NCRP REPORT No. 174

PRECONCEPTION AND PRENATAL RADIATION EXPOSURE: HEALTH EFFECTS AND PROTECTIVE GUIDANCE

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Preconception and Prenatal Radiation Exposure: Health Effects and Protective Guidance

Recommendations of the
NATIONAL COUNCIL ON RADIATION PROTECTION AND MEASUREMENTS

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National Council on Radiation Protection and Measurements
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Preface

The potential reproductive and developmental effects of ionizing radiation exposure on the gamete, embryo, fetus, and nursing infant from medical procedures or other sources of radiation are of considerable importance and concern with regard to radiation protection. The National Council on Radiation Protection and Measurements (NCRP) considered possible adverse outcomes of medical exposures of pregnant women and women of childbearing age in Report No. 54, *Medical Radiation Exposure of Pregnant and Potentially Pregnant Women* (1977). NCRP also published Commentary No. 9, *Considerations Regarding the Unintended Radiation Exposure of the Embryo, Fetus or Nursing Child* (1994), in which problems were discussed that could result from the administration of radioactive material in medical procedures. In 1997, NCRP held its Annual Meeting on *The Effects of Pre- and Postconception Exposure to Radiation*, and the proceedings were published in *Teratology* (1999).

Since the publication of NCRP Report No. 54, many advances have been made in understanding the reproductive and developmental risks of ionizing radiation exposure, as well as in updating risk assessments for other potential radiation health effects, including heritable disease and cancer. This Report represents a comprehensive evaluation of the current state-of-knowledge of ionizing radiation effects on the gamete, embryo, fetus, and nursing infant. It includes an in-depth review of radiation risks and potential outcomes, including congenital malformations, growth retardation, miscarriage and stillbirth, mental retardation and neurobehavioral effects, and cancer risks in the children of mothers exposed to radiation during pregnancy. Ionizing radiation exposure to medical, occupational and environmental sources are considered, together with the assessment of dose and discussion of the protective measures to mitigate risk to the gamete, embryo, fetus, and nursing infant. Effective methods of counseling and communicating the risk to a pregnant woman are described, along with examples of consultations concerning risk prior to and during pregnancy.

In addition to health effects of ionizing radiation, issues related to potential reproductive and developmental effects on the embryo and fetus of exposure to nonionizing sources (*i.e.*, high-frequency

electromagnetic fields and medical applications of magnetic-resonance imaging and ultrasound) as well as protective measures to mitigate risk from possible thermal effects are discussed.

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John D. Boice, Jr.
President

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1. Executive Summary

1.1 Background and Purpose

This Report updates and expands the National Council on Radiation Protection and Measurements (NCRP) Report No. 54, *Medical Radiation Exposure of Pregnant and Potentially Pregnant Women* (NCRP, 1977a). Scientific knowledge has increased and public concerns have changed in the nearly 36 y since NCRP (1977a) was published. The scope of this Report covers both ionizing radiation and nonionizing sources [*i.e.*, magnetic-resonance imaging (MRI), ultrasound imaging, and other radiofrequency (RF) fields]. For ionizing radiation, the Report considers preconception and prenatal exposure, and exposure of the nursing infant. The ionizing radiation sources discussed consist predominantly of low linear energy transfer (LET) radiation. For nonionizing sources, the Report focuses on prenatal exposure, with a limited amount of information on childhood and adult exposure.

1.2 Ionizing Radiation Exposures of Reproductive Relevance

Ionizing radiation associated with medical procedures is typically the radiation exposure that causes the greatest concern and anxiety to pregnant women. However, if imaging examinations are medically indicated and performed with proper equipment and careful technique, then the potential immediate benefit to the health of the patient and the embryo or fetus will outweigh the potential future radiation risk. Most diagnostic medical imaging procedures in radiography, computed tomography (CT), conventional fluoroscopy, and nuclear medicine subject the embryo or fetus to absorbed doses of 10 mGy or less. Doses delivered to the embryo or fetus during fluoroscopically-guided interventional procedures and during the course of radiation therapy may be higher. Particularly for radiation therapy, the dose to the embryo or fetus should be evaluated by a qualified expert.

1.3 Preconception Ionizing Radiation Risks

There is no convincing direct evidence of germline mutation manifest as heritable disease in the offspring of humans and attributable to ionizing radiation, yet radiation clearly induces mutations

in microbes and somatic cells of rodents and humans, and transgenerational effects in irradiated drosophila and mice are established. It would be imprudent to ignore the possibility of human germ-cell mutation, especially since progress in human genetics and genomics promises quantum improvements in being able to address the issue in the future.

The inheritance of mutations is a process that, in theory, has both a background component that is intrinsic in an individual and an induced component that results from environmental exposures such as ionizing radiation. A very small but undefined fraction of hereditary human disease is attributable to the environmental agents with mutagenic potential. In the absence of adequate human data, modeling and extrapolation have guided radiation protection.

Genetic risk is generally estimated using three components:

- doubling dose for radiation-induced germ-cell mutations in mice;
- background rate of sporadic genetic disease in humans; and
- population-genetics theory.

One additional consideration is that some deleterious mutations (spontaneous or as a result of preconception radiation exposure) would not be expressed as effects in an offspring because they are lethal to the developing ova (eggs) or sperm or to the developing embryo because of defective ova or sperm, a consideration that has been described as biological filtration.

There is little to no convincing or consistent evidence among the offspring of childhood cancer survivors, atomic-bomb survivors, environmentally-exposed populations, or occupationally-exposed workers for an excess of cytogenetic syndromes, single-gene disorders, malformations, stillbirths, neonatal deaths, cancer, or cytogenetic markers that would indicate an increase of heritable genetic mutations in the exposed parents.

1.4 Pregnancy Risks from Ionizing Radiation

All pregnant women are faced with a baseline risk to the embryo and fetus for reproductive and developmental problems. The background rate for major congenital malformations is ~3 % (i.e., in the absence of radiation exposure about 3 of every 100 children born have a recognizable major birth defect). Minor malformations that are minimally disabling occur in an additional ~4 % of births. Pregnancy loss (spontaneous abortion, miscarriage) in women who know they are pregnant occurs in 15 % of pregnancies with a wide standard deviation.

Doses to the embryo estimated to be in the range of 0.15 to 0.2 Gy during the preimplantation and presomite stages may increase the risk of embryonic loss. However, an increased risk of congenital malformations or growth retardation has not been observed in the surviving embryos. These results are primarily derived from mammalian animal studies and are referred to as the "all-or-none phenomenon."

The potential tissue reactions of ionizing radiation (previously referred to as deterministic effects) are congenital malformations, mental retardation, decreased intelligence quotient (IQ), microcephaly, neurobehavioral effects, convulsive disorders, growth retardation (height and weight), and embryonic and fetal death (miscarriage, stillbirth). Such effects are generally attributed to the killing of cells or serious disruption of cellular function during important stages of embryonic or fetal development. All these effects are consistent with having a threshold dose below which there is no increased risk. The data on IQ loss are somewhat difficult to interpret but even assuming that there might not be a true dose threshold, any IQ effects at low doses would be so small as to be undetectable and therefore not of practical or clinical significance. Doses to the embryo or fetus <0.1 Gy have not been found to increase the risk of tissue reactions in humans, including severe mental retardation, at any stage of pregnancy. Based on animal studies, the no-adverse-effect level (dose to the embryo or fetus) in humans is estimated at 0.2 Gy for anatomical congenital malformations during a very short period during early organogenesis, and is higher for most other tissue reactions.

Doses to the embryo or fetus due to radiation exposure to the maternal chest, extremities, neck and head from diagnostic x-ray procedures do not exceed 0.1 Gy and are thus less than the no-adverse-effect level for any of the previously mentioned tissue reactions. Doses to the embryo or fetus due to radionuclides used in diagnostic nuclear medicine and exposures during x-ray procedures of the maternal abdomen that do not exceed 0.1 Gy also do not increase the risk of tissue reactions.

The risk of cancer in offspring that have been exposed to diagnostic x-ray procedures while *in utero* has been debated for 55 y. High doses to the embryo or fetus (*e.g.*, >0.5 Gy) increase the risk of cancer. Most pregnant women exposed to x-ray procedures and other forms of ionizing radiation today receive doses to the embryo or fetus <0.1 Gy. The risk of cancer in offspring exposed *in utero* at a low dose such as <0.1 Gy is controversial and has not been fully resolved. A fuller discussion of the range of opinion on this cancer risk can be found in Section 5.2.6 and the conclusions in Section 10.1.

Nevertheless, diagnostic imaging procedures utilizing ionizing radiation that are clinically indicated for the pregnant patient should be performed because the clinical benefits outweigh the potential oncogenic risks. However, when it has been determined that the procedure is necessary, it should be tailored to effectively manage the dose to the embryo or fetus (*i.e.*, use only the least amount of radiation necessary to achieve the clinical purpose).

Table 1.1 summarizes for easy reference the health effects from ionizing radiation exposure of the embryo or fetus during various gestational stages of pregnancy.

1.5 Ionizing Radiation Risk to the Nursing Infant

If the mother has received a radiopharmaceutical, the nursing infant may be exposed, either as a result of transfer of the material to the infant by the mother's milk or by exposure to radiation from the mother's body. For diagnostic radiopharmaceuticals, recommended breast-feeding interruption intervals are provided. The most current of these are from the International Commission on Radiological Protection (ICRP, 2008). If the recommendations are followed, the effective dose that would be received by most infants would be far below 1 mSv. Iodine-131 therapy is a special case and should not be administered unless breast-feeding is terminated. To minimize the infant's dose from exposure to the mother's body, the mother should be advised to hold the infant as little as possible during the immediate postadministration period when doses from ^{131}I would be highest. If the mother is receiving brachytherapy, the infant could be exposed to a significant amount of radiation unless the amount of time that the infant is in close contact to the mother during treatment is limited.

When there is evidence that the mother has inhaled or ingested radioiodine from an accident or other incident, typically ^{131}I, lactating women should be administered potassium iodide for both their protection as well as to potentially reduce the radioiodine content of their breast milk (FDA, 2001). If the radioiodine burden in the mother is significant or if repeated doses to the mother of potassium iodide are required, the infant should be evaluated for hypothyroidism and discontinuation of breast-feeding may be warranted. In such rare instances, breast-feeding should be replaced by packaged feedings which are known to be free of contamination. Intake of ^{131}I by the infant from breast-feeding can be estimated using ICRP (2004).

TABLE 1.1—*Summary of health effects from ionizing radiation exposure of the embryo or fetus during pregnancy.*

Human Gestational Stage (weeks)	Comments[a]
Heritable Disease	
1st and 2nd weeks prior to conception (begins on the first day of the last menstrual period)	Irradiation of ova or sperm prior to conception. The mother has not yet ovulated. There is no convincing evidence of excess heritable disease in the offspring. [Section 4]
Embryonic or Fetal Loss, Malformations, Growth Retardation[b]	
3rd and 4th weeks of gestation (1st and 2nd weeks postconception)	Minimum human acute lethal dose for the embryo (derived from animal studies) is estimated to be in the range 0.15 to 0.2 Gy.[c] This is the most vulnerable period for the increased risk of radiation-induced embryonic death. The risk of a viable malformed fetus at term is not increased (all-or-none period). [Section 5.1.5]
5th to 7th weeks of gestation (3rd to 5th weeks postconception)	Minimum human acute lethal dose for the embryo (derived from animal studies) is estimated to be in the range 0.25 to 0.5 Gy. The no-adverse-effect level for the induction of birth defects increases during this period and doses >0.5 Gy are necessary to induce major malformations at the end of this period. The induced growth retardation during this period is not as severe as during the 8th to 15th weeks of gestation, and the embryos have a greater capacity to recover from the *in utero* growth retardation effect. The no-adverse-effect level is in the range of 0.2 to 0.5 Gy. [Sections 5 and 5.1.7]
8th to 15th weeks of gestation (6th to 13th weeks postconception)	Minimum human acute lethal dose for the fetus (derived from animal studies) is estimated to be >1 Gy. The most vulnerable period for irreversible whole-body growth retardation. The no-adverse-effect level is in the range of 0.25 to 0.5 Gy. [Sections 5 and 5.1.7]

TABLE 1.1—(*continued*)

Human Gestational Stage (weeks)	Comments[a]
16th to 25th weeks of gestation (14th to 23rd weeks postconception)	Minimum human acute lethal dose for the fetus (derived from animal studies) is estimated to be ~2 Gy. Growth retardation can be produced, although the effects are not as severe as occurs from the 8th to 15th weeks of gestation. Since all the organs have been formed, the important risk of irradiation is cell depletion in the brain and organs producing ova and sperm. [Section 5.1.7]
26th week to term delivery (24th week postconception to term)	During the last 15 weeks of pregnancy the doses that have deleterious effects on growth, mortality, the central nervous system, and the gonads would have to be increased. It is difficult to utilize animal studies to determine the no-adverse-effect level for various deleterious effects since there is marked discordance in human brain development and the rodent models that are used in this type of research. [Section 5.1.7]
Mental Retardation[b]	
10th to 27th weeks of gestation (8th to 25th weeks postconception)	Severe mental retardation observed at doses >0.5 Gy (lower 95 % CI value of ~0.3 Gy). Decreases in intelligent quotient also observed for this period. Severe mental retardation was not observed prior to the 8th week postconception or after the 25th week postconception. [Section 5.2.1.1]
Oncogenic Effects (cancer)	
Throughout gestation	The lifetime risk of oncogenic effects following *in utero* irradiation appears to be lower than that following irradiation during childhood. There is not data available that informs on which stages of pregnancy may be the most vulnerable to the oncogenic effects of irradiation. [Section 5.2.6]

[a]Extended discussions of the health effects are found in the sections indicated.
[b]There is no evidence of increased risks of these effects with doses to the embryo or fetus <0.1 Gy.
[c]All doses refer to the dose to the embryo or fetus and are for low-LET radiation.

1.6 Mitigation of Ionizing Radiation Risk for Pregnant or Potentially-Pregnant Women

Prior to any medical ionizing radiation exposure, it is important to assess if the woman is pregnant, or if there is the possibility that she may be pregnant. The conventional methods of pregnancy assessment range from verbal communication to a highly-sensitive biochemical assay of human chorionic gonadotropin produced by the developing placenta. Nevertheless, a woman should be considered potentially pregnant if she thinks she may be pregnant or:

- is between 12 and 55 y of age (with no history of menopause), younger than 12 y of age and has started menstrual cycles, or older than 55 y of age without a history of menopause;
- has no reliable history or documented condition which results in sterility; and
- has not had a menstrual period beginning within the last three to four weeks.

Strategies for managing the dose to a pregnant woman and reducing the radiation risk to the embryo and fetus should be employed for all medical procedures involving ionizing radiation (diagnostic imaging procedures, interventional procedures, and radiation therapy). However, any adjustments should not be made at the expense of obtaining the necessary diagnostic information, compromising treatment, or affecting maternal health. The use of radiation therapy should be avoided for pregnant woman diagnosed with cancer, whenever possible, without jeopardizing the woman's life. However, targeted radiation therapy to an extremity, or the head, neck, chest or breast, may not result in a dose to the embryo or fetus that would increase the reproductive or developmental risks of the pregnancy. The use of alternative treatment such as surgery, chemotherapy or both (after consultation with the medical oncologist), should be considered as well as postponing radiation therapy until after delivery. The possibility of adverse outcomes associated with other treatment modalities should also be considered. The risk of teratogenicity from certain chemotherapy agents, for example, has been reported to be as high as 10 to 25 % in the first trimester. However there has been no evidence of increased risk of teratogenesis during the second and third trimesters, although there have been reports of higher rates of developmental effects (*e.g.*, stillbirth and low birth weight).

Formal declaration of a pregnancy by a pregnant worker permits supervisors, if necessary, to take steps to control occupational exposure to radiation to less than that normally received. Mitigating unintentional exposures from involvement with accidents or

malicious use of radioactive materials is largely an after-the-fact process heavily dependent on the dose assessment and specific circumstances.

1.7 Risks to the Embryo or Fetus During Magnetic-Resonance Imaging

During magnetic-resonance imaging (MRI), the embryo or fetus is exposed to magnetic and electromagnetic fields from three sources:

- RF fields from the RF transmitter coil;
- time-varying magnetic field gradients with field changes on the order of 10 T s^{-1}; and
- the static magnetic field of the MRI system.

The main concern regarding the first source, RF electromagnetic fields, is direct heating of tissue. Excessive heating for prolonged time periods can overwhelm the thermoregulatory capacity of the body resulting in a variety of potential adverse health effects. Of special concern here is that sustained temperature elevation in the embryo or fetus may be teratogenic. Recommendations to minimize the RF exposure risk to the embryo or fetus include:

- avoid scanning the embryo or fetus at exposure parameters above the normal mode (Section 8.1.2);
- if the embryo or fetus or maternal abdomen are not the target organs of interest, then the embryo or fetus should be kept out of the transmit field of the RF coil if possible;
- particular care is necessary when scanning fetuses with poor placental function; and
- particular care is necessary when scanning pregnant women with conditions leading to impaired thermoregulation.

With regard to time-varying magnetic fields, current U.S. Food and Drug Administration guidelines (FDA, 2003) classify these fields as a significant risk when they are sufficient to produce severe discomfort or painful nerve stimulation. There is no evidence of harm to patients from the static field in the more than 300 million clinical MRI studies performed since the early 1980s. However, the International Commission on Non-Ionizing Radiation Protection (ICNIRP) has concluded that the current upper limit for whole-body static magnetic field strength during normal clinical MRI examinations should be 4 T (ICNIRP, 2009a).

An American College of Radiology (ACR) expert panel (Kanal *et al*., 2007) does not believe that current data have conclusively

documented any deleterious effects of MRI exposure on the developing embryo or fetus. The panel concludes therefore that "no special consideration is recommended for the first, versus any other, trimester in pregnancy." However, the panel recommends that the following considerations be documented in the radiology report or the patient's medical record:

- information requested from the MRI study cannot be acquired *via* other nonionizing modalities (*e.g.*, ultrasonography);
- data are needed to potentially affect the care of the patient or the embryo or fetus during the pregnancy; and
- the referring physician does not feel it is prudent to wait until the patient is no longer pregnant to obtain these data.

Contrast agents should not be routinely administered for MRI examinations in pregnant patients. Although the risk to the fetus following administration of gadolinium-based MRI contrast agents has not been determined, the decision to administer a gadolinium-based MRI contrast agent to a pregnant patient should be accompanied by a well documented and thoughtful risk-benefit analysis for the fetus and mother.

1.8 Risks to the Embryo or Fetus from Other Radiofrequency Sources

There is increasing exposure to other sources of electromagnetic radiation in the radiofrequency (RF) range from television and radio broadcast towers as well as from new wireless communication and information technologies. In addition, exposure to millimeter wave and terahertz sources is expected to increase as new communication, airport screening, scanning, and imaging technologies are developed. The only accepted mechanism for adverse health effects due to an interaction of electromagnetic radiation in the RF and terahertz range with biological tissue (with the exception of neurostimulation below ~5 MHz) is the generation of heat. In the range of wireless communication and information technologies, the most recent revision of the Institute of Electrical and Electronics Engineers (IEEE) C95.1 standard (IEEE, 2005) allows for a rate of absorbed RF energy in members of the general public (including those that are pregnant) equal to 0.08 W kg^{-1} averaged over the entire body, or a rate of 2 W kg^{-1} averaged over a local tissue mass of 10 g. It should be noted that these recommended limits do not apply to medical use such as diathermy.

While many experimental and epidemiological studies have failed to demonstrate any consistent or convincing evidence of

adverse health effects from low-level (nonthermal)[1] RF exposure, some associations have been reported in the scientific literature and reviewed by scientific working groups. In particular, based primarily on an international case-control study of adult cell-phone users by the INTERPHONE Study Group (ISG, 2010), the International Agency for Research on Cancer Working Group classified RF energy as a "possible human carcinogen" (IARC, 2013). In assigning this classification, IARC (2013) noted that while a positive association for increased risk of glioma (a rare form of brain cancer) at the highest exposure levels had been observed, chance, bias or confounding could not be ruled out as the cause for this association with reasonable confidence. Also, it should be noted that the study mentioned was not for *in utero* exposure. Subsequent to the ISG (2010) study and IARC (2013) classification, additional studies and evaluations provided no support for a causal association between RF exposure from cell phones and risk of brain cancer. In the absence of a causal connection between RF exposure and various adverse health endpoints, the current consensus regarding long-term exposure at nonthermal levels is that there are no established adverse health effects of RF energy that are not associated with excessive heating.

1.9 Risks to the Embryo or Fetus from Ultrasound Imaging

Diagnostic ultrasound has been in use for over 50 y in obstetrics and gynecology. Based on the epidemiological evidence to date, there is little to no convincing evidence to support a causal relationship with any adverse effect including: low birth weight, delayed speech, dyslexia, nonright-handedness, and decreased intellectual performance. Nearly all epidemiological studies published to date are based on information obtained with ultrasound machines manufactured prior to 1992. In 1992 the acoustic output of ultrasound systems was allowed to be increased nearly eightfold for fetal use. Newer higher power technologies and their applications have been introduced over the years and thus continued vigilance in monitoring for possible fetal harm is warranted.

Nonthermal effects of ultrasound are not as well understood as thermal effects. Nonthermal effects include acoustic radiation force, acoustic streaming, and acoustic cavitation. Prior to the first

[1]The term *nonthermal* is widely used in the literature to refer to low-level exposures that result in deposition of energy ultimately deposited as heat that is well within the body's thermoregulatory control thus avoiding a core temperature increase (IEEE, 2005).

breath of the newborn infant, however, there is a complete absence of air bubbles in the fetus and cavitation is not a concern. No adverse mechanical effects are known to occur in the fetus from diagnostic ultrasound examinations.

Presently there are several areas of importance pertaining to diagnostic ultrasound examinations performed during pregnancy. These are the use of Doppler in the first trimester, the use of contrast agents, and keepsake fetal imaging. The use of spectral Doppler ultrasound during the first trimester is currently considered a valuable diagnostic aid for some congenital abnormalities. The procedure requires considerable skill, and subjects the fetus to extended periods of relatively-high ultrasound exposure levels. Because of the potential for risk of adverse effects, it has been recommended that the use of Doppler ultrasound in the first trimester should only be employed when there is a clear benefit-risk advantage. The use of contrast agents in fetal imaging has been limited, and is usually advised against because of an increased possibility of a nonthermal adverse event. Imaging the fetus for keepsake purposes is not desirable and FDA has advised against exposing the fetus to ultrasound except for direct medical benefit to the patient or fetus, and when performed by trained health professionals.

