risks to the future offspring. These preconception exposure questions are answered on the website. One of the most common questions is how long do I have to wait if my sperm or ova have been exposed during a diagnostic radiological procedure. The accepted answer is 2 spermatic cycles for the man and 3 menstrual cycles for the woman. This is a very conservative approach because the risk of genetic disease after such low exposures is extremely small and there is no increased risk of infertility.

After reading the website information, 1442 individuals who were still concerned contacted the website directly about their particular exposure and its risk. The contact still had questions or was concerned and anxious. In 2007, we provided our 20,000th consultation. These consultations come from all over the world. Most contacts receive a response within 24 hours. Frequently, the contact has been sitting at the computer waiting for an answer to their questions. The benefit of the website to patients from all over the world and their appreciation for receiving an objective, compassionate response is very much appreciated by the consultants of the Health Physics website, Ask the Expert. The majority of contacts send simple notes of appreciation such as, "Thank you so much. You are doing a priceless job by reaching out to people."

Many notes of appreciation are extensive and inform the counselor that the information has been crucial in relieving distress and concern about the radiation exposure. These interactions also reveal how much misinformation physicians and other health professionals provide to the families.

Comments by health professionals include:

"You are healthy; why take a chance? Abort the baby and try again."

"Your baby will have a 50% chance of being mentally retarded from that chest x-ray."

Although counselors may provide misinformation to their patients, the internet is much worse.

A not infrequent comment is: "Thank God for the Health Physics website, Ask the Expert. It is a lifesaver."

Probably the most important accomplishment is the knowledge that hundreds and hundreds of planned or considered abortions were canceled. These decisions can radically modify the life of a family.

FIGURE 7
Three photographs of the Joergs family

Our laboratory has scores of photographs of mothers, who were told to interrupt their pregnancies because of a radiation exposure during their pregnancy, and their children. These families contacted our laboratory and obtained information that indicated that the embryo or fetus was not at increased risk. Mrs Nancy Joerg and her daughter Jeanette gave us permission to show this photograph, which demonstrates 3 generations in their family. Mrs Joerg was scheduled for an interruption of her pregnancy with Jeanette, the child in the photograph as an infant, before Mrs Joerg called our laboratory. Jeanette is shown at the age of 16 years when she came to the NCRP meeting along with her mother to tell their story as to how their lives were changed when the interruption was canceled. The photograph on the right is a picture of Jeanette with 2 of Mrs Joerg's grandchildren. In the text, there is a statement by Mrs Joerg explaining this episode in 1975 when Jeanette was born and how it has changed their family's lives.

Reprinted with permission from Jeanette Joerg Turley.

Brent. Saving lives and changing family histories. Am J Obstet Gynecol 2009.

Mrs Nancy Joerg's comments

Nancy Joerg was one of the participants at the 1977 annual National Council for Radiation Protection (NCRP) meeting. The annual meeting was devoted to the reproductive and developmental risks of all types of radiation. Mrs Joerg spoke to the NCRP about her personal experience of canceling a scheduled pregnancy interruption after receiving counseling by telephone in 1975. She had been told to abort her pregnancy by 3 physicians, 2 obstetricians, and a medical geneticist. Her story was published in the monograph dealing with the 1997 symposium.[156]

In a recent letter from Mrs Joerg, she informed me that the child who had been scheduled for a pregnancy interruption in 1975 is married and has 2 children (Figure 7). Mrs Joerg explains how that phone call in 1975 has changed her life.

An excerpt from a letter from Nancy Joerg, 2006

> I sometimes think back to 1975 and wonder what my life would have been like if Jeanette had not been born. Not only would I not have my beautiful daughter Jeanette and no granddaughters in my life, I would

have a lifetime of sadness and loss because I had followed the advice of 3 doctors who knew nothing about the risks of radiation. That is what was tormenting me when I called you in 1975. On what scientific or medical data was the decision to terminate the pregnancy based? The incredibly important scientific and medical work of the scientists studying the effects of radiation on the embryo has had a direct and personal impact on myself and my family. I can never thank you enough. The impact of that phone call in 1975 on my family and future generations of my family is beyond description.

A note of appreciation to all the individuals who have sought advice and counseling

Laboratory scientists who work with animals may never see their research benefit a single patient in their lifetime, although their research may be conceptually important and useful scientifically or clinically at a future date. Yet the results of radiation embryology research has affected and benefited the lives of thousands of families. Just as important is the willingness and persistence of scientists to debate the controversial issues, attempt to resolve the controversies, and then apply the best science to assist patients in turmoil about the risks of radiation to their offspring.

As a physician, I must thank the thousands and thousands of patients who have contacted a stranger that they have never met to reveal the intimate details of their reproductive problems. I have met only a very few of these contacts and twice have had the pleasure and honor to meet with Mrs Joerg and her daughter Jeanette (Figure 7), as an infant, teenager, and mother). Almost all of my contacts have been by telephone, letter, or the internet, so in most instances, we have never personally met. Fortunately, we have scores of photographs on the newborns in our files.

I have had the good fortune to experience a most memorable and exciting lifetime scientific journey in the filed of radiation biology and genetics. To be able to apply the result of this research to clinical situations involving radiation exposures has provided me with rewards that would be priceless to any physician: the opportunity to positively change the lives of thousands of patients. ■

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Appendix

Counseling patients exposed to ionizing radiation concerning reproductive and developmental risks

The obstetrician, radiologist, internist, family physician, radiologist, or health physicist may have the responsibility for evaluating the risks of environmental toxicant exposure to the pregnant patient and her embryo and men and women of reproductive age. When evaluating the risks of ionizing radiation, the counselor can be faced with various clinical situations. Four types of encounters are briefly described in the following paragraphs.