The thermal index (TI) and the mechanical index (MI) are ultrasound safety indices that have been developed to provide ultrasound users with a continuously updated on-screen guide to the relative level of risk of an ultrasound examination while it is being performed. Values ≤ 1 indicate minimal risk and that an ultrasound examination need not be withheld because of a safety concern. A value >1 indicates some risk and that the benefit-risk ratio should be evaluated in deciding whether to do or continue the examination. The higher acoustic outputs of Doppler-mode examinations are also reflected in higher TI values, where values as high as six may be seen and greater caution is needed. In general the TI and MI indices should be maintained as low as feasible while obtaining the required diagnostic information.

1.10 Communicating Benefits and Risks

Women exposed to radiation during pregnancy and members of their families often seek counseling about the associated radiation exposure and present with various levels of anxiety. Similarly, radiation exposure to future fathers or mothers before conception can be a concern. In such circumstances it is important that the counselor be well versed in the potential adverse consequences associated with various levels of radiation exposure, and the chances of the

effects occurring, so as not to inadvertently raise concern. Unfortunately, many professionals who provide care for pregnant patients have limited knowledge of the biological effects of ionizing radiation and exposure from nonionizing modalities in pregnancy. Consequently, more harm may be done by inadequate counseling after an exposure than that possible by the radiation exposure itself. The circumstances surrounding an inadvertent exposure of a patient or pregnant woman may also carry a burden that inaccurate counseling on the risk to the fetus may have medicolegal implications.

Many of the complex issues dealt with in this Report are unlikely to be fully understood by members of the public without professional assistance. A good source of information for a woman or family is their obstetrical care provider who has already established a relationship of trust. However, frequently the obstetrician does not have the experience or knowledge to provide appropriate counseling for all exposure circumstances and additional professional help is recommended.

Although decision making requires a consultation with a healthcare professional, the consultation should include not only verbal communication, but a written report with supporting information and clarifications.

2. Introduction

2.1 Background and Purpose

In 1977, NCRP published Report No. 54 entitled *Medical Radiation Exposure of Pregnant and Potentially Pregnant Women* (NCRP, 1977a). This subject was reconsidered at the 1997 NCRP annual meeting on *The Effects of Pre- and Postconception Exposure to Radiation*. Presentations from this meeting were published in *Teratology* (NCRP, 1999) (Adelstein, 1999; Boice and Miller, 1999; Brent, 1999a; 1999b; Byrne, 1999; Jensh and Brent, 1999; Miller, 1999; Neel, 1999a; O'Connor, 1999; Robert, 1999; Schull and Otake, 1999; Ziskin, 1999). In addition, many other review articles or important scientific papers on this topic have been published since 1977 (Brent, 1980; 1994; 1995a; 2006a; Brent *et al*., 1991; 1993; Brody *et al*., 2007; Davis *et al*., 1992; ICRP, 2000; 2003; Mulvihill and Byrne, 1985; NA/NRC, 2006; NCRP, 1977a; 1977b; 1994; Neel *et al*., 1990; Otake and Schull, 1984; Preston *et al*., 2008; Signorello *et al*., 2010; 2012; Stabin *et al*., 2008; Streffer, 1997; Streffer and Muller, 1996; UNSCEAR, 1986; Wakeford and Little, 2003; Winther *et al*., 2012; Yoshimoto *et al*., 1988).

These publications and the elapsed time of nearly 36 y indicate that there is a need to update NCRP (1977a). Specific gaps and progress are enumerated:

1. The original report did not address the risks of irradiating the ovary and testes before conception. Knowledge regarding the genetic, epigenetic, developmental and reproductive risks of radiation exposure to the gonads has increased in recent years, and a discussion of these and other areas of concern are included in this Report.
2. Advances have been made in many fields related to the technology and utilization of medical diagnosis and therapy. These include diagnostic radiology (especially computed and digital radiography), CT, MRI, sonography (ultrasound), nuclear medicine, and radiation therapy, including image-guided therapy.
3. New diagnostic and therapeutic uses of radionuclides have been introduced and new high-energy radiation-therapy facilities permitting more exact targeting of tumors have been developed.

4. NCRP Report No. 160 (NCRP, 2009) showed that in 2006 the U.S. population was exposed to more than seven times as much ionizing radiation (*i.e.*, collective effective dose) from medical diagnostic examinations and interventional procedures compared to the early 1980s.
5. A better understanding of the public concerns regarding radiation exposure has been gained from sources such as the Health Physics Society's "Ask the Expert" website (HPS, 2010), where 40 % of questions relate to pregnancy and ionizing radiation, and other nonionizing modalities or sources covered in this Report. The concerns include:
   a. all modalities that utilize ionizing radiation: diagnostic and therapeutic exposures [*i.e.*, radiographs (x rays), fluoroscopy, CT scans, radionuclides, and high-energy radiation therapy];
   b. diagnostic and therapeutic use of ultrasound;
   c. exposure to electrical and magnetic fields, power lines, cell phones, antennae for telephone transmission, fire and police communications, frequency modulation (FM) and amplitude modulation (AM) transmission towers, microwave ovens, diathermy treatments, computers, television sets, household appliances, and heating blankets;
   d. radiation exposure from airplane travel or airport security imaging detectors;
   e. risks of living close to, or being employed at, a nuclear power plant or any facility that utilizes radionuclides or x-ray equipment in the workplace;
   f. employee exposure from performing diagnostic or therapeutic radiological procedures that utilize radiopharmaceuticals; and
   g. potential exposures from terrorist use of radiation or radioactive material.
6. Both ICRP and NCRP have revised earlier radiation protection recommendations (ICRP, 1966; 1970; NCRP, 1968; 1971) upon which NCRP (1977a) was based. The later recommendations include ICRP (1991; 2007a) and NCRP (1987; 1993).
7. NCRP (1977a) stated that its recommendations should be regarded as tentative and subject to further evaluation and modifications based on future findings.

Families have great concern about having a miscarriage or a live-born child with a birth defect, neurological problem, mental

retardation, or cancer. This update and expansion of NCRP (1977a) presents the current understanding of the adverse effects of various exposures on the gamete, embryo and fetus, including the fact that for many diagnostic modalities no adverse effects have been observed. Included in this Report are a number of consultation statements, as well as questions and answers, designed to counsel concerned parents and family members on the risks from preconception exposure or exposure during pregnancy (Appendices A and B). Other audiences that may find this Report to be of value include regulators, industrial users of radiation, and the biomedical and lay media.

2.2 Scope of this Report

This Report provides information on the types, sources and magnitudes of ionizing radiation exposures of reproductive relevance. The risks from radiation exposure are explained in detail from preconception through pregnancy, and during the nursing of infants. Methods for managing dose and reducing risk from various medical procedures are also addressed. Finally, communication of the risk and patient counseling are discussed along with some practical examples. The Report ends with conclusions and recommendations (Section 10).

Ionizing radiation from medical care (diagnostic and therapeutic procedures) are included as well as occupational and common environmental exposures, and accidental or deliberate (*e.g.*, a terrorist incident) releases of radionuclides. Nonionizing modalities and sources covered are MRI, as well as RF electromagnetic fields and ultrasound. The terms *radiation* and *exposure*, when used in this Report, generally refer to ionizing radiation exposure unless specifically identified as referring to nonionizing radiation (*e.g.*, RF fields) or when discussed in the nonionizing modalities and sources section.

Outcomes and associated risks of preconception radiation that are covered include: infertility, stillbirths, birth defects, genetic alteration, and cancer. Outcomes and associated risks from ionizing radiation during pregnancy that are covered include: congenital malformations, growth retardation, embryonic and fetal death, mental retardation and neurobiological effects, and cancer. Outcomes and risks associated with nonionizing modalities include: low birth weight, delayed speech, dyslexia, nonright-handedness, and impaired intellectual performance.

2.3 Gestational Age Conventions

The interface of nomenclature between the basic science of embryology, basic biology education, and the clinical practice

of obstetrics and gynecology has led to some confusion related to the description of gestational age.

When the obstetrician refers to *gestational age*, the term refers to the time from the first day of the last menstrual period. Therefore, it includes two weeks before ovulation occurs and at which time the mother is not pregnant. In animal reproductive study, pregnancy begins on the day of fertilization and the stage of pregnancy in animal models is described as days or weeks postconception. Therefore, it is important for clinicians and animal researchers to be specific with regard to what term they use to describe the stage of pregnancy in their publications. Many patients, when they are informed of the baby's gestational age by their physician erroneously infer that the gestational age begins with fertilization. When animal teratologists describe the stage of pregnancy they should not use the term gestational age, a term which should only be used to describe human pregnancies. In some instances, based on the history provided by the mother and diagnostic studies, a clinician may utilize days postconception in describing a human pregnancy because it is evident when fertilization occurred.

Nevertheless, all clinical usage, including ultrasound confirmation of dates, standardized laboratory assessment of gestational age-dependent analyses, and patient counseling use this convention. As a result, many but not all women who have experienced pregnancy are familiar with the obstetric convention of dating the pregnancy from the first day of the last menstrual period (*i.e.*, the gestational age). Therefore, in this Report, the gestational age generally is included in all discussions referring to humans, and postconception age is used for all references referring to animals.

3. Ionizing Radiation Exposures of Reproductive Relevance

3.1 Quantities, Units, and Related Concepts in this Report

Absorbed dose (D) is the mean energy $\mathrm{d}\varepsilon$ imparted to matter of mass $\mathrm{d}m$ by ionizing radiation at a point of interest:

$$D = \frac{\mathrm{d}\varepsilon}{\mathrm{d}m}. \tag{3.1}$$

It is the fundamental dose quantity for ionizing radiation.

Mean absorbed dose in an organ or tissue (D_T) (also referred to as organ dose) is obtained by integrating or averaging the absorbed dose D over the entire volume of an organ or tissue (*i.e.*, the total energy deposited in the organ or tissue divided by the total mass of the organ or tissue). It is the primary quantity used in epidemiological and other research studies to relate specific health outcomes such as cancer to exposure from ionizing radiation. D_T is defined as:

$$D_T = \frac{\varepsilon_T}{m_T}, \tag{3.2}$$

where:

ε_T = total energy imparted in a tissue or organ T
m_T = mass of that tissue or organ

The Systeme International (SI) unit for D and D_T is joule per kilogram (J kg^{-1}) with the special name gray (Gy).

In this Report on the adverse effects of ionizing radiation on the embryo and fetus, the mean absorbed dose of interest is usually for the entire embryo or fetus (embryonic or fetal dose) (*i.e.*, the total energy deposited in the embryo or fetus divided by its mass).

Effective dose (E) is a quantity used primarily in implementing the radiation protection system. It is the sum over specified organs and tissues of the products of *equivalent dose* (H_T) in a specific tissue and the *tissue weighting factor* for that tissue or organ (w_T):

$$E = \sum_T w_T H_T, \tag{3.3}$$

where:

H_T = mean absorbed dose in a tissue or organ (D_T) weighted by the *radiation weighting factor* (w_R) (dimensionless) for the type of radiation. The set of w_R values are general and allow for differences in the biological effectiveness between different types of radiations. They are selected by judgment after review of a broad range of experimental relative biological effectiveness (RBE) data and are independent of the tissue or organ irradiated.

w_T = the dimensionless factor by which H_T is weighted to represent the relative contribution of that tissue or organ to the total health detriment resulting from uniform irradiation of the body (radiation detriment).

Effective dose applies only to stochastic effects. See the Glossary (effective dose) for additional details for E, w_T, H_T, and w_R. The SI unit for both E and H_T is joule per kilogram (J kg^{-1}) with the special name sievert (Sv). To avoid confusion, in this Report when the unit sievert is given, the relevant quantity (effective dose or equivalent dose) will be stated.

Regulatory agencies in the United States use a similar quantity called *total effective-dose equivalent* as defined by the U.S. Nuclear Regulatory Commission (NRC, 2009). In this Report, when that quantity is used in the context of a requirement or guidance from a regulatory agency in the United States, it is identified as total effective-dose equivalent.

The term *dose rate* refers to the dose delivered per interval of time (*e.g.*, Gy min^{-1}) and applies to any dose quantity.

The term *exposure* is used in this Report as a general term to express the act of being exposed to ionizing radiation (or to nonionizing modalities or sources). However, exposure is also a defined ionizing radiation quantity, and is the amount of ionization produced by the absorption of x-ray or gamma-ray energy in a small mass of air, with the SI unit coulomb per kilogram (C kg^{-1}) and previous special unit roentgen (R) (1 R = 2.58 × 10^{-4} C kg^{-1}). The original quantity and unit reported in some of the early animal studies (mouse or rat) that are discussed in this Report was exposure to the whole body of the animal expressed as roentgen. These data are presented in this Report as the approximate mean absorbed dose (whole body) (gray) in the mouse or rat.

Linear energy transfer (unrestricted L or LET) is the quotient of the mean energy dE lost by charged particles due to all electronic interactions in traversing a distance dl through a material:

$$L = \frac{\mathrm{d}E}{\mathrm{d}l}. \tag{3.4}$$

The SI unit for L is joule per meter (J m^{-1}), often expressed in keV μm^{-1} (where 1 keV μm^{-1} = 1.602 × 10^{-10} J m^{-1}).

Low-LET radiation, such as x rays, gamma rays, and light charged particles (*e.g.*, electrons) produce sparse ionizing events far apart on a molecular scale with $L \leq 10$ keV μm^{-1}. *High-LET radiation*, such as alpha particles, neutrons, and heavy charged particles (*e.g.*, carbon ions) produce ionizing events densely spaced on a molecular scale with $L > 10$ keV μm^{-1}. For the same absorbed dose, the dose-response relationship for radiogenic biological effects is generally less for low-LET radiations than for high-LET radiations (NCRP, 1990).

For a specified radiation, the *relative biological effectiveness* (RBE) is the ratio of the absorbed dose of a reference radiation ($D_{\text{reference}}$) required to produce a specific level of a response in a biological system to the absorbed dose of the specified radiation (D_{A}) required to produce an equal response, with all physical and biological variables, except radiation quality, being held as constant as possible. RBE is determined experimentally. Thus, for radiation type A (as characterized by its identity and nominal energy):

$$RBE(\text{A}) = \frac{D_{\text{reference}}}{D_{\text{A}}}. \tag{3.5}$$

The reference radiation normally is gamma rays or x rays with a LET ≤ 3.5 keV μm^{-1}. RBE generally depends on the magnitude of absorbed dose, the absorbed dose per fraction if the dose is fractionated, the absorbed-dose rate, and the biological endpoint. Because RBE represents a ratio of absorbed doses, it is a dimensionless quantity. When a high-LET radiation is involved in an epidemiological or other research study, it is necessary to take this difference in RBE into account. If experimental data were available, the embryonic or fetal dose could be adjusted by an appropriate RBE for the endpoint of interest and the type of radiation involved (*e.g.*, neutrons). If research studies using different types of radiation (*i.e.*, one with low-LET and one with high-LET) have enough statistical power, it may be possible to evaluate RBE by using the mean absorbed dose in the tissue or organ for both studies and then comparing the results for the two types of radiation. In that case, it may be possible to infer the difference in the magnitude of the effect for the two types of radiation directly, and avoid postulating an RBE *a priori*.

3.2 Primary Sources of Ionizing Radiation Exposure to Pregnant Women

Everyone is exposed to the ubiquitous background radiation, which is always present in the environment and results from the radiation emitted from naturally-occurring radionuclides both inside and outside of the body, and from cosmic radiation. In addition, everyone is potentially exposed to radiation from various medical procedures, consumer products, and industrial radiation sources, as well as from some educational and research activities. Individuals working in occupations that utilize radiation sources or radioactive materials can also be exposed as a result of proximity to these sources or materials.

NCRP (2009) presents in detail the sources and levels of ionizing radiation exposure to the U.S. population as evaluated in 2006. The primary sources that are relevant to the exposure of a pregnant woman and that impact the gamete, embryo, fetus, or nursing infant are discussed here under the categories of medical procedures (Section 3.2.1), occupational exposure (Section 3.2.2), and ubiquitous background exposure (Section 3.2.3). These categories cover the radiation sources that are encountered under normal conditions of use in the United States.

3.2.1 *Medical Care*

Ionizing radiation associated with medical care is typically the type of radiation exposure situation that causes the greatest concern and anxiety to pregnant women based on questions received by the Health Physics Society's *Ask the Expert* website (HPS, 2010). These radiological examinations should be performed only when there is a recognized or established medical need and, when possible, examination options that avoid the use of ionizing radiation should be considered prior to utilizing a radiological examination. If, in the judgment of the responsible healthcare provider, protection of the patient's health requires the use of a radiological examination appropriate for the patient's medical condition, then the examination should be performed. If the examination is performed with proper equipment and careful technique by trained personnel, then the potential benefit to the health of the patient and the embryo or fetus will outweigh the potential radiation risk. It is important to remember that the risk to the patient of not having a needed examination is also a potential risk to the embryo or fetus. Usually a properly performed single diagnostic procedure utilizing ionizing radiation should result in a dose to an embryo or fetus <0.1 Gy. The difficulty with determination of the immediate medical need stems from the fact that medical practitioners may disagree as

to the relative importance of a particular examination in a given situation. Over the past decade, the use of ionizing radiation in medicine has increased significantly (NCRP, 2009). As a consequence of this general trend, the use of radiological examinations on pregnant women also has increased (Lazarus *et al*., 2009). Some of the most common medical conditions that lead to the ordering of radiological examinations on pregnant women are listed in Table 3.1. Examinations that use nonionizing modalities (*i.e*., MRI, ultrasound) are also included in Table 3.1.

Typical values for the dose to the embryo, fetus and gonads from some common medical procedures that involve ionizing radiation are given in Table 3.2. Most diagnostic medical imaging examinations subject the embryo or fetus to doses <10 mGy. Exceptions to this may be prolonged fluoroscopic procedures including fluoroscopically-guided interventional procedures, CT examinations (especially multiphase) of the abdomen and pelvis, and a few nuclear medicine studies (*e.g*., myocardial-perfusion study, positron-emission tomography) (Table 3.2).

The dose to an embryo or fetus from an x-ray imaging study comes either from direct exposure to the primary radiation when the embryo or fetus is in the field of view, or from scattered radiation when imaging is performed in another area of the body. In nuclear medicine, the dose to the embryo or fetus comes from circulation of the radiopharmaceutical which may cross the placenta as well as from maternal cross-irradiation. When the embryo or fetus is directly exposed and the expected total dose to the embryo or fetus for one or more procedures is >100 mGy, a qualified expert (see Glossary) should determine a best estimate of the dose to the embryo or fetus for that patient.

Approximately 4,000 women per year in the United States require radiation therapy during pregnancy (Stovall *et al*., 1995). Doses delivered to the embryo or fetus during the course of radiation therapy, radiation oncology, or a nuclear medicine procedure should be evaluated when necessary by a qualified expert. Methodology for the calculation of dose to the embryo or fetus from nuclear medicine therapy is found in the *Fetal Dose Calculation Workbook* (Stabin, 1997). The American Association of Physicists in Medicine published data and techniques (Stovall *et al*., 1995) to allow a medical physicist in radiation oncology to estimate the dose to the embryo or fetus from external photon-beam radiation therapy and to potentially reduce that dose with appropriate shielding. Out-of-beam data were provided for a variety of photon beams, including ^{60}Co gamma rays and x rays from 4 to 18 MV. In addition, designs for simple and inexpensive to more complex and expensive

TABLE 3.1—*Types of examinations (that use ionizing radiation or other nonionizing modalities) ordered for common medical conditions in pregnant women.*

Medical Condition	Examination Type[a,b]
Acute abdominal-pelvic pain	Ultrasound, CT abdomen-pelvis, MRI
Appendicitis	Ultrasound, CT abdomen-pelvis, MRI
Cholecystitis	Ultrasound, HIDA
Pancreatitis	CT abdomen
Bowel obstruction	X-ray abdomen, CT abdomen-pelvis
Ovarian torsion	Ultrasound
Acute severe headache	CT head
New onset seizure	CT head
Back pain/disc compression	MRI
Pulmonary embolism	VQ, CTPA
Torso trauma	CT abdomen-pelvis

[a]When multiple examinations are listed, the examinations are given in the order in which it is recommended that they be accomplished.
[b] CT = computed tomography
CTPA = computed-tomography pulmonary angiography
HIDA = hepatobiliary iminodiacetic acid nuclear medicine scan
MRI = magnetic-resonance imaging
VQ = ventilation-perfusion nuclear medicine scan

types of shielding equipment are described. Clinical examples show that proper shielding can reduce the dose to the embryo or fetus by 50 % or more. Additional discussion of doses to the embryo or fetus from radiation therapy during pregnancy is given in Section 7.2.2.

3.2.2 *Occupational Exposure*

Occupational exposure is controlled by a limit on the annual effective dose to individual workers as recommended by NCRP (1993) and promulgated by various regulatory agencies. For example, the effective-dose limit for occupational exposure to ionizing radiation from licensed radioactive material in the United States is established by NRC (2007a). Although these dose limits were established for exposures to NRC-regulated radioactive material,

TABLE 3.2—*Typical doses (milligray) (D_T) to the embryo or fetus and gonads for selected medical procedures.*[a,b]

Type of Procedure	Description[c]	Dose to Embryo or Fetus (typical value or range)[d] (mGy)	Dose to Gonads (ovaries, testes) (typical value)[d] (mGy)	References
Radiography and fluoroscopy (conventional)	Skull	<0.01	<0.01, <0.01	UNSCEAR (2000), Wall *et al.* (2009)
	Chest	<0.01	<0.01, <0.01	Helmrot *et al.* (2007), McCollough *et al.* (2007), UNSCEAR (2000)
	Thoracic spine	<0.01	<0.01, <0.01	McCollough *et al.* (2007), UNSCEAR (2000), Wall *et al.* (2009)
	Mammography	<0.1	<0.01, NA	UNSCEAR (2000)
	Pelvis	0.1 – 1.1	2, 4	Helmrot *et al.* (2007), UNSCEAR (2000), Wall *et al.* (2009)
	Lumbar spine	1 – 2	4, 0.6	Helmrot *et al.* (2007), McCollough *et al.* (2007), UNSCEAR (2000)

TABLE 3.2—(*continued*)

Type of Procedure	Description[c]	Dose to Embryo or Fetus (typical value or range)[d] (mGy)	Dose to Gonads (ovaries, testes) (typical value)[d] (mGy)	References
	Abdomen	1 – 3	2.5, 0.7	Helmrot *et al.* (2007), McCollough *et al.* (2007), UNSCEAR (2000), Wall *et al.* (2009)
	Upper GI series	7	1, 0.1	McCollough *et al.* (2007), UNSCEAR (2000)
	Barium enema	7 – 8	10, 4	Helmrot *et al.* (2007), McCollough *et al.* (2007), UNSCEAR (2000)
CT	Brain	<0.1	<0.1	Wall *et al.* (2009)
	Chest, angiography of coronary arteries	0.1 – 1	<0.1, <0.1	Helmrot *et al.* (2007), Hurwitz *et al.* (2006), McCollough *et al.* (2007), Wall *et al.* (2009)
	Abdomen	4 – 16	1, 1	Helmrot *et al.* (2007), Lazarus *et al.* (2007), McCollough *et al.* (2007), Wall *et al.* (2009)

	Pelvis	10 – 32	25, 15	Hurwitz *et al.* (2006), Wall *et al.* (2009)
Interventional (fluoroscopically guided)	Abdomen	Variable, possibly >50	Variable	
Nuclear medicine[e]	Lung-ventilation study (rebreathing for 5 min); ^{133}Xe (740 MBq)[f]	0.02 – 0.3	0.5, 0.5	Bushberg *et al.* (2011), Stabin *et al.* (2008)
	Lung-perfusion study; ^{99m}Tc-MAA (148 MBq)	0.4 – 0.7	0.27, 0.16	Bushberg *et al.* (2011), Stabin *et al.* (2008)
	White cell scan; ^{111}In (18.5 MBq)	1.7 – 2.4	2.2, 0.8	Bushberg *et al.* (2011), Stabin *et al.* (2008)
	Renal scan; ^{99m}Tc-MAG3 (370 MBq)	1.9 – 6.7	2, 1.4	Bushberg *et al.* (2011), Stabin *et al.* (2008)
	Bone scan; ^{99m}Tc-MDP (740 MBq)	1.5 – 4.4	2.7, 1.8	Bushberg *et al.* (2011), Stabin *et al.* (2008)
	Cerebral blood flow; ^{99m}Tc-HMPAO (740 MBq)	3 – 6.7	4.9, 1.8	Bushberg *et al.* (2011), Stabin *et al.* (2008)
	Positron-emission tomography; ^{18}F-FDG (740 MBq)	13 – 16	10, 8.1	Bushberg *et al.* (2011), Stabin *et al.* (2008)

TABLE 3.2—(*continued*)

Type of Procedure	Description[c]	Dose to Embryo or Fetus (typical value or range)[d] (mGy)	Dose to Gonads (ovaries, testes) (typical value)[d] (mGy)	References
	Myocardial perfusion; ^{99m}Tc-sestamibi (1,110 MBq)	5 – 6	9.0, 4.1	Bushberg *et al*. (2011), Stabin *et al*. (2008)
	Cancer therapy – 5 % uptake; ^{131}I (3,700 MBq)	66 – 1,000	163, 107	Bushberg *et al*. (2011), Stabin *et al*. (2008)
	Benign therapy – 50 % uptake; ^{131}I (555 MBq)	40 – 150	23, 14	Bushberg *et al*. (2011), Stabin *et al*. (2008)

[a]The dose to the organ being studied may be significantly higher than the dose to the embryo, fetus or gonads.

[b]An additional compilation of doses to the embryo or fetus for procedures in conventional radiography and fluoroscopy, CT, and fluoroscopically-guided interventions can be found in Dauer *et al*. (2012).

[c] FDG = fluorodeoxyglucose
HMPAO = hexamethylpropylene amine oxime
MAA = macroaggregated albumin
MAG3 = mercaptoacetyltriglycine
MDP = methylene diphosphonate

[d]For the embryo and fetus entries for nuclear medicine, the range is over the gestation period; for all other entries, the range is over the literature sources. NA = not applicable.

[e]For nuclear medicine procedures, the radiopharmaceutical and typical administered activity are also provided.

[f]37 MBq = 1 mCi (*e.g*., 740 MBq = 20 mCi).

individual states have often adopted the dose limits for exposures from other sources of ionizing radiation. As a further measure, employers are also required to establish a program to ensure that doses are as low as reasonably achievable (the ALARA principle).

NCRP (2009) separated occupational exposures into six subcategories grouped by the nature of employment and associated types of sources encountered. These categories were medical; aviation; nuclear power (commercial); industry and commerce; education and research; and government, U.S. Department of Energy, and military activities. The average annual effective dose in 2006 for each of these categories of occupational exposure is provided in Table 3.3.

More relevant to this Report is the dose limit (equivalent dose) for the embryo and fetus of a pregnant worker. NCRP (1993) recommends a 0.5 mSv monthly limit (equivalent dose) for the embryo and fetus (excluding medical and ubiquitous background radiation) once the pregnancy is known. U.S. Environmental Protection Agency (EPA, 1987) guidance is 5 mSv during the entire gestation period. NRC (1998) has a regulatory limit of 5 mSv during the entire pregnancy of a declared pregnant woman, with further guidance as to how to apply the limit. In the United States, workers subject to the NRC regulations who do not wish to declare their pregnancy are not required to do so (NRC, 1999). The Federal Aviation Administration (FAA) has issued an advisory regarding in-flight radiation exposure to aircrew and recommends an equivalent dose limit of 1 mSv to the embryo and fetus for pregnant crew members, with no more than 0.5 mSv in any month (FAA, 2006). ICRP (2007a) recommends that after a worker has declared her pregnancy, her working conditions should ensure that the additional dose to the embryo and fetus does not exceed 1 mSv (equivalent dose) during the remainder of the pregnancy. While differing somewhat in the details, the EPA (1987) guidance, NCRP (1993) recommendation, and NRC (1998) regulation are generally consistent with each other on the overall limit, while the FAA (2006) advisory and ICRP (2007a) recommendation have a lower overall limit (1 mSv). Further discussion of implementation in the United States of the dose limit for the embryo and fetus for occupationally-exposed pregnant woman is found in Section 7.2.3.

Some of the most common occupations where workers are exposed to radiation are in medicine (nuclear medicine technologists, physicians using fluoroscopy, radiologic technologists, radiochemists that prepare radiopharmaceuticals, brachytherapists, and nurses). Other occupations are nuclear power plant staff, industrial radiographers, airline crew, the military, and researchers. Anyone who is occupationally exposed to ionizing radiation

TABLE 3.3—*Average annual effective dose (millisievert) for workers with recordable dose for 2006 and percent of the annual dose limit (50 mSv), for the United States (adapted from NCRP, 2009).*[a]

Occupational Category	Effective Dose (mSv)	Dose Limit (%)
Medical	0.75	1.5
Aviation[a]	3.07	6.1
Nuclear power	1.87	3.7
Industry and commerce	0.81	1.6
Education and research	0.72	1.4
Government, U.S. Department of Energy, and military	0.59	1.2

[a]The results presented in NCRP (2009) were derived from personal monitoring data for all categories except aviation. Aviation estimates were calculated from cosmic-ray doses for various flight routes.

should be informed of this fact. Therefore, employers are required to provide hazard awareness training to their employees upon initial hire and then periodically, usually annually, thereafter.

One area in medicine where effective doses from occupational exposures are consistently higher than in other medical applications is during fluoroscopically-guided interventional procedures. Effective doses to physicians performing these procedures vary widely depending on the type of fluoroscopically-guided interventional procedure, the type of equipment used, the types of safety features employed as well as the training the physicians have received (Kim *et al*., 2008; NCRP, 2010). Some of the more complex procedures with over-table x-ray equipment could result in annual effective doses exceeding 20 mSv for a workload of 1,000 cases per year (NCRP, 2010). As efforts to effectively manage the dose that the patient receives from such procedures continues (NCRP, 2010), the dose to the performing physician should also decrease as there is a strong interrelationship between the levels of dose to the patient and the physician performing the procedure.

3.2.3 *Ubiquitous Background Exposure*

Ubiquitous background exposure consists of various naturally-occurring sources:

- space radiation (external exposure from solar particles and cosmic rays);
- terrestrial radiation (external exposure from radionuclides in earth such as ^{40}K);
- radionuclides in the body (internal exposure from the intake of radionuclides such as ^{40}K); and
- radon and thoron and their progeny, primarily from inhalation of elevated radon levels in homes.

The nominal annual effective dose to an individual in the U.S. population from the first three background sources (space radiation, terrestrial radiation, and radionuclides in the body) is on the order of 1 mSv (0.83 mSv in 2006) (NCRP, 2009). This annual effective dose from these sources can be treated to a first approximation as a whole-body dose, where each organ and tissue in the body receives an annual equivalent dose of 1 mSv. Thus, an estimate of the equivalent dose from these sources to the embryo and fetus of a pregnant woman during the nine-month gestation period would be three-quarters of the annual value (0.75 mSv based on the nominal 1 mSv) (~0.6 mSv based on the average estimated for 2006).

Radon (^{222}Rn) is a radioactive gas that comes from the radioactive decay of uranium in soil, rock and water. The soil under a structure, such as a house, always contains traces of uranium that eventually decays into radium that then decays into radon. The radon then gets into the air. In some locations, the prevalence of terrestrial sources of uranium cause elevated levels of radon in homes. Thoron (^{220}Rn), a decay product of thorium in soil also contributes a small amount to such levels. Radon and thoron are inhaled and their progeny are deposited primarily in the lungs, thus the dose to individuals is almost entirely to the lungs. The estimate of the average annual effective dose to an individual in the U.S. population from the progeny of naturally-occurring radon and thoron for 2006 is 2.3 mSv; 2.1 mSv from radon progeny (NCRP, 2009). However, because the dose is limited primarily to the lungs, the exposure does not significantly impact the embryo and fetus of a pregnant woman. Only a very low dose due to photon emissions of radon and thoron progeny in the lungs of a pregnant woman could be received by the embryo or fetus.

3.3 Principles of Ionizing Radiation Protection

The primary objectives of radiation protection with regard to exposed persons are: (1) to prevent tissue reactions (deterministic

effects),[2] and (2) to reduce the risk of stochastic effects (*e.g.*, cancer, hereditary effects) to a degree that is acceptable in relation to the benefits to the individual and society from activities that generate such exposures (NCRP, 1993).

To achieve the objectives of ionizing radiation protection, a conceptual framework was developed and includes justification of practices, optimization of radiation protection, and dose limitation (ICRP, 1991; 2007a; NCRP, 1993).

- *Justification of practices*: Any practice involving radiation exposure should be justified. The practice should result in a net positive benefit to the exposed individual or society. Justification often goes beyond the scope of protection and risks because the radiation detriment is often just one of many considerations. Decisions will necessarily be influenced by broader political, economic and social concerns. Regardless, the net benefit should be positive. For clinical diagnosis and therapy of a particular patient, the health provider, usually the physician justifies use of radiation for obtaining the necessary information.
- *Optimization of radiation protection*: Once a procedure utilizing radiation is justified, the resulting doses to patients, occupational workers, and members of the public should be optimized with regard to radiation protection. Doses should be maintained as low as reasonably achievable (the ALARA principle), economic and social factors taken into account. Doses from medical exposures should be commensurate with the medical purpose.
- *Dose limitation*: No individual should have an unacceptable level of risk as a consequence of an exposure. The upper limits for justified and optimized exposures are provided by a system of dose limits for occupational workers and members of the public. Doses from ubiquitous background radiation are not included in these dose limits. Importantly, dose limits do not apply to medical exposure of patients, because such limits may, by reducing the effectiveness of the patient's diagnosis or treatment, do more harm than good.

[2]The term *tissue reactions* has been adopted by ICRP (2007a; 2012) to replace the term *deterministic effects* (see Glossary). The two terms are synonymous. In this Report, as a transitional step, the term *tissue reactions* is used followed by the term *deterministic effects* in parentheses.

For exposure of patients from medical procedures, justification of practices and optimization of radiation protection are the relevant principles. Application of these two principles to the exposure of patients is further discussed in Section 7.2.1.1.

3.4 Dose-Response Relationships for Stochastic Effects

Figure 3.1 (Brenner *et al*., 2003) presents a schematic representation of various types of dose-response relationships that have been proposed for ionizing radiation-related stochastic effects. They include:

- *Curve a*: linear-nonthreshold dose-response relationship over the entire dose range, down to zero dose;
- *Curve b*: linear-nonthreshold relationship only at low-to-intermediate levels of dose, above which the curve bends upward (as is characteristic of the linear-quadratic type of relationship);
- *Curve c*: threshold dose-response relationship, in which no effect is produced at doses below the threshold indicated on the intercept;
- *Curve d*: supralinear response in which the effects per unit dose at low doses exceeds that of higher doses; and
- *Curve e*: hormetic response in which the frequency of effect is reduced at low doses and increased only at higher doses.

Figure 3.1 is included in this Report solely to help define the dose-response relationships that may be mentioned later in this Report with regard to stochastic effects from preconception or prenatal exposures, or exposures of the nursing infant. No attempt is made in this Report to present the arguments pro and con for the various dose-response relationships. Currently a linear-nonthreshold dose-response relationship is widely applied for radiation protection purposes (ICRP, 2007a; NCRP, 1993) and for quantitative risk assessment (NA/NRC, 2006; NCRP, 2001a). NCRP (2001a) stated that there is no conclusive evidence on which to reject the assumption of a linear-nonthreshold dose-response relationship for many of the stochastic effects attributable to low-dose ionizing radiation. NCRP (2001a) also noted that further efforts to clarify the relevant dose-response relationships in the low-dose domain are strongly indicated.

From the viewpoint of protecting individuals and populations exposed to ionizing radiation by establishing a practical radiation protection system, use of the linear-nonthreshold hypothesis is a

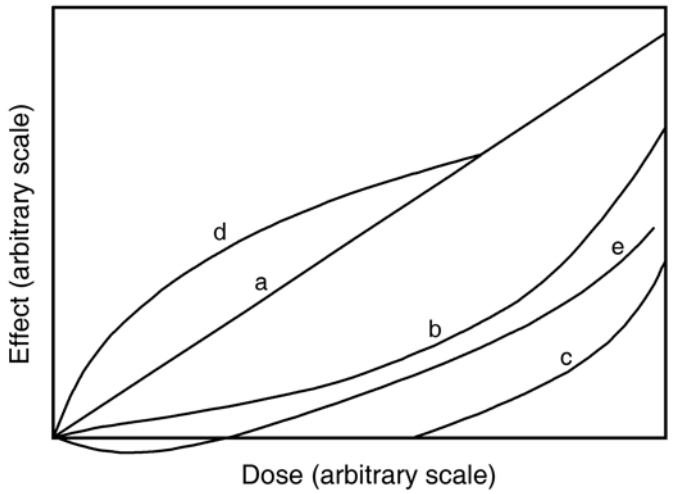

Fig. 3.1. Schematic representation of various types of dose-response relationships for ionizing radiation-related stochastic effects: (a) linear-nonthreshold, (b) linear-quadratic, (c) threshold, (d) supralinear, and (e) hormetic (adapted from Brenner *et al*., 2003).

cautious and functional approach. From the viewpoint of quantitative risk assessment at the lower levels of organ or whole-body dose (*e.g*., <0.1 Gy) experienced by most individuals and populations from the prevalent ionizing radiation sources, use of a linear-nonthreshold dose-response relationship is more uncertain. Based on the evaluation of health effects presented in this Report, this uncertainty in quantitative risk assessment is particularly the case at these lower doses for stochastic effects on the gamete, embryo, fetus, and nursing infant.

4. Preconception Ionizing Radiation Risks

4.1 Importance of Preconception Exposures

It is important to evaluate ionizing radiation effects on germ cells as the source of gametes that produce the next generation of human beings. Considerable information has accrued since NCRP Report No. 54 (NCRP, 1977a) and NCRP Commentary No. 9 (NCRP, 1994) (*e.g.*, UNSCEAR, 2009). There are extensive data on mutations induced by ionizing radiation in microbes and somatic cells of rodents and humans. However, these data alone cannot be used to assess mutational risk in human germ cells, possibly because of the biological characteristics of human gametogenesis, compared to that of other mammals and to somatic cells of either humans or other mammals (Sobels, 1993). To accurately assess the influence of ionizing radiation on the genome of human germ cells, it is necessary to conduct studies in human populations.

Since the discovery of the induced germ-cell mutation in an animal (by ionizing radiation in *Drosophila*) (Muller, 1927), various animal model systems have shown that ionizing radiation and certain chemicals can induce heritable mutations. However, despite the similarities in many aspects of germ-cell biology among humans and mammalian model systems, studies during the past 80 y have failed to find convincing evidence of heritable mutations in humans induced by ionizing radiation.

Apart from the unlikely possibility that there are no radiation-induced mutations in human germ cells, the reasons for this disparity between human and animal studies are many, including insufficient numbers of human subjects, insensitive methods to detect mutations, the diversity and lack of specificity of defects in deoxyribonucleic acid (DNA) and chromosomes induced by ionizing radiation, inadequate lengths of observation of the offspring, different intensities or types of exposure, inadequate dosimetry, and differences in the lethality of germ cells from radiation exposure. There is still no confirmed mutagen that produces transmissible human germ-cell mutations. Yet, it would not be prudent to put the possibility aside from further consideration, especially since progress in human genetics and genomics promises quantum improvements in being able to address the issue in the future (Yauk *et al.*, 2012).

The one epidemiologic study that suggested human germ-cell mutagenesis involved not radiation, but exposure from a chemical acting on the ovary (Czeizel *et al*., 1993). In the rural village of Rinya, Hungary, an excess of Down syndrome was detected by monitoring national birth-defects rates. The epidemic correlated with the introduction of new methods for raising pond fish commercially. The residents realized that the local fish farm had begun using a pesticide that resulted in fish floating to the surface temporarily, easy pickings especially for their Easter feasts which demanded fresh fish. Molecular studies showed all aneuploidies that could be tested were due to errors in the second meiotic division, not the first (which is typical of most Down syndrome babies). When the farming practice was changed, the epidemic ceased. Although not due to radiation exposure, the episode points to the merit of population-based birth-defects monitoring and interdisciplinary study and the need to interpret findings by focusing on molecular mechanisms of action. Adjusting for maternal age, reanalysis of 1960s data on Down syndrome claimed a small effect of advanced paternal age (13 % increase per decade) (De Souza *et al*., 2009), incriminating environmental factors on spermatogenesis, but not specifically radiation. Two temporal clusters of Down syndrome births in Berlin and Bavaria could not be convincingly associated with the Chernobyl nuclear reactor fallout (Burkart *et al*., 1997).

4.2 Biology of Human Gametogenesis

With regard to germ-cell biology and its relevance to the susceptibility of germ cells to ionizing radiation, common themes are sexual dimorphism and the unique characteristics and susceptibilities of distinct germ-cell stages (Mulvihill and Garlow, 2007; Wyrobek *et al*., 2007). The timelines for the production and maturation of germ cells are dramatically different in female and male mammals (Figure 4.1). Female germ cells complete meiotic prophase I during fetal development and remain arrested in diplotene at least until puberty.

In contrast, male germ cells undergo mitosis prior to birth but have a meiotic division only after puberty. In human females, all germline mitotic divisions are completed within days during embryonic development. Completion of meiosis I division requires years and does not begin until puberty; and completion of meiosis II division occurs within hours *after* fertilization. There is limited mitotic proliferation in females, and the number of female germ cells is finite. In human males, mitotic proliferation begins near puberty and continues throughout life well into senescence. Spermatogonial stem cells undergo asymmetric division, generating a stem cell

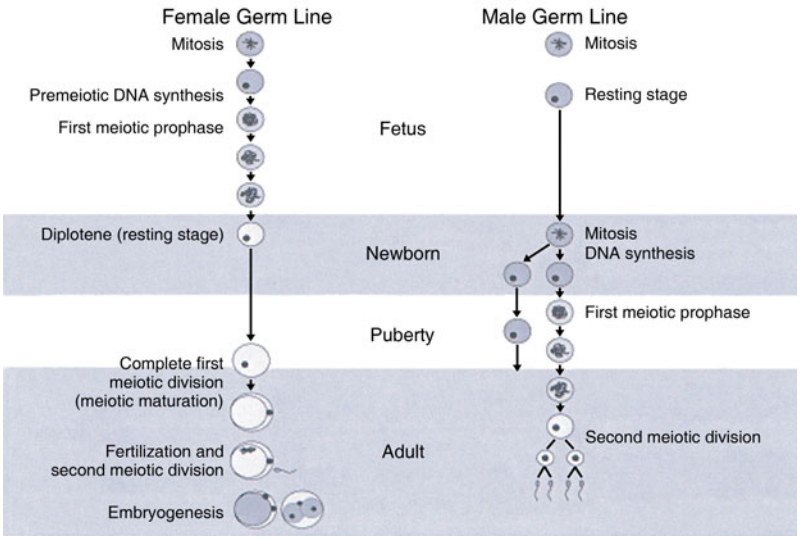

Fig. 4.1. Comparative human gametogenesis, by sex (Andersen and Byskov, 1996).

and a differentiating germ cell that undergoes numerous mitotic divisions over several weeks, followed by two meiotic divisions that occur with a few hours of each other.

There is sex-specificity of checkpoints during germ-cell maturation, as well as sex- and stage-specificity of DNA repair capacity. The relative competence of the various germ-cell stages, both for checkpoint control of the cell cycle and for DNA repair, has a clear impact on the ability of environmental agents to induce mutations at various germ-cell stages. Male germ cells appear to have a more efficient meiotic checkpoint than female germ cells; however, male germ cells are DNA repair-deficient in postmeiotic stages, while postmeiotic female germ cells retain the capacity for DNA repair. Discussions of DNA repair in germ cells can be found in Jeggo *et al*. (2011), Marchetti and Wyrobek (2008), Marchetti *et al*. (2007), Mukherjee *et al*. (2010), and Parliament and Murray (2010).

4.3 Detecting Radiation Damage in Sperm and Eggs

Laboratory detection of gene mutations, DNA damage, and chromosome defects in human sperm offers the major advantage of analyzing numerous sperm directly, rather than counting individual offspring. In other words, many gametes per individual can be assessed for genomic defects in contrast with the small numbers of

affected offspring typically available for epidemiological studies of male-mediated effects. The statistical advantage of sperm studies was illustrated by estimating the number of families with offspring that would need to be screened to detect a doubling of affected offspring with various adverse effects over the background rate after a hypothetical parental exposure to ionizing radiation: ~900 families for birth defects, ~300 for spontaneous abortions, and ~250,000 for childhood leukemia. In contrast, sperm studies usually require as few as 10 men in each group to detect a doubling effect, depending on the specific assay used (Mulvihill and Garlow, 2007; Wyrobek *et al*., 2007).