1. The first situation involves a pregnant or possibly pregnant patient who presents with clinical symptoms that need to be evaluated. What is the appropriate utilization of diagnostic radiological procedures that may expose the embryo or fetus to ionizing radiation? A pregnant or possibly pregnant woman complaining of gastrointestinal bleeding or pain or an abdominal or pelvic mass that cannot be attributed to pregnancy deserves the appropriate studies, including radiological ones, to diagnose and treat her clinical problems. The studies should be performed in a timely and appropriate manner to minimize the exposure and maximize the goal of making the correct diagnosis. The studies should be performed at the time they are clinically indicated, whether the woman is in the first or second half of the menstrual cycle. Furthermore, these studies should not be relegated to 1 portion of the menstrual cycle. The first half of the menstrual cycle is a time when the woman is not pregnant. Conception occurs midway during the menstrual cycle. The second half of the menstrual cycle is when the embryo has not yet initiated differentiation and is less sensitive to the teratogenic effects of radiation, although it is sensitive to the lethal effects of radiation. Animal studies indicate that the threshold for lethality during this very early stage of development is between 0.15 and 0.2 Gy, but one cannot apply these results directly to the human embryo.
2. In another example, a radiologist has been asked to perform an elective radiological diagnostic study for employment or follow-up that is not an emergency, so the approach should be different. The radiological study can be postponed until the beginning of the next menstrual period. If the patient and physician are certain the patient is not pregnant or has a negative pregnancy test and has not had intercourse for a lengthy period, then the elective examination can be performed at that time. The situation is complicated when the woman has irregular menstrual cycles. In that situation, the diagnostic study can be performed after the next menstrual cycle begins. However, even in that situation, a pregnancy test should be performed.
3. Another clinical situation that the counselor may face is that the patient has completed a diagnostic procedure that has exposed her uterus to ionizing radiation. This can occur with the following studies: (1) abdominal flat plate or CT of the abdomen or pelvis; (2) barium enema; (3) gastrointestinal series; (4) x-rays of the lower spine; (5) intravenous pyelogram (IVP); (6) hysterosalpingogram; (7) bladder x-rays; or (8) hip x-rays or IVP. For example, the procedure was necessary to rule out a gastrointesti-

nal disease or a genitourinary problem because of abdominal pain. The examination revealed that the patient had a duodenal ulcer. The procedure was necessary; however, the patient now believes she was pregnant at the time of the procedure. If you are the counselor, what is the proper response to this situation?

4. Explain that you would have proceeded with the necessary x-ray diagnostic test whether she was pregnant or not because diagnostic studies that are indicated in the mother have to take priority over the possible risk to her embryo because almost no diagnostic studies increase the developmental risks to the embryo. At this time, obtain the calculated dose to the embryo and determine the woman's stage of pregnancy. If the dose is below 0.1 Gy (ie, 10 rads), you can inform the mother that her risks for birth defects and miscarriage have not been increased. In fact, the threshold for these effects is 0.2 Gy or greater; thus, the 0.1 Gy exposure is far from the threshold exposure. If the exposure is less than 0.10 Gy, then the risks are also not increased. Even higher total exposures from multiple procedures over a period of days may not increase the risk of developmental effects; however, decisions about what is appropriate advice becomes more complex. Remember that we are concerned about the fetal exposure, not the dose estimate to the skin or other parts of the body.
5. Another clinical situation that the counselor may face is that a woman delivers a baby with a serious birth defect. On her first postpartum visit, the woman recalls that she had a diagnostic x-ray study early in her pregnancy. What is your response when she asks you whether the baby's malformation could be caused by the radiation exposure? In most instances, the nature of the clinical malformation will rule out radiation teratogenesis. Radiation-induced malformations have a confined group of malformations that identifies the radiation teratogenic syndrome, and many malformations have never been reported, even following intrauterine radiation exposures that are known to produce congenital malformations. In this situation a clinical teratologist or radiation embryologist could be of assistance. On the other hand, if the exposure is below 0.1 Gy, it would not be scientifically appropriate to indicate that the radiation exposure was the cause of the malformations. As mentioned before, the threshold for major malformations is 0.20 Gy. Dose, timing, and the nature of the malformation would enter into this analysis. With approximately 15-25% of malformed children, a genetic disease is diagnosed. If that is the case, the malformations could not have been caused by an intrauterine exposure to ionizing radiation.
6. For a counselor, the most difficult situation of the 4 possible ones mentioned is when external radiation therapy or high exposures of radionuclides have been utilized in a pregnant woman or a woman who became pregnant during the radiation therapy. Although this is a serious situation, there are instances when the exposure to the embryo is low. Low exposures to the embryo may occur when radiation therapy is directed toward the head, neck, upper chest, or the extremities. Administered radionuclides are special problems because each radionuclide has a different half-life, metabolism, and excretion. Therefore, each patient needs the expert evaluation of a competent medical or health physicist to determine what the fetal exposure will be or has been, depending on the nature of the radiation exposure. Rarely, the patient may have received the course of therapy or be in the middle of the therapy when the pregnancy is discovered. That can be very upsetting to everyone: patient and physician. The exposure to the fetus can be calculated and appropriate counseling can be delivered. When the radiation therapist knows that the patient is pregnant, then the situation is much more advantageous because the fetal exposure can be estimated before the onset of therapy.

To appropriately and more completely respond to all these situations, the counselor should rely on the extensive amount of information that has accumulated on the effects of radiation on the embryo. In fact, there is no environmental hazard that has been more extensively studied or on which more information is available.