A main limitation of sperm assays is that they are, of course, restricted to exposures of males, and the phenotypic effect in live-born offspring of the gametic changes are not known. In addition, research is needed to elucidate the cellular and biochemical events that occur after sperm release that may modify the probability of a genetically-defective sperm producing a child with a heritable defect of paternal origin. Selection pressures for or against defective sperm could act during fertilization *via* maternal DNA repair of sperm DNA lesions in the zygote, and by epigenetic modifications of sperm DNA. Nevertheless, sperm assays may seem to be an attractive approach for screening for potentially-hazardous exposures to ionizing radiation because of low cost and relative ease of access and the reassurance that negative results might offer. In the end, it would be imprudent to assume an absence of risk for hereditary disease in the next generation, based solely on sperm assays (Arnheim and Calabrese, 2009).

Polymerase chain reaction (PCR) and direct sequencing-based assays can measure mutant frequency at a specific nucleotide, as demonstrated with the fibroblast growth factor receptor genes *FGFR2* or *FGFR3*, that are associated with dominantly inherited Apert syndrome and achondroplasia, respectively. The two specific nucleotides have a mutation frequency that is much higher than average. Mutations in these two genes occur predominantly in the paternal genome at the same nucleotide, accounting for the high rate of *de novo* (sporadic) cases, associated with advanced paternal age (Crow, 2003). The mutations have, in fact, been observed in the sperm of fathers of children with Apert syndrome (Wyrobek *et al*., 2006). Recently, the molecular tools of detecting copy number variants have also documented a paternal age effect for *de novo* effects for complex disorders, including autism and schizophrenia (Kong *et al*., 2012; Neale *et al*., 2012; O'Roak *et al*., 2012, Sanders *et al*., 2012). Finally, total sequencing of 20 individual human sperm from one person showed a recombination rate comparable to

prior population genetics estimates, but also showed enormous variation from sperm to sperm, verifying that sperm studies have a role in understanding but cannot predict hereditary disease in the offspring (Wang *et al*., 2012a). None of the recent studies specifically addressed radiation exposure.

Three molecular techniques can analyze DNA damage and cytogenetic defects directly in human sperm:

- sperm comet assay;
- sperm chromatin structure assay; and
- sperm fluorescence *in situ* hybridization (FISH) (Wyrobek *et al*., 2006).

The sperm comet assay is a gel electrophoretic method typically applied to ~100 sperm nuclei per sample to quantitate single- or double-strand DNA breaks. Sperm chromatin structure assay is a flow cytometric method that employs acridine orange to measure the relative proportions of single- and double-stranded DNA in several thousand sperm. Results represent the degree of DNA fragmentation per specimen and the proportions of sperm with immature (no protamines) chromatin. Several human sperm FISH methods detect aneuploidy and structural chromosomal alterations, including breaks as well as partial chromosomal duplications and deletions (Wyrobek *et al*., 2006). Multicolor FISH has been applied to detect aneuploidies for multiple chromosomes in ~10,000 sperm per specimen; DNA probe combinations can detect sperm associated with increased risks for aneuploidy syndromes including Down, Edwards, Turner, Klinefelter, XXX, and XYY, as well as other autosomal trisomies (Wyrobek *et al*., 2006). Sperm samples from cancer patients who received radiation (or chemotherapy or both) show that the sperm-cell stage, the time of exposure, and the dose of radiation all influence the frequency of aneuploidy and chromosome aberrations in the sperm that are subsequently produced (Martin *et al*., 1995).

Experimental studies of the *human oocyte* genome have used FISH, spectral karyotyping, and comparative genomic hybridization. These preliminary studies were carried out with unfertilized human oocytes generated from assisted reproductive technology (Adriaens *et al*., 2009; Shen *et al*., 2008). FISH and comparative genomic hybridization analyses indicate aneuploidy rates from 20 to 52 % in human oocytes. In contrast, studies using conventional chromosome analysis methods estimated a lower frequency of 11 %. Besides reflecting differing sensitivities of the assays, the results, which do include some radiation exposures, may be associated also

with maternal age effects. The extent of total aneuploidy and specific types of chromosome abnormalities strongly increased with the age of the female donor.

Modulators of gene expression in gametes and embryos are epitomized by the mechanism of DNA methylation, one of the best-characterized epigenetic mechanisms for modulating gene function. Gene imprinting by DNA methylation is required for chromosome X inactivation and gene silencing. Defective imprinting is associated with human diseases such as Prader-Willi, Angelman, and Beckwith-Wiedemann syndromes, and aberrant DNA methylation is one feature of some human cancers (Ballestar, 2011; Le Bouc *et al*., 2010). It may occur in human embryos produced by artificial reproductive technologies (DeBaun *et al*., 2003). The mechanisms by which DNA methylation patterns are inherited are complex. Most methylation is maintenance methylation, which occurs post-replicatively on hemi-methylated DNA. However, the genome is "reprogrammed" twice, once during gametogenesis and once during embryogenesis. Reprogramming occurs at different times in male and female gametogenesis. Male progenitor germ cells begin to be methylated before birth and continue to be methylated at some sites after birth. In contrast, female germ cells are reprogrammed primarily after birth. In the somatic tissue of the mouse embryo, reprogramming takes place during 15th to 17th days postconception. However, the exact timing of methylation in embryonic cells varies in a gene-specific manner. Little is known about how environmental agents such as ionizing radiation affect DNA methylation in somatic or germ cells. However, molecular approaches have been developed for detailed analysis of DNA methylation in specific genes or on a genome-wide basis (Barlow, 2011). These methods, including bisulfite sequencing, restriction landmark genome scanning, and methylation profiling, can be used to begin to address this question and to study the consequences of defects in DNA methylation in animal model systems.

The genome is continuously assaulted by many exogenous and endogenous agents (*e.g*., reactive oxygen species) that induce lethal or mutagenic DNA lesions. Such lesions or their inhibitory effects on the processes of replication or transcription trigger cellular responses that may arrest the cell cycle, induce apoptosis, or up-regulate the expression of DNA repair enzymes to repair DNA damage. There are three DNA excision repair pathways: nucleotide excision repair, base excision repair, and mismatch repair targeted to different types of DNA damage, but with a considerable degree of overlap in the specificity of substrate. Additionally, recombinational mechanisms are utilized to deal with double-strand breaks,

interstrand crosslinks, closely spaced lesions on the respective DNA strands, and some types of replication fork arrest. Mutations in genes encoding DNA repair proteins cause phenotypic effects on growth, cell-cycle progression, susceptibility to DNA damage, meiosis, and other biological processes. Discussions of these topics can be found in Jeggo *et al*. (2011), Mukherjee *et al*. (2010), and Parliament and Murray (2010).

Several human diseases, usually predisposing to cancer, arise from genetic defects in enzymes that repair damage to DNA. Best known are the defects in DNA repair of damage by ultraviolet light, epitomized by xeroderma pigmentum. Genetic susceptibility to ionizing radiation is seen in patients with ataxia-telangiectasia, hereditary retinoblastoma, and the nevoid basal cell carcinoma syndrome. The susceptibility is manifested as carcinogenesis, but could contribute to germ-cell mutation (Arnheim and Calabrese, 2009; Paterson *et al*., 1984).

4.4 Detecting Human Germ-Cell Mutagenesis in Offspring: Theory

The inheritance of mutations is a process that, in theory, has both a *background* component that is intrinsic in an individual and an *induced* component that results from environmental exposures such as ionizing radiation. A very small but undefined fraction of hereditary human disease is certainly attributable to the environmental agents with mutagenic potential. In the absence of adequate human data, modeling and extrapolation have guided public policy. The current paradigm for assessing human genetic risk from exposures to ionizing radiation is based on the assumption that adverse effects of radiation will be manifested in progeny of exposed individuals as genetic diseases similarly distributed to those that occur naturally in the population (Sankaranarayanan, 2006; UNSCEAR, 2001). With limited human data, risk is generally estimated using three components: the doubling dose for radiation-induced germ-cell mutations in mice, the background rate of sporadic genetic disease in humans, and population-genetics theory. Sankaranarayanan (2006) and UNSCEAR (2001) estimate that the genetic risk associated with chronic, low-dose irradiation is ~4,000 affected cases per million births per gray (parental gonadal dose). This estimate for genetic risk represents ~0.5 % of the baseline frequency of affected births (738,000 cases per million births). The baseline estimate includes chronic multifactorial diseases in the population (650,000 per million, mostly of adult onset), congenital abnormalities (60,000 per million), Mendelian diseases (24,000 per million), and chromosomal diseases (4,000 per million).

Sankaranarayanan (2006) predicted the rate at which nonlethal radiation-induced multigene deletions should occur in the mouse or human genome. His analysis is based on molecular understanding of the mechanisms by which such deletions occur and the distribution of nonsegmental duplications in the mouse and human genomes. A large fraction of the biological impact of radiation on the cellular level is likely due to misrepair or lack of repair of radiation-induced double-strand breaks, which are repaired by three major pathways in mammalian cells: nonallelic homologous recombination, homologous recombination, and nonhomologous end-joining. Sankaranarayanan (2006) has suggested that germ cells may favor the first pathway (nonallelic homologous recombination repair) and that low-copy repeats are hot spots for radiation-induced deletions. Thus, if this hypothesis is correct, detailed analysis of genome architecture should allow one to predict the sites where a multigene deletion mediated by a pair of low-copy repeats will not be lethal. These ideas await testing in experimental studies in mice or through molecular analysis of human fetuses or neonates (*i.e.*, infants aged one month or less). Additional analysis of the distribution of low-copy repeats in the human and mouse genome is also needed.

Many technologies can assess DNA and genomic defects and relate them to the biological endpoints that could potentially be measured or analyzed with those technologies (Table 4.1). The most promising technologies are PCR-based sequencing, PCR-based conformation analysis, sequencing by hybridization, end-sequence profiling, primer extension, FISH, comparative genomic hybridization, optical mapping, genome subtraction, expression arrays, serial analysis gene expression for both ribonucleic acid (RNA) and DNA, chromatin immunoprecipitation assays, protein lysate arrays, one- and two-dimensional gel electrophoresis, and mass spectrometry.

One additional consideration is that some deleterious mutations (spontaneous or as a result of preconception radiation exposure) would not be expressed in an offspring because they are lethal to the developing ova or sperm or to the developing embryo because of defective ova or sperm, a consideration that has been described as biological filtration (Brent, 1999a).

4.5 Human Germ-Cell Mutagenesis: Practice

For lack of practical implementation, little has changed in the three decades since the principles of epidemiologic study of human germ-cell mutagenesis due to ionizing radiation (and other environmental hazards) were deliberated and set down *in extenso* by

TABLE 4.1—*Technologies for assessing DNA and genomic defects.*

Genome Analysis Technology	Major Utility	Applicable to Single-Cell Analyses	Genomic Resolution
PCR-based assays (sequencing or conformation)[a]	Single-gene assessment, methylation	Yes	Single base
Sequencing by hybridization	Allelotyping, mutation detection	Yes	Single base
End sequence profiling (DNA and transcripts)	Structural rearrangements, large-scale resequencing, genome immortalization	No	1 to 100 base pairs
Primer extension	Antibody based multiprotein interrogation	No[a]	Single protein
FISH[b]	Numerical and structural chromosomal aberrations	Yes	Megabase
Comparative genomic hybridization	Copy number gains and losses, allele specific, methylation specific	Possibly	$(10 \text{ to } 100) \times 10^3$ base pairs
High throughput loss of heterozygosity	Loss of heterozygosity mapping, gene localization	Possibly	100×10^3 base pairs
Optical mapping	Numerical and structural chromosomal aberrations	Yes	100 base pairs
Genome subtraction	Mapping and cloning of lost or gained regions	Possibly	Megabase

TABLE 4.1—(*continued*)

Genome Analysis Technology	Major Utility	Applicable to Single-Cell Analyses	Genomic Resolution
Expression arrays	Comprehensive, semi-quantitative expression, splicing	Yes	Single exon
Serial analysis gene expression (RNA and DNA)	Comprehensive, quantitative expression, splicing	No	Single gene
Chromatin immunoprecipitation assays	DNA binding proteins, chromatin structure	No	Single gene
Protein lysate arrays	Antibody based multiprotein interrogation	No[a]	Single protein
One- and two-dimensional gel electrophoresis	Mutant protein detection	No[a]	Single protein
Mass spectrometry	Qualitative protein composition	No[a]	Single protein
Total exomic[c] or genomic DNA sequencing	Small DNA changes	Yes	Single base

[a]Approximately 100 cells are needed.
[b]Technologies adapted to the analyses of genomic defects in human and animal sperm.
[c]The exome is the most functionally relevant part of the genome for coding proteins (1.5 % of the total genome).

the Committee on Epidemiology of the International Commission for Protection Against Environmental Mutagens and Carcinogens (Buwe *et al*., 2005; Eichenlaub-Ritter *et al*., 2007; Elespuru and Sankaranarayanan, 2007; Marchetti and Wyrobek, 2005; Miller *et al*., 1983; Mulvihill, 1982; Mulvihill and Miller, 1984; Wyrobek *et al*., 2005). In theory, the two different strategies depend on whether one starts with a putative radiation exposure or with a putative adverse outcome. One, a prospective or cohort study, begins with a population known or suspected to have been exposed to radiation and follows the subjects for evidence of adverse outcomes possibly attributable to germ-cell mutation. Another, a case-control design, begins with a population with an adverse outcome and seeks antecedent factors, like radiation, that are associated and could be causal. Both study designs suggest ionizing radiation is a cause of some cancers. Further, biomarkers of carcinogenicity make causal inference feasible. But, the approach has not been feasible for detecting the possible germ-cell mutagenicity of radiation because the timing of germ-cell mutagenicity requires accurate recall of environmental exposure by the grandmother while the mother was a fetus (*i.e*., the mother's eggs are undergoing miosis 1 when the mother is a fetus in the third trimester and that would be the relevant exposure that led to an offspring with a genetic disease). Also, a large population size is needed to address the diverse clinical markers of germ-cell mutation.

4.5.1 *Endpoints for Studies of Mutagenesis*

Since every human illness or trait has genetic determinants (some are obvious, some are subtle), all adverse health effects, including decreased lifespan, could possibly reflect a mutational event. The fraction of the incidence of a genetic disease that is changeable by mutation is called the "mutation component" (Crow and Denniston, 1981).

However, a particular disease might have multiple causes resulting from gene-gene or gene-environmental interactions, so attributing a common disease to a specific mutation is fraught with uncertainty. Nine endpoints seem relevant to addressing the issue of germline mutagenesis possibly due to ionizing radiation: infertility, fetal death, sex ratio at birth, chromosomal abnormalities, congenital malformations, childhood cancer, single-gene (Mendelian) disorders, variations in proteins, and variations in nucleic acids (DNA and RNA).

4.5.1.1 *Infertility.* Defined as the inability to conceive within 1 y of frequent, unprotected intercourse, infertility affects 7 to 14 % of

U.S. couples. Of known causes, about half are male and half female, and sometimes each partner has an abnormality that alone might not cause infertility. Of causes in males, 15 to 30 % are major genetic causes:

- Klinefelter syndrome;
- Robertsonian chromosomal translocations;
- microdeletions of the Y chromosome (especially of the azoospermia factor regions a, b and c, and of the chromodomain protein Y-linked gene);
- increased copy numbers of the testis-specific protein Y-linked gene;
- mutations of autosomal genes, famously those for cystic fibrosis, sex hormone-binding globulin, estrogen and gonadotrophin receptors, and cryptorchism;
- mutations of X-linked genes, especially the androgen receptor (causing androgen insensitivity and Kennedy syndromes); and
- Kallmann syndrome genes [Kallmann syndrome-1 sequence (*KAL1*) and fibroblast growth factor receptor 1 (*FGFR1*)].

Genetic determinants in females include:

- Turner syndrome;
- translocations;
- single-gene defects (such as hypogonadotropic hypogonadism, including Kallmann syndrome);
- premature ovarian failure;
- fragile X mental retardation 1;
- congenital absence of the uterus and vagina;
- polycystic ovary syndrome;
- uterine leiomyomas; and
- endometriosis.

Such information on infertility can be found in articles by the European Society of Human Reproduction and Embryology (ESHRE, 2008) and O'Flynn O'Brien *et al*. (2010).

4.5.1.2 *Fetal Death*. By convention suggested by the Centers for Disease Control and Prevention, fetal death is comprised of intrauterine death before 20 weeks of pregnancy (miscarriage or spontaneous abortion) and after 20 weeks (stillbirth). The causes include:

- chromosomal problems [especially chromosome mosaicism 45,X; common autosomal trisomies (*e.g*., trisomies 16, 21, 22); polyploidies; and chromosome translocations]; and

- single-gene defects (especially the hereditary thrombophilias, such as factor V Leiden defect, prothrombin abnormalities, and pathogenic polymorphisms of plasminogen activator inhibitor-1 and methylenetetrahydrofolate reductase).

Structural defects of the uterus due to congenital malformation or tumors can cause repeated fetal deaths or premature delivery, as can twins and other multiple gestations, vascular hypertension, and maternal diabetes mellitus. Such information on fetal death can be found in Coletta and Simpson (2010), Fretts (2010), Pauli (2010), and Smith (2010).

4.5.1.3 *Sex Ratios at Birth*. Germ-cell mutation could alter the sex ratio at birth, defined as the number of male births divided by the number of female births. In the past six decades, it ranged from 1.058 in 1948 to 1.046 in 1991, ~5 % more males than females. In short, if a woman sustains X chromosome germ-cell mutation, fewer males will be born; if a man does, fewer females will be born (Speicher *et al*., 2010).

4.5.1.4 *Congenital Malformations and Childhood Cancer*. Although these conditions are different pathogenetically, these two groups of disorders are combined since most are considered sporadic (that is with a negative family history and "developmental" in origin), with a suspected but unclarified mutation component. The common isolated birth defects are events of the first seven weeks of gestation, such as congenital heart defects, neural-tube defects, renal anomalies, cleft lip, and other major organ malformation. Some are Mendelian traits, but often aggregated with defects in multiple organ systems as a syndrome of multiple congenital anomalies with mental retardation, when chromosomal and single-gene mutations are often the underlying cause. A few childhood cancers likewise are Mendelian, such as hereditary retinoblastoma, Wilms tumor, and other malignancies that are a feature of hereditary predisposition to several tumors, like the nevoid basal cell carcinoma syndrome and the multiple endocrine neoplasias (Mulvihill, 1999).

4.5.1.5 *Chromosomal abnormalities*. Whereas the preceding adverse pregnancy outcomes have some "genetic" component that could reflect mutagenicity, chromosome anomalies are classic genetic endpoints. Variations in number of chromosomes in a cell and in large, visible (by light microscopy) linear arrangements of DNA, when defective, comprise translocations, breaks, or large deletions. As molecular genetic techniques improve the submicroscopic resolution, the boundary with single-gene defects vanishes and is seen as artificial.

4.5.1.6 *Single-Gene (Mendelian) Disorders*. Russell and Russell (1992) developed the mouse specific-locus test, which allowed quick and objective detection of visible mutations among seven loci that largely determine external features, like coat color. They utilized the specific-locus test to study the effects of different qualities of radiation, total dose, dose protraction, and dose fractionation. Their results with dose protraction showed that certain germ cells could repair premutational damage. They explored the roles of sex, parity, age, and (most importantly) germ-cell stage on mutation rate and type. For years the experimental work in whole organisms was focused on mice, mostly male mice, at the Oak Ridge National Laboratory (Russell and Shelby, 1985; Russell *et al*., 1998), the Institut fur Saugetiergenetik, Gesellschaft fur Strahlen-und Umweltforschung (Munich, Germany) (Favor, 1989), and the International Centre for Mouse Genetics, Medical Research Council (Harwell, England) (Lyon and Renshaw, 1986). Key discoveries at these laboratories regarding the nature of mutations detected in mouse germ cells following specific radiation exposures revealed that radiation produced primarily large lesions (*e.g*., deletions and inversions), in postspermatogonial stages, but not in premeiotic or meiotic stages.

In a sense, the human homologies of the specific-locus tests of rodents are the so-called sentinel phenotypes, that are clinical disorders that result from highly penetrant mutations in dominant (or X-linked) genes; they have a high mutational component (Mulvihill and Czeizel, 1983). Studies on the effect of paternal age on human germline mutations (the so-called paternal age effect) have focused on several well-characterized human disease syndromes such as Apert syndrome, achondroplasia, the X-linked hemophilias, hereditary retinoblastoma, and neurofibromatosis type 1. A logical leap is made that ties possible radiation or other environmental exposure to increasing paternal age, assuming a greater duration of exposure and greater chances of hazardous exposures at the workplace of males than females. Clinical observations suggest that, for these diseases, the number of affected offspring increases with increasing paternal age. This association suggests that the germline mutation rate increases with paternal age but not with maternal age and that the mutation rate is higher in human males than in females. Molecular analysis of human and mouse germ cells has confirmed some of these clinical observations.

Further, four classes of mutations have been identified that contribute differentially to the paternal age effect: hot spots, insertions or deletions (indels), base substitutions, and, recently, copy number variants (Crow, 2003; Kong *et al*., 2012; Neale *et al*., 2012; O'Roak

et al., 2012; Sanders *et al*., 2012). When present, as in the genes underlying Apert syndrome and achondroplasia, hot-spot mutations tend to occur in males only, and in some cases they increase dramatically with paternal age. However, hot-spot mutations are gene- and sequence-specific and are, therefore, relevant only to paternal age effects in a subset of genes (Crow, 2003). Approximately two-thirds of the documented new mutations in the human genome are base substitutions, with the remaining one-third of mutational events being mostly small and large indels that show no increase with paternal age. Crow (2003) argued that base substitutions show a slight paternal bias and a smaller, but significant, paternal age effect than hot-spot mutations. The total paternal age effect in a specific gene reflects the relative contributions of base substitutions, indels, and hot-spot mutations. Thus, the magnitude of the paternal age effect should vary significantly from one gene to another.

4.5.1.7 *Variations in Proteins and Nucleic Acids*. Biochemical techniques for proteins matured well before those for nucleic acids. Still, the central dogma of molecular genetics supports the close proxy that protein changes reflect gene mutations. Hence, protein polymorphisms were explored extensively in the offspring of atomic-bomb survivors by enzyme activity and even by two-dimensional electrophoretic separations that added molecular quantification of the negative data from clinical adverse pregnancy outcomes (Neel *et al*., 1988). Molecular methods could be used to identify genomic mutations in exposed human populations by assaying aneuploidy, chromosome aberrations, inversions, deletions, copy number variants, and point mutations.

Apart from copy number variants, the human genome has three types of repeated DNA sequences: minisatellites, microsatellites, and extended simple tandem repeats (ESTRs). The spontaneous mutation rate at microsatellite and ESTR loci is several orders of magnitude higher than in the rest of the human genome, and these types of loci account for up to 15 % of all gamete genomes. Minisatellites appear to have a high mutation rate in both human somatic cells and germ cells, so they seem suitable for studying induced mutations in the human germline. Most mutations in ESTRs are gains or losses of repeats, suggesting that they arise *via* replication slippage. Importantly, because of the high mutation rate in ESTRs and minisatellite sequences, fewer samples are needed to detect exposure-induced mutations in these sequences than in single-copy genes. Thus, it is estimated that minimum sample sizes of 240, 2,400, or 240,000 individuals are sufficient to detect induced mutations over the background rate in human minisatellites or mouse

ESTR, microsatellite, and single-copy genes, respectively (Bouffler *et al*., 2006; Dubrova, 2003a; 2003b; 2003c; Verhofstad *et al*., 2008). Positive findings for various exposures in the former Soviet Union (Dubrova *et al*., 1996; 2002a; 2002b; 2006) have not been replicated (Furitsu *et al*., 2005; Kiuru *et al*., 2003; Livshits *et al*., 2001; Slebos *et al*., 2004). A similar approach for offspring of Japanese survivors of the atomic bombs was negative (Kodaira *et al*., 2004; 2010) as were studies of the children of cancer survivors treated with radiotherapy (Tawn *et al*., 2011). Mutations in minisatellite DNA sequences are discussed more fully in Section 4.6.4.

4.5.2 *Relative Biological Effectiveness*

Rao *et al*. (1991) published relative biological effectiveness (RBE) values for induction of sperm head abnormalities (Table 4.2) in mouse testes for a variety of types of ionizing radiation emitted by radionuclides in the testes. Substantially lower RBE values were obtained for the spermatogonial cell survival assay that was conducted 9 d prior to the sperm head assay (Table 4.2). Induction of sperm head abnormalities is a radiosensitive endpoint (Wryobek, 1979; Wyrobek and Bruce, 1978). The data in Table 4.2 provide a basis for the varied RBE values that arise as a consequence of different types of ionizing radiation: ^{7}Be (gamma-ray emitter), ^{125}I (Auger-electron emitter), ^{111}In (Auger-electron emitter), and ^{210}Po (alpha-particle emitter). Note the testicular absorbed dose required to increase the abnormal fraction (Table 4.2, the column expressed as initial slope in percent abnormalities per 0.01 Gy).

Additional RBE data are also available for spermatogonial cell killing in the testes by alpha particles (Howell *et al*., 1994; 1997). A linear dependence between RBE and initial alpha-particle energy was observed. RBE values were also reported for the imaging agent ^{201}Tl (Rao *et al*., 1983) and for a variety of ^{99m}Tc radiopharmaceuticals used in nuclear medicine (Narra *et al*., 1994).

4.6 Heritable Disease in Exposed Populations

Animal experiments provide strong evidence that radiation-induced germline mutations occur but, to date, there is no convincing direct evidence in humans (ICRP, 2007a; NA/NRC, 2006; UNSCEAR, 2001; Wyrobek *et al*., 2007). UNSCEAR (2001) concluded that "no radiation-induced genetic diseases have so far been demonstrated in humans … [therefore] estimates of risk have to be based on mouse experiments." The epidemiological studies of heritable disease include populations exposed to high residential background radiation from natural or technologically-enhanced sources, Japanese atomic-bomb survivors, survivors of nuclear accidents,

TABLE 4.2—*RBE for various radiations from radionuclides incorporated in mouse testes (Rao et al., 1991).*

Radiochemical[a]	Radionuclide Subcellular Distribution[b]	Optimal Assay Day Post-Injection[c]	Initial Slope[d]	RBE for Abnormalities[e]	Dose Reduction Factor for Abnormalities[f]	RBE for Survival[g]
X rays (120 kV)	—	38	0.029 ± 0.002	—	—	—
^{7}Be-chloride	46 % Cy; 54 % N	38	0.086 ± 0.005	3.0 ± 0.3	—	1.1
^{125}I HIPDM	100 % Cy	38	0.07 ± 0.002	2.5 ± 0.2	—	1.0
^{125}IUdR	100 % N; 100 % D	38	1.7 ± 0.1	59 ± 4	—	7.9
^{111}In-citrate	70 % Cy; 30 % N; 9 % D	43	0.35 ± 0.02	12 ± 1	—	2.0
^{111}In-oxine	8 % Cy; 92 % N; 4 % D	43	1.4 ± 0.1	48 ± 4	—	5.6
^{210}Po-citrate	80 % Cy; 20 % N; 45 % D	45	7.1 ± 0.5	245 ± 23	—	6.7
^{125}IUdR + MEA	100 % N; 100 % D	38	0.12 ± 0.01	—	14 ± 1	—
^{210}Po-citrate + MEA	80 % Cy; 20 % N; 45 % D	38	0.70 ± 0.04	—	10 ± 1	—

[a]HIPDM = N,N,N^{1}-trimethyl-N^{1}-(2-hydroxy-3 methyl-5-iodobenzyl)-1,3-propanediamine
IUdR = iododeoxyuridine
MEA = cysteamine
[b]% Cy = percentage of activity in cytoplasm
% N = percentage of activity in nucleus
% D = percentage of activity in cell nucleus bound to DNA
[c]Days post-injection at which epididymal sperm head abnormalities are assayed.
[d]Initial slope (percent abnormalities per 0.01 Gy) of dose-response curves for induction of abnormalities.
[e]Abnormal sperm head assay: RBE compared to x rays generated at 120 kV (peak tube potential).
[f]Dose reduction factor for radioprotective agent MEA.
[g]Sperm head survival assay: RBE at 37 % survival compared to x rays generated at 120 kV.

occupational groups of radiation workers, and patients undergoing diagnostic or therapeutic medical exposures (especially cancer survivors treated with radiation therapy).

4.6.1 *Residential Exposures from High or Enhanced Background Radiation*

Studies of possible heritable effects associated with increased or enhanced levels of background radiation have been conducted in India (Jaikrishan *et al*., 1999), China (Wei *et al*., 1990), Ireland (Dean *et al*., 2000), and the former Soviet Union (Dubrova *et al*., 1996). Studies have attempted to find associations between radiation and Down syndrome, major malformations and certain genetic markers such as germline mutations in minisatellite DNA sequences, mitochondrial DNA or the Y chromosome. The radiation sources include thorium-containing monazite sands, nuclear weapons-testing fallout, nuclear-accident contamination, and effluents from nuclear facilities.

Most studies of Down syndrome and other genetic anomalies in populations residing in areas of increased background radiation have been ecological and limited because individual doses and potential confounding influences are unknown.

An early study in China of an increased rate of Down syndrome among residents in areas of high background radiation was later attributed to increased maternal age at birth and to better case ascertainment in the exposed compared with the control areas (UNSCEAR, 1993; Wei *et al*., 1990). A reported cluster of Down syndrome on the east coast of Ireland that was attributed to airborne radiation released from the Sellafield Nuclear Fuel Reprocessing Plant was later discounted (Dean *et al*., 2000). Studies in Kerala, India of some 140,000 inhabitants residing in areas of high natural background radiation (15 to 25 mGy) (annual whole-body dose) reported increased rates of Down syndrome (Kochupillai *et al*., 1976), which were not borne out in subsequent studies based on more reliable sources of information (Kesavan, 1997). A comprehensive study of over 40,000 newborn children and stillbirths in Kerala found no correlation between increased levels of natural background radiation and malformation, stillbirth or twinning (Jaikrishan *et al*., 1999). Mental retardation and cleft lip or cleft palate also were not correlated with background radiation in Kerala (Koya *et al*., 2012). Certain inherited genomic changes to mitochondrial DNA (Forster *et al*., 2002) and to the Y chromosome (Premi *et al*., 2009) were reported among the offspring of residents in Kerala but have not been replicated and there is some uncertainty as to the actual gonadal dose received and the adequacy of the control groups.

4.6.2 *Japanese Atomic-Bomb Survivors*

The most comprehensive study of heritable genetic effects following preconception irradiation in humans is that of the Japanese atomic-bomb survivors which involved nearly 70,000 pregnancies (Izumi *et al*., 2003; Nakamura, 2006; Neel, 1998; Neel and Schull, 1991; Schull, 2003; Schull *et al*., 1981). A broad range of gonadal doses were examined with respect to eight indicators of genetic damage:

- untoward pregnancy outcomes (*i.e*., infant stillborn, major congenital malformation, dying within the first two weeks of life);
- cancer in the offspring;
- death among offspring;
- chromosomal aberrations;
- frequency of sex-chromosome aneuploids;
- frequency of mutation-altering protein change or function;
- sex ratio among children of exposed survivors; and
- growth and development of the F1 offspring population.

The rarity of individual outcomes such as specific birth defects necessitated the grouping of certain classes of outcomes. Associations with most if not all of these outcomes with dose were in the positive direction, although none was statistically significant. The mean gonadal dose was of the order of 0.3 Gy. Based on these data, Neel (1998; 1999a) estimated that ~2 Gy is the most probable doubling dose (dose to a population that would produce the same amount of genetic damage that occurs spontaneously each generation) for acute exposure and ~4 Gy for chronic exposure.

4.6.3 *Exposed Occupational Groups*

Studies of preconception radiation and genetic disease occurring in subsequent children have included nuclear radiation workers and x-ray technologists. These studies are limited by small sample sizes, low gonadal doses, lack of dosimetric information, or inadequate comparison groups and are summarized below.

A 1983 report of a cluster of leukemia and non-Hodgkin's lymphoma in young people living in Seascale, Cumbria, United Kingdom generated substantial interest and research. A case-control study by Gardner *et al*. (1990) suggested an association between preconception irradiation and leukemia and non-Hodgkin's lymphoma in children of male workers at the Sellafield Nuclear Fuel Reprocessing Plant. Subsequent studies failed to confirm the possibility that low doses to the testes received by a father

before conception is a cause of cancer (Doll *et al*., 1994; Kinlen, 1993; Kinlen *et al*., 1993; Little *et al*., 1996; Neel, 1999b; Tawn, 1995; UNSCEAR, 1994; Wakeford, 2000). A subsequent cohort study confirmed the previously reported statistical association between preconception radiation of Sellafield workers and leukemia and lymphoma (Dickinson and Parker, 2002), but could not be considered an independent test of the hypothesis since it included the same cases previously studied by Gardner *et al*. (1990). An infectious agent associated with a high level of population mixing was raised as a possible explanation (Kinlen, 1995; Sorahan *et al*., 2003). The hypothesis that a proportion of childhood leukemia cases might be associated with an increase in minisatellite germline mutations resulting from parental exposure could not be sustained, when no increase in inherited germline minisatellite mutations was found in children with leukemia (Davies *et al*., 2007). A weak association was reported between maternal radiation work during pregnancy and childhood cancer in offspring although the evidence was limited by small numbers (Bunch *et al*., 2009). There was no convincing evidence for an association between parental occupational exposure and childhood cancer in the offspring of U.S. radiologic technologists (Johnson *et al*., 2008a).

Studies of workers at the Sellafield Nuclear Fuel Reprocessing Plant have also reported a statistical association between paternal preconception exposure and stillbirth (Parker *et al*., 1999) which was not consistent with a larger study of workers in the U.K. nuclear industry (Doyle *et al*., 2000) or with the atomic-bomb survivors study (Little, 1999a; Otake *et al*., 1990). Maternal factors also were not considered (Boice *et al*., 2000). A comprehensive study of the children of cancer survivors found no association between the paternal dose to the testes (mean = 0.53 Gy) and the occurrence of stillbirth and neonatal death (Signorello *et al*., 2010). Congenital malformations have been studied among live-born children of workers in the Canadian nuclear power industry but no correlation was found with preconception doses (Green *et al*., 1997). Twelve major congenital anomalies were evaluated in a study of Hanford workers with respect to preconception radiation, including Down syndrome, for which an association was believed to be the most likely (Sever *et al*., 1997). There was no evidence for a radiation association except for neural-tube defects which was based on only three cases. Studies of medical radiographers are in large part negative with respect to adverse inherited outcomes but are hampered by a lack of adequate dosimetry (Boice *et al*., 1992; Roman *et al*., 1996). The low gonadal doses in most occupational studies preclude statistically powerful evaluations.

4.6.4 *Mutations in Minisatellite Deoxyribonucleic Acid Sequences*

Because mutations in minisatellite regions are approximately 1,000 times more common than mutations in genes that code for proteins, studies of mutations at these hypervariable loci might provide insights into radiation-induced human germline mutations (Dubrova, 2003b; Dubrova *et al*., 2006). These minisatellite sequences have no clear function, but evaluation of length changes might be related to radiation-induced germline mutations that could be evaluated in relatively small population samples. Mutation frequencies have been reported to be twice as high in children whose parents were exposed to Chernobyl nuclear reactor fallout (Dubrova *et al*., 1996). However, control samples were obtained from England and not from Belarus making results difficult to interpret and raising questions regarding confounding factors such as ethnicity, health status, and environmental contamination other than radiation (Neel, 1999b). Dubrova *et al*. (1997) extended their analysis in a further report to include additional families and more minisatellite probes and reported a twofold higher mutation rate in exposed families compared with nonirradiated families from the United Kingdom. Increased minisatellite mutation frequencies have also been associated with exposure to presumed radioactive fallout from the Semipalatinsk nuclear test site (Dubrova *et al*., 2002b). A study of a population living along the Techa River, contaminated by discharges from the Russian Mayak Plutonium Facility, also was reported to have an increase in paternal germline minisatellite mutations (Dubrova *et al*., 2006). These studies have highly uncertain estimates of radiation gonadal dose, uncertain control for potential confounding factors and have not been independently replicated as discussed below.

In contrast, no statistically-significant increase in the minisatellite mutation rate was observed in studies of the Japanese atomic-bomb survivors who experienced much higher doses and dose rates (Kodaira *et al*., 1995), or in other studies of Chernobyl nuclear reactor liquidators and their offspring. Livshits *et al*. (2001) reported no elevation of mutation frequency in the offspring of Chernobyl nuclear reactor cleanup workers from the Ukraine. Results of a study of offspring of Estonian Chernobyl nuclear reactor cleanup workers (Kiuru *et al*., 2003) indicated a slightly higher mutation rate in those children born post-exposure compared with those conceived prior to the Chernobyl nuclear reactor accident. Two further studies of Chernobyl nuclear reactor cleanup workers also reported no statistically-significant increase in germline mutations using multi-locus minisatellite probes (Slebos *et al*.,

2004) and microsatellite markers (Furitsu *et al*., 2005). No evidence of an increase in minisatellite mutations was observed in a study of germline cells from seminoma patients treated with radiation (May *et al*., 2000). Similarly, no increase in minisatellite mutations was observed in a study of childhood cancer survivors and their families, which compared those survivors treated with radiation therapy with their unexposed partners (Tawn *et al*., 2011).

4.6.5 *Medical Groups*

Genetic studies of the offspring of patients receiving diagnostic radiation are largely negative. Diagnostic x-ray procedure for scoliosis (Goldberg *et al*., 1998) and radiation therapy for hemangiomas in childhood (Kallen *et al*., 1998) have not been linked to congenital malformations in offspring nor has low-dose radiation therapy for infertility (Kaplan, 1959). Down syndrome has been extensively studied as a possible consequence of diagnostic x-ray procedures but an association has not been established (Verger, 1997). Some medical studies have been plagued by differential recall bias between mothers of affected and normal children, as well as publication bias in not reporting negative findings (Carter *et al*., 1961). Practically all such studies, however, involved relatively low doses to the testes or ovaries so that statistical power to detect an effect was low.

Studies of cancer survivors are particularly important because they are numerous and, most importantly, because the timing and dose of their exposure to radiation (and potentially-mutagenic chemicals) is accurately documented. An early comprehensive study by Byrne (1999) and Byrne *et al*. (1998) defined genetic disease as a syndrome of malformations known to have an associated cytogenetic abnormality, a single-gene (*i.e*., Mendelian) disorder, or any one of 15 common simple birth defects. They studied 2,198 offspring of 1,092 cancer survivors and 4,544 offspring of 2,032 control parents. The list of Mendelian diseases included achondroplasia, acrocephalosyndactyly, aniridia, Apert syndrome, myotonic dystrophy, Gardner syndrome, Marfan syndrome, multiple polyposis, neurofibromatosis, osteogenesis imperfecta, polycystic kidney disease, retinoblastoma, and Steinert syndrome. The rates of genetic defects in offspring of survivors and of sibling controls were not statistically significant (3.4 versus 3.1 %), and there was no association of the risk of sporadic genetic disease in children with the treatment status of the parents (Table 4.3). However, the dosages of radiation and chemotherapeutic agents were not estimated.

Studies of the frequency of cancer or leukemia in offspring of cancer survivors have shown no statistically-significant differences

TABLE 4.3—*Genetic disease in children of cancer survivors (<20 y of age at diagnosis) and sibling controls from the NCI Five-Center Study (Byrne et al., 1998) and the Childhood Cancer Survivors Study (Green et al., 2009; Mulvihill et al., 2007).*

Type of Genetic Condition	Childhood Cancer Survivors Study		NCI Five-Center Study	
	Survivors (n = 3,343)	Sibling Controls (n = 1,568)	Survivors (n = 1,062)	Sibling Controls (n = 2,032)
	Number (%) of Offspring with Genetic Disease		Number (%) of Offspring with Genetic Disease	
	Survivor Offspring (n = 5,777)	Sibling Offspring (n = 3,000)	Survivor Offspring (n = 2,198)	Sibling Offspring (n = 4,544)
Cytogenetic syndrome	9 (0.2)	6 (0.2)	4 (0.2)	6 (0.1)
Single-gene (Mendelian) disorder	16 (0.3)	10 (0.3)	14 (0.6)	10 (0.2)
Simple malformation	133[a] (2.2)	104[a] (3.4)	59[b] (2.7)	127[b] (2.8)
Total[c]	158 (2.7)	120 (4)	74 (3.4)	142 (3.1)

[a]Includes 21 validated birth defects tracked by the CDC's birth-defects surveillance program (CDC, 2011).

[b]Includes 14 specific malformations: anencephaly, spina bifida, hydrocephalus, transposition of the great vessels, septal defects, patent ductus, cleft lip with or without cleft palate, tracheo-esophageal fistula, rectal atresia/stenosis, hypospadias, clubfoot, limb-reduction deformity, hip dislocation, and renal agenesis.

[c]Numbers may not be strictly comparable because of slightly different methods used in ascertaining and validating the self-reported genetic conditions.

from the average frequency in the population or in control subjects (Friedman *et al*., 2005; Hawkins *et al*., 1989; 1995; Mulvihill *et al*., 1987; Sankila *et al*., 1998), or with congenital malformations (Byrne, 1999; Byrne *et al*., 1998; Chiarelli *et al*., 2000; Green *et al*., 1997; Hawkins, 1991; 1994; Hawkins and Smith, 1989; Mulvihill *et al*., 2007). Offspring of female survivors of Wilms tumor have increased rates of low birth weight, prematurity, and possibly birth defects, possibly due to radiation-induced damage to uterine musculature and blood flow and other abdominopelvic structures and/or genetic factors (Critchley *et al*., 1992; Fossa *et al*., 2005; Green *et al*., 1982; 2000; Li *et al*., 1987; Signorello *et al*., 2006). Studies of pregnancy outcomes in female and male survivors of childhood and adolescent cancer failed to find compelling evidence for adverse effects except preterm deliveries and low birth weight among female survivors, but therapy information was not available (Chow *et al*., 2009; Mueller *et al*., 2009). Among 9,877 Finnish children born after their parent's diagnosis of cancer, an increase in cancer risk was statistically significant {standardized incidence ratio = 1.7 [95 % confidence interval (CI) = 1.3 to 2.1; n = 67], but not when those with hereditary cancer syndromes were excluded (standardized incidence ratio = 1.0; 95 % CI = 0.7 to 1.4; n = 40) (Madanat-Harjuoja *et al*., 2010). Among 1,715 Danish children born after their parent's treatment with radiation, the risk of congenital malformation was increased but was not statistically significant [relative risk (RR) = 1.2; 95 % CI = 0.9 to 1.8; n = 36] (Winther *et al*., 2009) and there was no evidence of a correlation between birth defects and gonadal dose reconstructed based on individual patient treatment records (mean doses were 1.3 Gy to ovaries and 0.5 Gy to testes) (Stovall *et al*., 2004; Winther *et al*., 2012). These data suggest that the agents and doses to which these individuals have been exposed do not induce transmissible mutations in human spermatogonial stem cells and resting oocytes at a frequency high enough to be detected over the background of spontaneous mutations.

A large-scale international collaboration, the Genetic Consequences of Cancer Therapy, has evaluated comparable data in four countries, looking at similarly defined heritable disease among the children of cancer survivors. Variation in radiation response was examined using *in vitro* cytogenetic assays. Precise calculations of the estimated gonadal doses of radiation (based on original radiation-therapy records and phantom reconstructions) were made (Stovall *et al*., 2004). Current studies total 35,801 offspring conceived after all therapy ended in 21,205 cases of cancer diagnosed under 35 y of age in two total national populations (of Denmark and

Finland) and, under 20 y of age at 25 institutions in the United States and one in Canada. Overall, no associations between birth defects and gonadal doses were found (Signorello *et al*., 2012; Winther *et al*., 2012). Increased rates of spontaneous abortions (miscarriages), preterm births and stillbirths were linked to high-dose radiation therapy to the uterus received by female cancer survivors, indicative of a somatic but not a genetic effect (Signorello *et al*., 2006, Winther *et al*., 2008). A small but not statistically-significant difference was also seen in cytogenetic abnormalities [*e.g*., Down syndrome (RR = 1.1) and Turner syndrome (RR = 1.3)] among the children of cancer survivors compared with the children of their siblings (Winther *et al*., 2004). The sex ratio among the live-born children of cancer survivors treated with radiation therapy, however, provided no indication of a possible transgenerational or germline effect (Winther *et al*., 2003).

Molecular analyses of cancer family blood samples provided an opportunity to study a number of mechanistic processes related to transgenerational effects and cancer predisposition. Analysis of unstable chromosome aberrations provided no evidence of radiation therapy related induction of persistent genomic instability (Tawn *et al*., 2005). G2 chromosomal radiosensitivity studies were inconclusive but did establish that the radiosensitivity phenotype is heritable (Curwen *et al*., 2010). Polymorphic variation in DNA repair genes showed statistically-significant genotype differences between survivors and their partners for the *APEX* Asp148 Glu site but this initial observation was not borne out with subsequent study (Curwen *et al*., 2011; Wilding *et al*., 2007). No statistically-significant increased rates of minisatellite mutations were seen in either irradiated fathers or mothers (mean gonadal dose ~0.5 Gy) (Tawn *et al*., 2011). No transgenerational effects of maternal exposure to cancer treatment were seen in an evaluation of mutations in mitochondrial DNA but the size of the population was small (Guo *et al*., 2012).

4.6.6 *Summary of Heritable Disease in Exposed Populations*

In summary, there is little to no evidence among the offspring of childhood, adolescent, and young adult cancer survivors; atomic-bomb survivors; residentially-exposed populations or radiation-exposed workers for an excess of cytogenetic syndromes, single-gene disorders, malformations, stillbirths, neonatal deaths, cancer, or cytogenetic markers that would indicate an increase of heritable genetic mutations in the exposed parents (COMARE, 2004; Nakamura, 2006; Winther and Olsen, 2012).

5. Pregnancy Risks from Ionizing Radiation

5.1 General Principles

5.1.1 *Background Pregnancy Risks*

The developing embryo and fetus can be affected by environmental toxicant exposures to the maternal organism throughout pregnancy. A high dose of ionizing radiation during pregnancy is just one of the recognized agents that can produce mental retardation, neurobehavioral effects, convulsive disorders, congenital malformations, fetal growth retardation, embryonic death, and cancer (Blot and Miller, 1973; Boice and Miller, 1999; Burrow *et al*., 1965; DeKaban, 1968; Doll, 1941; Goldstein and Murphy, 1929a; 1929b; Kato, 1971; Kraemer, 1931; Mayer *et al*., 1936; Miller, 1969; 1990; Miller and Mulvihill, 1976; Murphy, 1929; Murphy *et al*., 1942; Otake and Schull, 1984; 1998; Petenyi, 1923; Plummer, 1952; Preston *et al*., 2008; Wood *et al*., 1967a; 1967b; 1967c; Yamazaki *et al*., 1954; Yoshimoto *et al*., 1988).

There is a significant background risk of these events occurring in the population of pregnant women. This background risk is 0.5 to 1 % for mental retardation (Miller, 1999) and 3 % for major congenital malformations (Brent, 1999a) (Tables 5.1 and 5.2). There are over 50 types of major malformations reported by CDC which necessitate hospitalization, surgical intervention, or continued special care for various reasons, including decreased intellect. Additionally, there is a 3 % background risk for growth retardation (Brent, 1999a) (Table 5.1), 15 % for miscarriage (spontaneous abortion) (WHO, 1970), 11 % for genetic diseases (Brent, 1999a) (Table 5.1), and 7 % for prematurity (Brent, 1999a) (Table 5.1), Also, in the United States there is a 21 % background risk for lifetime fatal cancer in the offspring (overall for both sexes) (NCI, 2012a).

5.1.2 *Embryonic and Fetal Developmental Stages and the Deleterious Dose*

The biological effect of ionizing radiation on the embryo or fetus is strongly dependent on two factors: (1) the stage of development

TABLE 5.1—*Reproductive risks per million recognized pregnancies (Brent, 1999a).*

Reproductive Risks	Frequency
Immunologically and clinically diagnosed spontaneous abortions per million conceptions (20 % have lethal malformations or chromosome abnormalities that cause spontaneous abortion before the end of the first month of gestation, when the woman first becomes aware that she is pregnant)	350,000
Clinically recognized spontaneous abortions per million clinically recognized pregnancies (spontaneous abortion after the first missed menstrual period)	150,000
Genetic diseases per million births:	
• Multifactoral or polygenic (genetic environmental interactions)	90,000
• Dominantly inherited disease	10,000
• Autosomal and sex-linked Mendelian recessive genetic disease	1,200
• Cytogenetic (chromosomal abnormalities)	5,000
• New mutations in the developing ova or sperm prior to conception	3,000
	110,000
Major malformations (genetic, unknown, environmental)	30,000
Prematurity (Ireland 55,000; United States 124,000)	69,000
Fetal growth retardation	30,000
Stillbirths (>20 weeks)	4,000 – 20,900
Infertility	7 % of couples

and (2) the dose received. In addition, it makes a significant difference if the dose is received all at once (worst case), or if it is protracted or spread over several hours or days. Figure 5.1 demonstrates the three phases of embryonic development with regard to their vulnerability to radiation (Wilson, 1973).

During the preimplantation and presomite 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 totipotential (stem cells) and can replace adjacent cells that have been deleteriously affected. This early period of development has been designated as the all-or-none period (Figure 5.1)

TABLE 5.2—*Etiology of congenital malformations observed during the first year of life (adapted from Brent, 1999a).*

Suspected Cause	Percent of Total
Unknown • Polygenic • Multifactoral (gene-environment interactions) • Spontaneous errors of development • Synergistic interactions of teratogens	65
Genetic • Autosomal and sex-linked inherited Mendelian genetic disease • Cytogenetic (chromosomal abnormalities) • New mutations	15 – 25
Environmental	10
Maternal conditions: Alcoholism, diabetes, endocrinopathies, phenylketonuria, smoking and nicotine, starvation, nutritional deficits	4
Infectious agents: Rubella, toxoplasmosis, syphilis, herpes simplex, cytomegalovirus, varicella-zoster, Venezuelan equine encephalitis, parvovirus B19	3
Mechanical problems (deformations): Amniotic band constrictions, umbilical cord constraint, disparity in uterine size and uterine contents	1 – 2
Chemicals, prescription drugs, high-dose ionizing radiation, hyperthermia	2

(Russell, 1954; 1956). Predifferentiated embryos 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. It is also the stage when mammalian embryos have the lowest LD_{50} (*i.e.*, lethal dose, 50 %; the dose required to kill 50 % of a test population) (Brent, 1970; 1977a; Brent and Bolden, 1968; Nakano *et al.*, 2007; Russell and Russell, 1950; 1954; Schlesinger and Brent, 1978; Wilson *et al.*, 1953a) (Table 5.3).

During early organogenesis (fourth to eighth week of gestation) the embryo is very vulnerable to the growth retarding, teratogenic, and lethal effects of high-dose irradiation, but these embryos have the ability to recover somewhat from the growth-retarding effects during pregnancy and in the postpartum period (Rugh, 1962; 1965; Russell, 1956; Russell and Russell, 1954, Wilson *et al.*, 1952, 1953b). However, during the early fetal period (8th to 15th week of

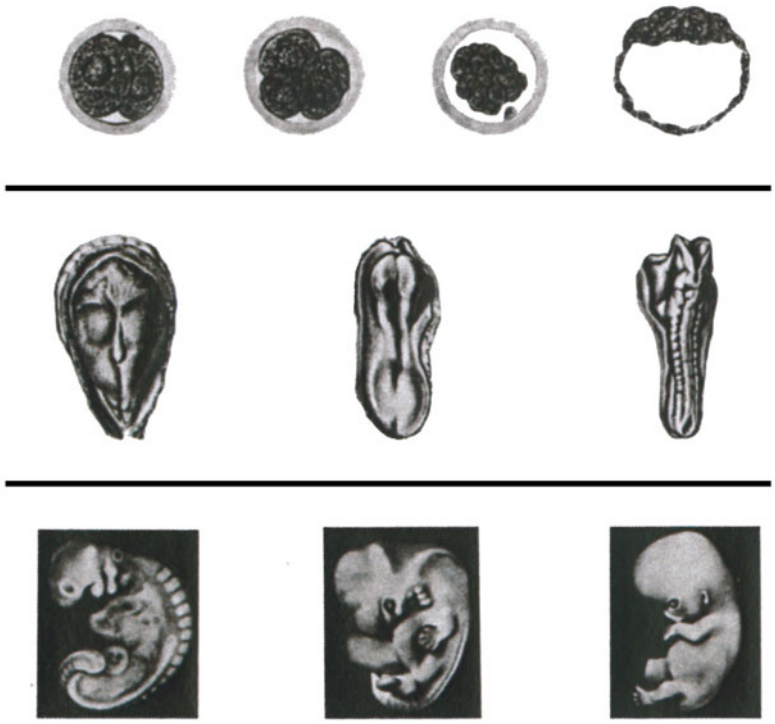

Fig. 5.1. Demonstration of the three stages of embryonic development with regard to their vulnerability to radiation effects (Wilson, 1973). The period during preimplantation and presomite development referred to as the "all-or-none period" is due to the fact that the cells in the embryos on the top row contain cells that are totipotential or pluripotential. In the very early stages, each cell if isolated and implanted in the uterus could develop into a normal embryo. These cells are referred to as stem cells. They are very susceptible to the lethal effects of radiation but the surviving cells can develop into embryos that do not appear to have an increased risk for anatomical malformations at delivery or the embryos are severely malformed and do not survive [Table 5.7 (Section 5.1.5) and Table 5.8 (Section 5.1.6)]. During these early stages, many of the embryonic cells maintain their pluripotentiality and can replace damaged adjacent cells. The second group of embryos is in the very early stages of organogenesis, from the beginning of differentiation on the 14th to 18th days postconception to the 40th day postconception in humans (28th to 32nd days of gestation to 54th day of gestation). This is a very vulnerable stage for the production of major anatomical malformations. From the 40th day postconception (54th day of gestation) until delivery, the vulnerability of the fetus to radiation gradually decreases although serious radiation effects to the CNS, gonads and growth can result if the dose is high enough (Table 5.3).

TABLE 5.3—*Estimates of the risks of ionizing radiation in the human embryo and fetus based on mouse and rat embryological studies and human epidemiological studies.*[a]

Human Gestational Age (weeks) [corresponding weeks postconception (pc)]	Minimum Lethal Dose (embryo or fetus) (Gy)[b]	Approximate LD_{50} (Gy)[b]	Minimum Dose for Permanent Growth Retardation in the Adult (Gy)[b]	Minimum Dose for Gross Anatomic Malformations (Gy)[b]	Increased Incidence of Mental Retardation (Gy)[c]	Minimum Dose for the Induction of Genetic, Carcinogenic and Minimal Cell Deletion Effects (Gy)[d]
1st and 2nd [prior to conception]	The first two weeks of gestation from the 1st day of the last menstrual period to the approximate time of ovulation is the gestational period when the woman is not pregnant. Radiation risk due to exposure before conception is discussed in Section 4.					
3rd to 4th [1st to 2nd pc]	In the range of 0.15 to 0.2	<1	No increased incidence of growth retardation in survivors	No increased incidence of congenital malformations in survivors		Unknown
5th to 7th [3rd to 5th pc]	In the range of 0.25 to 0.5	1.4 – 2	0.2 – 0.5	>0.2 Gy but most malformations require doses >0.5 Gy		Unknown
8th to 15th [6th to 13th pc]	>1	>2	0.25 – 0.5	—[e]		Unknown
16th to term [14th pc to term]	>1.5	Same as for the mother	>0.5	—[e]		Unknown

10th to 27th [8th to 25th pc]		Severe mental retardation at doses >0.5 Gy (lower 95 % CI value of ~0.3 Gy). Decreases in IQ scores also. Severe mental retardation not observed prior to the 8th week pc or after the 25th week pc (Figures 5.5 and 5.6)

[a]There is no evidence that doses to the embryo or fetus <0.1 Gy are associated with an increased incidence of mental retardation, congenital defects (malformation), growth retardation, miscarriage or stillbirth, neurobehavioral effects, convulsive disorders, and impaired school performance.
[b]Based on mouse and rat embryological studies.
[c]Based on human epidemiological studies.
[d]From mouse, rat and human studies.
[e]Anatomic malformations of a severe type cannot be produced this late in gestation except in the genitourinary system and tissue hypoplasia in specific organ systems, such as the brain, total body growth, and gonads.

gestation) the fetus has diminished vulnerability to multiple organ teratogenesis but the central nervous system (CNS) and growth potential can be seriously affected from high doses of ionizing radiation at this stage (Blot and Miller, 1973; Boice and Miller, 1999, Burrow *et al*., 1965; DeKaban, 1968; Doll, 1941; Goldstein and Murphy, 1929a; 1929b; Kato, 1971; Kraemer, 1931; Miller, 1990; Miller and Mulvihill, 1976; Murphy, 1929, Murphy *et al*., 1942; Otake and Schull, 1984; 1998; Petenyi, 1923; Plummer, 1952; Rugh, 1962; Schull and Otake, 1999; Wood *et al*., 1967a; 1967b; 1967c; Yamazaki *et al*., 1954).

During later stages, the fetus is not grossly deformed by radiation but can exhibit permanent cell depletion of various organs and tissues if the dose is high enough (Brent, 1977a; Brent and Gorson, 1972; Jensh and Brent, 1986; 1987; 1988a; 1988b; Jensh *et al*., 1986; 1987; Kameyama and Inouye, 1994) (Table 5.3).

Some radiation effects may not be immediately obvious and can only be measured or ascertained in the postpartum or adult stages. For instance, neuronal depletion, neurobehavioral effects, convulsive disorders, infertility, tissue hypoplasia, neoplasia, or shortening of life span are phenomena that can only be evaluated at later life stages (Brent, 1970; Brent and Bolden, 1961; Brent and Gorson, 1972; Cowen and Geller, 1960; Furchtgott, 1963; Hicks and D'Amato, 1966; Jensh and Brent, 1986; 1987; 1988a; 1988b; Jensh *et al*., 1986; 1987; Kamayana and Inouye, 1994; Miller, 1969; Murphree and Pace, 1960; Preston, *et al*., 2008; Rugh and Wohlfromm, 1964a, 1964b; Wood *et al*., 1967a; 1967b; 1967c).

The most likely mechanisms that explain the ionizing radiation-induced embryopathy are:

- cell death or mitotic delay beyond the recuperative capacity of the embryo or fetus;
- inhibition of cell migration, differentiation, and cell communication; or
- interference with histogenesis by processes such as cell depletion, necrosis or scarring.

Radiation-induced cell death may be minimally important at one stage because of the ability of the embryo to replace the killed cells. At another stage of gestation, cell death may be a primary factor because the embryo has lost the ability to replace damaged cells and the fetus may be permanently cell-depleted. This is probably one of the important mechanisms for the production of mental retardation and growth retardation during the mid-stages of human gestation.

Other radiation-induced effects that have been invoked to explain embryo-pathologic conditions are cytogenetic abnormalities

and somatic mutations (Russell and Major 1957; Russell and Saylors, 1963). Cytogenetic abnormalities may be responsible for preimplantation death from irradiating the fertilized ovum (Brent and Bolden, 1967a; 1967b; Nakano *et al*., 2007; Pampfer and Streffer, 1988; Pampfer *et al*., 1992; Rugh, 1965; Russell, 1977; Russell and Major, 1957; Russell and Saylors, 1963; Russell *et al*., 1963; Streffer and Muller, 1996). However, point mutations are less likely to be a contributing factor to abnormal morphogenesis. If the known radiation-induced mutation rate in mammalian cells as determined by Russell and colleagues in the mouse (Russell, 1956; Russell and Major, 1957; Russell and Russell, 1959; Russell and Saylors, 1963; Russell *et al*., 1958) is used for estimating potential teratogenicity, then radiation-induced point mutation could not account for even a small proportion of radiation-induced teratogenicity, unless it simply involved cell death.

5.1.3 *Types of Effects*

The potential detrimental outcomes from high doses of ionizing radiation (Section 5.2) are mental retardation, microcephaly, decreased IQ, epilepsy, neurobehavioral effects, birth defects (congenital malformations), growth retardation, embryonic or fetal death, and cancer. All are tissue reactions (deterministic effects) except for cancer, which is treated as a stochastic effect.

Since tissue reactions (deterministic effects) have a threshold dose below which the effect is not able to be produced, these effects are said to have a *no-adverse-effect level*. Almost all diagnostic radiological procedures involve doses that are below the no-adverse-effect level for these developmental effects, especially when pregnant women have diagnostic x-ray studies of the head, neck, chest or extremities (Brent, 1960a; 1960b; 1969a; 1969b; Brent and Bolden, 1967a; 1967b; Brent and McLaughlin, 1960; Schlesinger and Brent, 1978). However, most diagnostic radiological studies that expose the abdomen do not result in a dose to the embryo or fetus of >0.1 Gy.

Radiation-induced carcinogenesis is assumed to be a stochastic effect with no threshold dose, so that theoretically there is a risk at low doses. The increased risk of cancer following high doses of ionizing radiation to adult populations has been demonstrated in the atomic-bomb survivors and in many other populations receiving high doses. However, the magnitude of the risk of cancer from embryonic and fetal exposures following diagnostic radiological procedures remains controversial (ICRP, 2003). The arguments center around interpreting the same observed data, with some emphasizing the strong statistical associations seen in many case-

control studies of prenatal x ray (Wakeford, 2008) and others questioning the causal nature of the association because of possible interview bias as well as the absence of a statistically-significant increase in risk in cohort investigations (Boice and Miller, 1999). Recent publications and analyses of the Japanese atomic-bomb survivor data indicate that the risk is lower for the irradiated embryo and fetus than for the irradiated child (Preston *et al*., 2008).

5.1.4 *Protraction and Fractionation*

Protraction and fractionation of doses to the embryo and fetus decrease the severity and increase the threshold for the deleterious tissue reactions (deterministic effects). Examples of protracted radiation include continuous exposure while flying, some occupational exposures, exposure to a radionuclide with a long half-life, or living at a very high altitude. Exposures that are fractionated are intermittent over a period of time (*e.g*., multiple diagnostic x-ray procedures over a period of hours or days).

Planned diagnostic radiological procedures may occur over a period of hours or days and it is important to consider the modifying biological effect of the protraction or fractionation when evaluating reproductive and developmental risks. Fractionation and protraction are important when a pregnant patient has received radiation therapy to areas other than the abdomen. For example the embryo or fetus may receive a daily dose of 0.01 to 0.03 Gy during a course of radiation therapy for breast cancer. Evaluating the developmental risks under these circumstances is problematic. The majority of the studies in animals demonstrated that protraction and fractionation diminishes the deleterious developmental effects of radiation (Tables 5.4 and 5.5) (Auerbach, 1956; Beckman *et al*., 1994; Brent, 1971; Brizzee, 1964; Brizzee and Brannon, 1972; Brizzee *et al*., 1967; Coppenger and Brown, 1962; 1965; 1967; Gentry *et al*., 1959; Gowen and Stadler, 1964; Grahn and Kratchman, 1963; Harvey and Chang, 1964; Konermann, 1969; Kriegel and Langendorff, 1964; Laskey *et al*., 1973; Roennbaeck, 1965; Rugh and Grupp, 1960; Russell *et al*., 1959, 1963; Segall *et al*., 1964; Sikov and Lofstrom, 1962; Stadler and Gowen, 1964; Vorisek, 1965; Wesley, 1960).

The doses (in gray or milligray) cited in Sections 5.1.4, 5.1.5, and 5.1.6 for studies in the mouse and rat refer to an approximate whole-body dose in the mouse or rat to facilitate the discussions in these sections. The experimental studies were typically whole-body irradiations expressed in the original references in the quantity exposure (in roentgen).

TABLE 5.4—*Effect on reproduction of varying whole-body dose and dose rate[a] throughout pregnancy for the mouse and rat (adapted from Brent, 1971).*

References	Species	Radiation Type	Dose per Day (Gy)[a]	Dose per Pregnancy (Gy)[a]	Effect
Russell *et al.* (1963)	Mouse	X ray	0.125[b]	1.7[b]	Decreased fertility
Roennbaeck (1965)	Mouse	^{137}Cs	0.084	1.7	None
Vorisek (1965)	Rat	^{60}Co	0.025	0.52	None
Stadler and Gowen (1964)	Mouse, many generations	^{60}Co	0.022[b]	0.46[b]	Decreased fertility
Coppenger and Brown (1962; 1967)	Rat	^{60}Co	0.5[b]	10[b]	Increased mortality and malformations
Konermann (1969)	Mouse	^{60}Co	0.1	1.8	None
			0.2[b]	3.6[b]	Increased incidence of congenital malformations

[a]The original quantity and unit used in the studies referenced was exposure expressed as roentgen. The dose given here is the approximate whole-body absorbed dose in the mouse or rat in gray.

[b]Indicates doses (per day and per pregnancy) that resulted in deleterious developmental effects.

TABLE 5.5—*The effect of varying the whole-body dose rate*[a] *on the incidence and type of malformations in term rat fetuses irradiated at the 9th day and 7th hour postconception (adapted from Brent, 1971).*

	Total Dose (~1.5 Gy)			
	Dose Rate (Gy min^{-1})			
	0.005	0.0125	0.34	1
Exposure time	5 h	2 h	5 min	1.5 min
Number of term fetuses	78	64	73	66
Type of Malformation	Percent Malformed			
Anencephaly	0	3.1	13.7	30.3
Encephalocele	24.4	45.3	37	48.5
Bilateral anophthalmia	50	68.8	56.2	72.7

[a]The original quantity and unit used in the study referenced was exposure expressed as roentgen. The dose given here is the approximate whole-body absorbed dose in the mouse or rat in gray.

Brizzee and Brannon (1972) irradiated rats with a dose of 1.5 Gy on the 12th day postconception with an acute exposure and various fractionated doses over a period of 12 h. The brains of the adult rats that were irradiated *in utero* 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. However, the animals that received a dose of 1.5 Gy in nine fractions over a period of 12 h were not statistically different than the unirradiated controls, although there was a slight visible reduction in the thickness of the cerebral cortex. Thus, fractionation reduces the neuropathological effectiveness of the exposure even when it is administered over a period of only 12 h.

Gowen and Stadler (1964) and Stadler and Gowen (1964) studied the effects of 22 h d^{-1} continuous irradiation with ^{60}Co. The daily whole-body doses varied on average between 0.01 to 0.03 and 0.02 to 0.06 Gy d^{-1}, depending on the position of the mouse cages. An analysis based on 10 completed generations showed that the first litter productivity of the irradiated mice did not differ from those of a corresponding sample of the same inbred strains that did not receive radiation exposure (Stadler and Gowen, 1964). In mice that received 0.027 Gy d^{-1}, one strain reached the 24th generation

of progeny and four other strains continued their productivity. If irradiation continued above these levels, sterility occurred in those mice receiving >0.04 Gy d^{-1} over a period of time. The results showed that within these ranges the mice maintain numbers in their first litters which were directly comparable with those observed for unirradiated mice of each strain at the same corresponding reproductive periods within the colony.

Similar observations on sex ratios of these progenies, as measures of possible lethal changes in the sex chromosomes, showed that these changes do not support increased radiation-induced lethal mutations since the sex ratios remained nearly constant throughout the 10 generations. A search for visible gene mutations did not reveal any in the untreated series of mice, although the breeding pattern was such as to bring them out had they occurred.

The total accumulated high-energy whole-body dose was in the neighborhood of 1.5 Gy to the 10th generation mice. By the time the first-generation litters were born the mothers had received total whole-body doses that were more than sufficient to sterilize most of them if the radiation had been given at a single acute treatment, yet reproductivity and sex ratio remained normal for these parental pairs. The same reproductive performances were observed in the mice that became parents in the successive generations even though the whole-body doses during ancestral development increased much beyond those of the acute lethal range. There was considerable variability in radiation vulnerability among the various strains that were exposed. A few strains were sterile after four generations of exposure. One strain was fertile up to 24 generations of exposure. These results raise the question of whether there is considerable genetic variability among humans with regard to radiation vulnerability.

Brown *et al*. (1964) and Coppenger and Brown (1962; 1965; 1967) studied the effects of continuous, low-dose rate ^{60}Co irradiation on the developing pregnant rat beginning on the day of conception. The whole-body dose was 0.5 ± 0.05 Gy (delivered at ~0.024 Gy h^{-1} for 20 h each day). The ^{60}Co source, with a capacity of 74 TBq (2,000 Ci), irradiated a semicircular field 45.7 m (150 feet) in radius. Prenatal effects were determined by examination of the embryos, fetuses, and the uteri on days 10 through 20 postconception. Irradiation at this level did not affect the total number of implantations, but a great increase in mortality was observed at the 12th day. Most radiation-induced deaths and resorptions occurred prior to the 15th day postconception. From the 15th day postconception until term, the irradiated embryos or fetuses were severely growth retarded. There were gross abnormalities in the irradiated fetuses that included

microencephaly and reduction of spleen weight. Other abnormalities observed were anophthalmia, sternal malformations, and severe edema. There were no skeletal malformations in the surviving fetuses and no fetal deaths during the latter portion of the pregnancies. The investigators reported support for the all-or-none phenomenon that had been reported by Russell (1956) (Brent, 1980; 1999a; Brent and Bolden, 1968; Schlesinger and Brent, 1978; Wilson *et al*., 1953a).

Russell *et al*. (1963) utilized protracted continuous exposure from x rays during the day to pregnant mice for the entire pregnancy. Russell *et al*. (1963) did not observe any effects following 0.125 Gy d^{-1} except that the female offspring had a reduced number of litters because there was a reduced number of oocytes in the ovary of the female offspring (Table 5.4).

In another experiment, rats were irradiated on the 9th day postconception with 1.5 Gy utilizing four different dose rates; 0.005, 0.012, 0.34, and 1 Gy min^{-1} (Brent, 1971). Protracted irradiation demonstrates that the effect is reduced if the radiation is delivered over a 5 h period. The acute whole-body dose of 1.5 Gy to 9 d old rat embryos delivered in 1.5 min resulted in 30.3 % anencephaly at term (Table 5.5). The irradiation that delivered the 1.5 Gy over a period of 5 h resulted in 0 % anencephaly. There were deleterious effects in the group of animals that had received the protracted irradiation; however, the effects were less severe (Brent, 1971) (Table 5.5).

In summary, the experimental data indicate that the developmental effects of protracted and fractionated irradiation are diminished compared to the effects of acute irradiation. While 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:

- multiple radiological procedures over a period of days;
- the use of radionuclides with long and short half-lives;
- background radiation from flying at high altitudes or occupational exposures; and
- radiation therapy during pregnancy to body areas other than the abdomen over a period of weeks.

5.1.5 *The All-or-None Phenomenon*

Irradiation of rats and mice with up to 1.5 to 2 Gy during the preimplantation and presomite development stage results in high embryonic mortality. However, malformation rates in the surviving

fetuses at term are similar to the controls, not because malformations cannot be produced at this stage (Figures 5.1 and 5.2), but because at this early stage of pregnancy, high levels of radiation induce cell loss or chromosome abnormalities that most likely result in zygote death or malformations that are lethal. On the 1st day postconception, the approximate threshold for an increase in embryonic mortality is 0.15 to 0.2 Gy. There was no weight reduction in the surviving rat embryos at term (Table 5.6).

Russell and Russell (1956) used the term all-or-none effects to name this phenomenon. Wilson *et al*. (1953b) also reported the fact that the early embryo is more likely to be killed by the radiation but if the embryo survives it does not have an increased risk of being malformed. Wilson *et al*. (1953a) were able to describe the time when the embryo was susceptible to the teratogenic effect of x rays. The transition to the stages of teratogenic vulnerability in the rat occurred just before the first somites were formed (8th day and 3rd hour postconception).

Numerous articles utilizing the rat and mouse confirm the all-or-none phenomenon (Brent, 1960a; 1970; 1999a; Brent and Bolden, 1967a; 1967b; 1968; Coppenger and Brown, 1967; Friedberg *et al*., 1973; Hicks *et al*., 1953; Jacquet *et al*., 1995; Job *et al*., 1935; Mazur, 1984; Roux *et al*., 1983; Russell and Russell, 1950; 1954; 1956; Schlesinger and Brent, 1978; Wilson *et al*., 1953b). Many other investigators have confirmed these findings including Kim *et al*. (2001), indicating no increase in malformations or growth retardation in mice following 2 Gy (gamma rays) at a preimplantation stage (Table 5.7). Mole (1993) concluded that the preimplantation period is not a stage where viable malformations will result from irradiation.

High exposures to ethylnitrosourea, retinoic acid, ethylene oxide, and high-dose radiation early in pregnancy have resulted in lethality and a small increased incidence of malformations (Generoso *et al*., 1987; 1991; Muller *et al*., 1994; Nagao, 1996; Nagao *et al*., 1986; Pampfer and Streffer, 1988; 1989; Russell, 1950; 1956; Russell and Saylors, 1963; Rutledge, 2000; Rutledge and Generoso, 1989; Rutledge *et al*., 1992; 1994; Streffer, 1995; Streffer and Molls, 1987; Streffer *et al*., 1980).

Nagao *et al*. (1986) performed an interesting group of experiments demonstrating, at least in those studies, that when mitomycin C was administered on the 2nd or 3rd day postconception, many embryos died early and late and some were obviously malformed. When treated embryos were transferred to untreated dams or normal embryos were transferred to treated dams, Nagao *et al*. (1986) observed that the malformations were due to the effect of

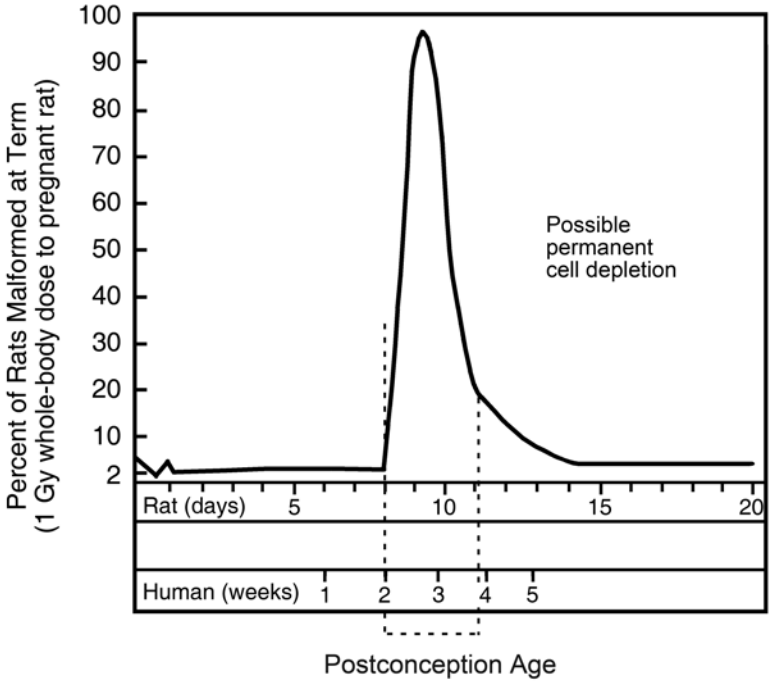

Fig. 5.2. Illustration of the time frame for major organ malformations observed in the rat after irradiation during pregnancy, and the approximate corresponding stage of gestation in the human. The experimental data following 1 Gy whole-body dose to the pregnant rat on each postconception day of pregnancy in separate experiments are depicted (adapted from Brent, 1980). The statements given here are based entirely on the rat experiments and not from any actual human data. The embryos in the first eight days postconception of rat pregnancy do not exhibit an increased risk for viable malformations at term, and this corresponds to approximately the first two weeks postconception (second two weeks of gestational age) of human pregnancy. The most vulnerable period for major organ malformations (*i.e.*, heart, brain, craniofacial, spinal cord, limbs, kidney, lungs, and other visceral malformations) following irradiation is from after 8th to 11th days postconception in the rat, which corresponds to after 2nd to ~4th week postconception (after 4th to ~6th weeks of gestational age) in the human. In addition, severe effects can occur after the period when major anatomical malformations cannot be produced (the region noted in the figure as "possible permanent cell depletion"), because of irreparable cell depletion that may occur in the later part of pregnancy.

TABLE 5.6—*Effect of x irradiation on the 1st day postconception in the pregnant rat (Brent, 2007).*

Whole-Body Dose (Gy)	Litters	Embryos	Resorptions (%)	Fetal Weight (g)
0	77	902	5.73	5.264
0.05	58	699	6.49	5.199
0.1	76	944	7.75	5.207
0.2	71	851	11.41	5.148
0.3	43	490	18.57	5.015

TABLE 5.7—*Incidence of malformations at various stages of pregnancy in mice following 2 Gy (whole body, gamma rays) (Kim et al., 2001).*

	Postconception Exposure Day			
	Control	2.5 d	5.5 d	7.5 d
Mortality (%)	7	66	22	45
Term weight (g)	1.59	1.61	1.33	1.26
Defects (%)	0	0	24	77

mitomycin C on the mother, indicating that the malformations were due to a maternal toxic effect, not a direct effect on the zygote. Rutledge (2000) wrote a commentary on Nagao *et al*. (1986) and concluded that the Nagao *et al*. (1986) observations indicated that the malformations were due to a maternal toxic effect. However, Rutledge (2000) concluded that the malformations produced in his own studies were more likely due to a direct effect on the embryo.

Some results that refuted the all-or-none phenomenon were not confirmed. Rugh (1962; 1965) and Rugh *et al*. (1969) irradiated pregnant CF-1 mice on the 1st day postconception and reported an increase in the incidence of exencephaly. In the various Rugh studies there were no dose-response relationship (Brent, 1999a; Rugh, 1962). The fact that there was no dose-response curve and that the various Rugh studies have never been duplicated make the results problematic.

Pampfer and Streffer (1988; 1989), Pampfer *et al*. (1992), Streffer and Molls (1987), Streffer and Muller (1996), and Streffer *et al*. (1980) published research concerning the all-or-none phenomenon. 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 to 4 % incidence of gastroschisis. Irradiation of this strain with 2 Gy on the 1st day postconception results in an increase in embryonic mortality and a moderate, but statistically increased incidence of gastroschisis. In their laboratory, C57Bl mice or HLGxC57Bl hybrids when irradiated on the 1st day postconception 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" (Pampfer and Streffer, 1988; Streffer and Molls, 1987, Streffer *et al*., 1980). Streffer (1995; 1997) analyzed the all-or-none phenomenon concerning preimplantation irradiations in the mouse 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."

Actually, known teratogens can produce malformations in the pregnant mouse or rat when administered during the preimplantation period if the teratogen has a long half-life. This has been reported with Trypan blue and teratogenic antibodies, because the teratogen is still present in the maternal circulation when organogenesis begins, not because it affected the 1 d old zygote (Brent *et al*., 1990).

Streffer was also one of the authors of ICRP Publication 90 (ICRP, 2003), which stated, "The dominant effect of preimplantation irradiation is early death of the conceptus. Risk of induction of cancer and malformation is unlikely." Further elaboration on the risks of preimplantation radiation in ICRP (2003) is as follows: "The data confirm embryonic vulnerability to the lethal effects of irradiation in the preimplantation period but provide no good reason to believe that, in general, there are significant risks to health after birth. In this respect, it would be premature to generalize experimental findings on the induction of genomic instability and malformations in genetically predisposed mice."

The all-or-none phenomenon concept indicates that the predominant effect of embryotoxic irradiations 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 <0.2 Gy, even in the genetically susceptible strains. The biologic basis to explain the all-or-none phenomenon is depicted in Figures 5.1 and 5.2 (Nakano *et al*., 2007; Wilson, 1973; Wilson *et al*., 1953b). Each totipotential or pluripotential cell has the potential for forming an embryo or replacing adjacent cells. While induced cell death can result in malformations during early organogenesis, cell death during preorganogenesis can result in embryonic death. However, if enough totipotential cells survive, they can reorganize and result in normal development (Figures 5.1 and 5.2).

The fact that the reported malformations are specific for susceptible strains of mice indicates that these are genetically *susceptible* strains, 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 deleterious effects. *Induced* genetic changes in the one cell embryo would not result in an increase in only one type of abnormality, such as gastroschisis or exencephaly. The mutagenic effect of ionizing radiation is not site directed. Radiation should produce mutations randomly. There would be no biologic basis to conclude that radiation would only raise the incidence of one genetically determined malformation from a radiation-induced mutation.

Therefore, these unusual instances of malformations surviving to term following radiation exposures of mice on the 1st day postconception have little applicability to the human situation. The doses utilized by Muller *et al*. (1994), Streffer (1995), Streffer and Muller (1996), and Streffer *et al*. (1980) were not in the diagnostic range and the malformation that was present in the mouse had a significant 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 doses. Therefore the all-or-none phenomenon can be very helpful in evaluating the developmental risks of exposures during the first two weeks of human pregnancy. When the dose is in the diagnostic range and the pregnancy stage is in the first two weeks postconception (second two weeks of gestation), there is minimal likelihood that the developmental risks of surviving embryos will be measurably increased.

5.1.6 *Lack of Indirect Effect on a Shielded Embryo During Maternal Irradiation*

In the past, there has been some discussion as to whether maternal irradiation without direct exposure of the embryo can result in embryonic effects. Biological plausibility arguments would conclude

that the embryo or fetus is not at increased risk, for example, if a pregnant woman had a chest or head x-ray procedure. However, scientific data to support this conclusion came from a series of experiments in which the pregnant rat received 4 Gy whole-body irradiation on 9th day postconception, while the embryos protected by a lead-shielded uterus received low doses (~5 mGy) (Brent and McLaughlin, 1960) (Figure 5.3). Table 5.8 summarizes the results for fetal growth and mortality. These experiments clarified the issue as to whether ionizing radiation to maternal organs other than the uterus would have an indirect effect that would cause embryonic death, resorptions, growth retardation, or congenital malformations. These findings even occurred at the most vulnerable stage for producing congenital malformations and supported the conclusion that the zygote has to be irradiated directly in order to have a deleterious developmental effect.

In another experiment, maternal irradiation or placental irradiation was performed when the embryo was 12 d old (12th day postconception). The embryos were shielded and the maternal organism or placenta was irradiated. In these experiments, when the embryo was shielded, there were no deleterious tissue reactions (deterministic effects) (Brent, 1960a; 1960b; 1969a; 1969b; Brent and McLaughlin, 1960). When the doses are in the range of radiation therapy, growth retardation and embryonic death may occur, because the pregnant rats exhibit signs of radiation sickness (Brent and McLaughlin, 1960).

The animal experiments demonstrated that irradiating the pregnant rat's maternal organs, placenta, and even the uterus before the fertilized embryo entered the uterus did not increase the risk for birth defects, pregnancy loss, or fetal growth retardation.

- The first studies consisted of designing lead shields to protect the pregnant uterus on the 9th day postconception. This stage is the most vulnerable to the teratogenic effects of radiation. Exposure of the embryos to a dose of 1 Gy would result in severe malformations of the eye and brain in 90 and 40 % of the embryos, respectively. The pregnant rats were anesthetized and were exposed to a dose of 4 Gy except for the shielded embryos. Table 5.8 summarizes the results. There was no increase in the percent of malformations or fetal growth retardation (Brent and McLaughlin, 1960).
- Twelve-day pregnant rats were anesthetized. This is the first day after conception that the location of the placenta and embryo can be readily identified, allowing the embryo and the placenta to be either exposed or shielded. Irradiating the embryo with a dose of 1 Gy while shielding the placenta,

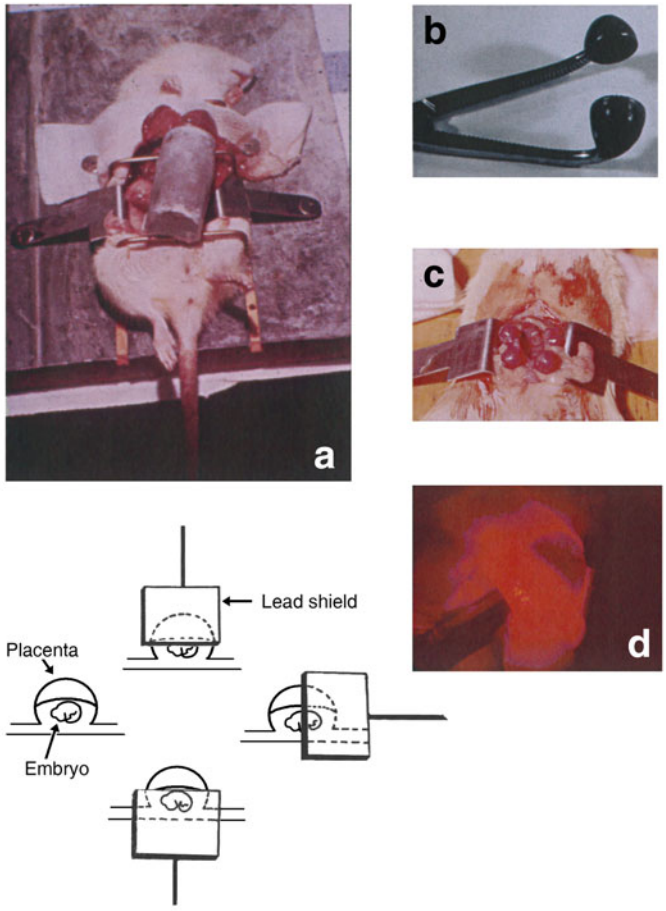

Fig. 5.3. Photographs and a schematic from rat experiments performed to study whether there is an indirect effect on the developing embryo from the irradiation of the pregnant mother or parts of the mother when the embryo is shielded (Brent and McLauglin, 1960). (a) shielding technique that was used to prevent the pregnant uterus from being exposed on the 9th day postconception while the mother received high doses of ionizing radiation; (b) hemostat prepared with lead cups so that the oviduct, the ovary, or both could be shielded from the radiation; (c) pregnant uterus later on the 12th day postconception; (d) transillumination of the uterus with a sinus illuminator demarcates the blood filled placenta and the embryonic sac containing clear amniotic and yolk sac fluid as demonstrated; and schematic of the various shielding techniques that were used to irradiate either the embryo or the placenta or both in various experiments.

TABLE 5.8—*Fetal growth and mortality following irradiation of the pregnant rat while shielding the embryo (Brent and McLaughlin, 1960).*

	Maternal Irradiation on 9th Day Postconception			
	Controls	Whole Body 4 Gy	Partial Body 10 Gy	Partial Body 14 Gy
Fetal deaths (%)	13.2	22.1	20.4	39
Fetal weight at term (g)	4.7	4.84	4.57	3.86
Fetal length (cm)	3.77	3.76	3.83	3.6
Malformations (%)	1.8	2.2	1.4	0.8
Maternal mortality (%)	4	21	0	0
Increase in maternal weight (%)	31.3	35.8	17.9	10.8

resulted in serious embryonic defects. Irradiating the placenta, while shielding the embryo had no effect on the embryos. Also, the placenta was radioresistant to radiation injury (Brent, 1960b).

- Pregnant rats were anesthetized on the 1st day postconception. On the first day the zygote is a one- or two-cell embryo in the oviduct or fallopian tube. A hemostat was modified by having two oval lead cups annealed to the hemostat in order to shield the embryo in the oviduct. The results indicated that if the mother received a dose of 1.5 Gy, the shielded embryos implanted and developed normally (Brent, 1969a; 1969b; Brent and Bolden, 1967a; 1967b; 1968).

In addition to the above-mentioned studies that specifically analyzed for an indirect effect on a shielded embryo from irradiation of the mother during pregnancy, there are scores of whole-body irradiation animal experiments indicating that the no-adverse-effect level for congenital malformations and fetal growth retardation is above a dose of 0.2 Gy when the embryo is also irradiated.

In spite of the many studies on the lack of an indirect effect on a shielded embryo during maternal irradiation and the lack of biological plausibility, Hujoel *et al*. (2004) published a report indicating that dental x-ray procedures averaging a dose of 0.4 mGy to the jaw and neck of pregnant woman may be responsible for babies

being born with low birth weight due to irradiation of the maternal thyroid or pituitary. As a result of this publication, many pregnant women became concerned and wanted to know whether they should refrain from visiting the dentist while they were pregnant. A commentary by Brent (2005) responding to Hujoel *et al*. (2004) provided supporting data and references as to why the Hujoel *et al*. (2004) conclusions were incorrect and biologically not plausible. Dental radiography during pregnancy is not a risk for any fetal effects, including fetal growth retardation.

In conclusion, diagnostic radiological studies of the chest, head, neck or extremities are very unlikely to expose the embryo to a dose >0.1 Gy. Therefore there is no evidence of increased risk for birth defects, miscarriage, neurobehavioral effects, convulsive disorders, decreased IQ, or mental retardation for the offspring of women who have been exposed to the above-mentioned diagnostic radiological studies during their pregnancy.

5.1.7 *Evaluation of the Evidence for Radiation-Induced Effects*

Critical analysis of the reproductive and developmental effects of ionizing radiation requires that all the available scientific information be utilized in the analysis (Brent, 1986a; 1986b). There are five areas of evaluation that can be utilized to critically validate risk estimates:

1. epidemiological studies;
2. secular trend data;
3. animal developmental toxicity studies;
4. dose-response relationships; and
5. biological plausibility.

These are summarized below (adapted from Brent, 1986b; 1995b) and the three most important areas are discussed in Section 5.1.7.1 (Area 1), Section 5.1.7.2 (Area 3), and Section 5.2.7.3 (Area 5).

1. *Epidemiological studies*: Epidemiological studies with adequate numbers and a significant range of exposures may demonstrate an increased or decreased incidence of a particular spectrum of embryonic or fetal effects in exposed human populations. Any associations observed, however, may not be causal because of study biases or uncontrolled confounding factors.
2. *Secular trend data*: Secular trends may demonstrate an association between the changing exposures to an environmental agent to which human populations are commonly

exposed and the incidence of a particular embryonic or fetal effect. These descriptive data, however, may reflect other changes that are unrelated to the exposure under study.

3. *Animal developmental toxicity studies*: There is support for the observation of human developmental toxicity if an animal model mimics the human developmental effect at clinically comparable exposures. Since mimicry may not occur in all animal species, animal models are more likely to be developed once there is good evidence for the embryotoxic effects reported in the human. Developmental toxicity studies in animals are indicative of a potential hazard in general rather than the potential for a specific adverse effect on the fetus when there are no human data on which to base the animal experiments.
4. *Dose-response relationships*: Developmental toxicity in the human increases with dose and the developmental toxicity in animals occurs at a dose that is pharmacokinetically or physically (quantitatively) equivalent to the human dose.
5. *Biological plausibility*: The mechanisms of developmental toxicity are understood and the effects are biologically plausible.

5.1.7.1 *Epidemiological Studies*. Epidemiological studies are the foundation for determining human risks. While experimental studies are an important consideration when concluding whether an association is causal, it is rare that *in vitro* studies or animal studies can refute either negative or positive findings in epidemiological studies if high-quality epidemiological studies are available. However, the data obtained from many studies are not robust enough to provide the ability to accurately determine the risks for reproductive and developmental effects at all doses and all stages of pregnancy. Statistically-significant associations for an effect and a dose are not sufficient in themselves to conclude that an association, whether positive or negative, is causally related to the dose (Blot and Miller, 1973; Boice and Miller, 1999; DeKaban, 1968; Goldstein and Murphy, 1929a; 1929b; 1929c; Miller, 1970; 1990; Miller and Mulvihill, 1976; Ornoy *et al*., 1996; Otake and Schull, 1984; 1998; Otake *et al*., 1987; 1988; 1996; Preston *et al*., 2008; Wood *et al*., 1967a; 1967b; 1967c; Yoshimoto *et al*., 1988). The case for causality can be made stronger based on the strength of the association (a high relative risk), the consistency of findings with other human studies (conducted with different designs and by different investigators around the world), biological plausibility (is there a plausible mechanism and supporting animal evidence),

dose-response data (does risk increase with dose), and specificity (although this latter guideline is infrequently used but relates to a well-defined outcome rather than a general one) (Hill, 1965).

5.1.7.2 *Animal Developmental Toxicity Studies*. The reproductive and developmental effects of drugs and chemicals in humans cannot always be determined from animal studies. Because of the differences in maternal drug absorption, metabolism, excretion and placental transport between humans and animals, predicting the developmental effects of chemicals and drugs from animal studies is problematic. However, the response of mammalian cells to radiation is very similar. Therefore, there is reasonable confidence of utilizing reproductive and developmental risks obtained from pregnant animal studies for estimating human embryonic risks. Animal studies involving the irradiation 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, in many cases metabolized by the liver, and transported by the placenta, while 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 assessment of human risks difficult. That is much less true for ionizing radiation effects.

5.1.7.3 *Biological Plausibility.* Biological plausibility is a powerful tool in evaluating allegations of human risks. For example, consider a young child who is born with the left arm missing (*i.e.*, a congenital limb-reduction defect) (Figure 5.4). This unilateral defect is most likely due to vascular disruption, amniotic band syndrome, or a placental embolus to the limb. A malformation such as this may be mistakenly alleged to have resulted from an *in utero* radiation exposure in spite of the fact that there was no indication that radiation exposure had even occurred. Such a unilateral malformation in a child, who had a normal weight at birth, had normal intelligence, and a normal head circumference could not have resulted from an exposure to ionizing radiation (Graham *et al*., 1999). It is not biologically plausible.

Clinical evaluation of children with congenital malformations has become more sophisticated and accurate over the past 50 y. There are trained genetic counselors and birth-defect counselors (clinical teratologists) who can identify the etiology of a birth defect in a child by their clinical expertise and the wealth of literature available which support or refute an allegation of a hypothesized

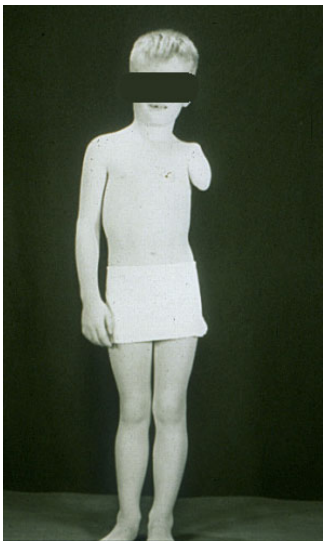

Fig. 5.4. Example of the type of malformation discussed in Section 5.1.7.3 with regard to biological plausibility.

radiation-induced malformation (Aase, 1990; Graham, 1988; Graham *et al*., 1999; Jones, 1997; OMIM, 2011; TERIS, 2011).

5.1.8 *Relative Biological Effectiveness*

Some relative biological effectiveness (RBE) data are available for preimplantation embryos. Narra *et al*. (1991) showed that DNA-incorporated ^{125}I is approximately 12 times more effective at preventing mouse embryos from advancing from the two-cell stage to the blastocyst stage. Given the paucity of RBE data that are available for early-stage embryos, this is an understudied area. In contrast, a large effort has been devoted to calculating doses and interpreting responses at later stages of pregnancy.

Jiang *et al*. (1994) have obtained RBE values in excess of 200 for developing hematopoiesis in the fetus. These higher RBE values are similar in magnitude to that of Rao *et al*. (1991) for sperm head abnormalities (Section 4.5.2). Ishida *et al*. (2006) obtained an RBE of 9.8 for neutron irradiation of fetal cerebral neurons with apoptosis serving as the biological endpoint.

Solomon *et al*. (1994) utilized 0.43 MeV neutrons to irradiate rat embryos 9.5 day postconception and compared the effects against x rays generated at 250 kV (peak tube potential). At a neutron absorbed dose of 0.25 Gy, 40 % of the embryos did not survive to

term or were malformed, which was comparable to the mortality and incidence of malformations in embryos exposed to an x-ray dose of ~2 Gy. An RBE of eight was estimated for the lethal and teratogenic effect of a neutron absorbed dose of 0.43 Gy. Beckman *et al*. (1994) irradiated rat embryos at 9.5 day postconception with 14.1 MeV neutrons or x rays generated at 250 kV. The total neutron absorbed dose was 0.75 Gy. There were four dose-rate groups, exposed to 0.75 Gy in either 1.5, 3, 5, or 7.5 h. When exposure to low-LET x rays is protracted the teratogenic and lethal effects of irradiation are ameliorated. However, a similar incidence of teratogenic and lethal effects was observed for each of the four dose-rate groups of embryos irradiated with 14.1 MeV neutrons.

5.2 Risks and Outcomes

5.2.1 *Mental Retardation and Other Neurological Effects*

5.2.1.1 *Mental Retardation*. Ionizing radiation to the developing human fetus has the potential to increase the risk of mental retardation and microcephaly (Blot and Miller, 1973; Dekaban, 1968; Doll, 1941; Doll and Murphy, 1930; Flaskamp, 1930; Goldstein and Murphy, 1929a; 1929b; 1929c; Kraemer, 1931; Mayer *et al*., 1936; Miller, 1969; 1990; 1999; Miller and Mulvihill, 1976, Murphy, 1929; Murphy *et al*., 1942; Otake and Schull, 1984; 1998; Otake *et al*., 1996; Petenyi, 1923; Schull and Otake, 1999; Wood *et al*., 1967a; 1967b, Yoshimaru *et al*., 1995).

In an early publication pertaining to the children who were irradiated *in utero* at Hiroshima and Nagasaki, Otake and Schull (1984) suggested that mental retardation may be a stochastic effect with risks <0.1 Gy (weighted uterine dose)[3] and no threshold. Otake and Schull (1998), Otake *et al*. (1996), Schull and Otake (1999), and Yoshimaru *et al*. (1995) have reevaluated the calculations and have indicated that a threshold dose for mental retardation is possible. Otake *et al*. (1996) estimate a threshold of 0.55 Gy with a 95 % lower limit at 0.31 Gy for the population exposed from the 8th to 15th week postconception.[4,5] The threshold for the 16th to 25th week postconception was estimated at 0.87 Gy with a 95 % lower limit at 0.28 Gy.

[3]Weighted organ doses for individuals have typically been calculated for Radiation Effects Research Foundation (RERF) studies as the estimated absorbed dose from gamma rays plus 10 times the estimated absorbed dose from neutrons. In this Report, the weighted organ dose (in this case the weighted uterine dose) is presented in gray; it has also been reported in the literature in sievert.

[4] See Otake *et al*. (1996) for Model II, all individuals without five probable nonradiation related cases.

Otake *et al*. (1996) concluded that the most vulnerable period for the induction of mental retardation was from the 8th to 15th week postconception and that 40 % of the fetuses that received a dose of 1 Gy during this stage were mentally retarded (IQ < 70) (Figure 5.5). They also indicated that from the 15th to 25th week postconception much higher doses were required to produce mental retardation and the incidence was lower (Figure 5.5). After 15 weeks postconception, 15 % of fetuses exposed to a dose of 1 Gy were mentally retarded. Before the 8th week and after the 25th week postconception an increase in mental retardation was not observed even in the group exposed to a weighted uterine dose of 1 Gy (Figure 5.5). Otake *et al*. (1996) do not indicate that the fetus is not vulnerable to the mental retardation effects of ionizing radiation after the 25th week postconception, only that they did not observe this finding, even in the group exposed to a weighted uterine dose of 1 Gy. It is possible that the threshold for mental retardation after the 25th week postconception is a dose >1 Gy.

Otake and Schull (1998) judged a child to be mentally retarded on the basis of the clinical judgment of physicians. There were 30 cases of severe mental retardation. Eighteen were microcephalic. Fifteen of these children were exposed during the 8th to 15th week postconception. These results focused their attention on this very vulnerable stage of development.

Besides Otake and Schull (1998), 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 (Wood *et al*., 1967a; 1967b; 1967c). Miller (1999) reviewed the issue of radiation-induced mental retardation and observed that when the weighted uterine dose is <0.5 Gy, the risk of severe mental retardation appeared similar to the unexposed population (Table 5.9). Mental retardation is not an uncommon occurrence with a prevalence of approximately one per 100 births. After inspection of the data in Table 5.9, Miller (1999) suggested that the threshold dose for severe mental retardation may be >0.5 Gy.

5.2.1.2 *Intelligence Quotient and School Performance*. There were 1,673 Hiroshima school children who were exposed *in utero* who were tested for the level of their IQ when they were 10 to 11 y of age

[5]In Section 5.2.1, all the time periods pertaining to the children who were irradiated *in utero* at Hiroshima and Nagasaki are given in weeks postconception, as reported in the relevant references. To convert to weeks of gestation, add two weeks (*e.g*., 8th to 15th week postconception would be 10th to 17th week of gestation).

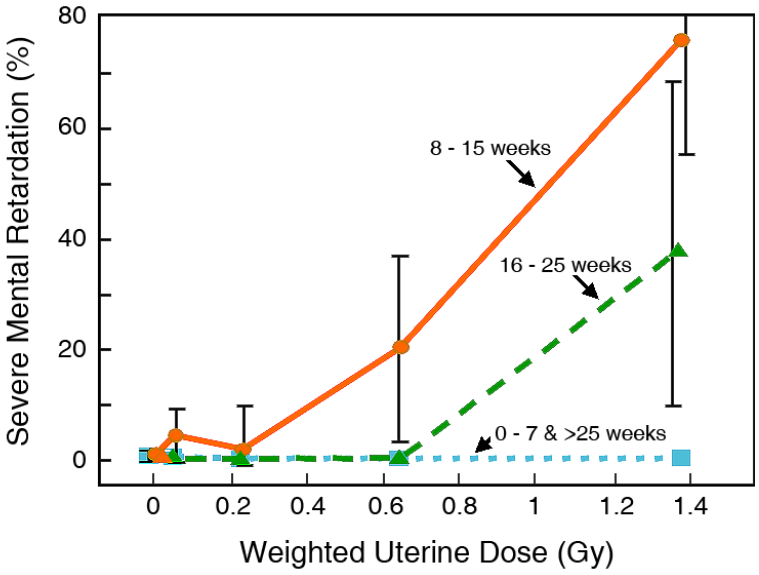

Fig. 5.5. Mental retardation in children who were irradiated *in utero* at Hiroshima and Nagasaki as a function of weighted uterine dose and the number of weeks postconception (Otake *et al*., 1996).

TABLE 5.9—*Risk of mental retardation in the in utero atomic-bomb survivors (Miller, 1999).*

Weighted Uterine Dose (Gy)	Number with Mental Retardation	Number at Risk	Rate of Mental Retardation
1+	12	26	1 in 2
0.5 – 0.99	4	43	1 in 11
0.1 – 0.49	2	215	1 in 100
0.005 – 0.09	3	212	1 in 70
<0.005	9	1,069	1 in 118

(Otake and Schull, 1998; Schull and Otake, 1999) (Figure 5.6). Eleven of the children were mentally retarded with an IQ range between 56 and 64. The average score for the entire population was 107.8 ± 32.1 (*i.e.*, there is a 95 % probability that the IQ of a random child drawn from the population would fall within the stated interval). No statistically-significant difference was observed between the average IQ score of those with a small head size without mental retardation and the average IQ of the entire population.

From the standpoint of counseling, one of the most important conclusions in Otake and Schull (1998) states: "No evidence of a radiation effect on intelligence was seen among children exposed prior to week 8 or at 26 or more weeks after ovulation." Animal studies support the conclusion that the CNS is less vulnerable to the effects of radiation during early organogenesis, probably because of its resiliency and repairability.

Most counseling is performed after radiation exposures to pregnant women from diagnostic radiological procedures (dose to the embryo or fetus <0.1 Gy) that were conducted before the 8th week postconception. The Otake and Schull (1998) and Schull and Otake

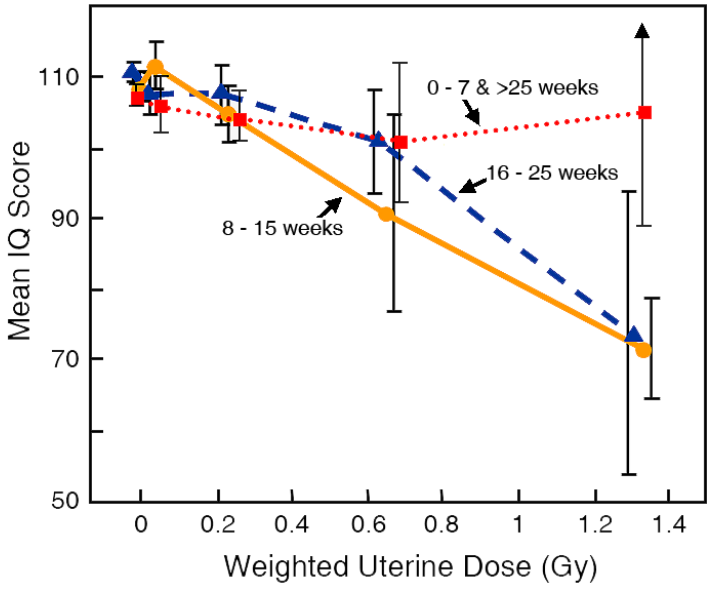

Fig. 5.6. IQ for Hiroshima school children who were exposed *in utero* as a function of *in utero* weeks postconception at time of exposure and weighted uterine dose (adapted from Otake and Schull, 1998).

(1999) analyses, and the animal studies support the conclusion that there is no increased risk for a loss in IQ with such doses.

In Figure 5.7, school performance is plotted for three exposure groups: 8th to 15th, 16th to 25th, and >25th weeks postconception. There was no decrease in school performance in any of the three exposure groups at weighted uterine doses <0.1 Gy. School performance was most affected in the 8 to 15 week exposure group and not affected in the >25 week group with doses as high as 1 Gy.

While not a study of exposure *in utero*, Hall *et al*. (2004) reported on a cohort of 3,094 Swedish men who had received radiation therapy for cutaneous hemangioma in infancy (before 18 months of age) during 1930 to 1959. Treatment was primarily with ^{226}Ra surface applicators, but in some cases with x-ray contact therapy (≤60 kV peak tube potential, <1 mm aluminum filtration). For the cohort, the mean doses to the brain were 60 mGy (frontal lobe) and 44 mGy (posterior lobe). The dose categories (in milligray) were: 0, 1 to 20, >20 to 100, >100 to 250, and >250. When the men were tested for cognitive function (learning ability, logical reasoning, spatial recognition) at time of military enlistment (at 18 or 19 y of age), a statistically-significant dose-response relation (decreasing test results with increasing dose) was seen for learning ability

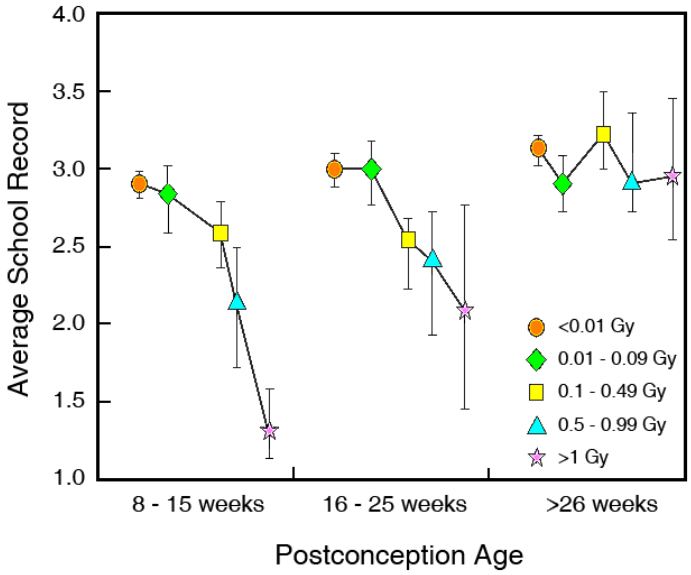

Fig. 5.7. School performance for Hiroshima school children who were exposed *in utero*, as a function of *in utero* weeks postconception at time of exposure and weighted uterine dose (Otake and Schull, 1998).

and logical reasoning, but not for spatial recognition. Hall *et al*. (2004) concluded that "low doses of ionizing radiation to the brain in infancy influence cognitive abilities in adulthood." The conclusions of the study were discussed in several subsequent letters to the editor (BMJ, 2004). No attempt is made in this Report to assess the significance of this study for exposure of the embryo or fetus.

5.2.1.3 *Seizures.* Convulsive disorders (epilepsy, seizures) are very common and have multiple etiologies, variable manifestations and many diagnostic categories. In order to simplify their task, Dunn *et al*. (1990), Otake and Schull (1998), and Schull and Otake (1999) evaluated the subjects with unprovoked seizures in order to reduce the number of patients with seizures that were genetic or had other proven etiologies. There were 52 cases of seizures identified; 24 had no identifiable concomitant acute insult (unprovoked seizures). Among the survivors exposed from conception to the end of the seventh week there were no subjects with seizures in any dose group <0.1 Gy. Seizures were most frequent among 22 mentally-retarded children exposed in the 8th to 15th week postconception group (Figure 5.8). When these mentally-retarded children were excluded

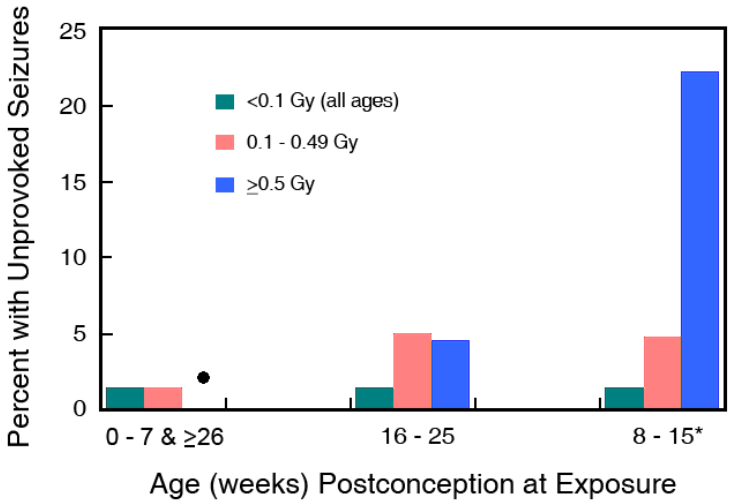

Fig. 5.8. Childhood seizures of unknown etiology (unprovoked) in survivors prenatally exposed to the atomic bombing of Hiroshima and Nagasaki by *in utero* age at exposure and weighted uterine dose (adapted from Dunn *et al*., 1990). • = no seizure cases occurred in this group with a weighted uterine dose ≥0.5 Gy. ∗ = the dose trend-test comparison of 8th to 15th weeks postconception versus 0 to 7th and ≥26th weeks postconception combined was $p < 0.001$.

from the analysis the risk for seizures in the remaining children in the 8th to 15th week postconception group was on the borderline of statistical significance. One conclusion of these studies is that the unprovoked seizures occurred predominantly in the children exposed during the 8th to 15th week postconception. The highest incidence of convulsive disorders was in the offspring that were irradiated *in utero* from the 8th to 15th week postconception and who were mentally retarded.

There was no increase in the incidence of convulsive disorders in the children who were irradiated *in utero* and who were exposed to a dose <0.1 Gy. Following doses of >0.5 Gy disorganization of neuronal synapses were observed histologically (in animal models), as well as heterotopia (Figures 5.9 and 5.10) and neuronal depletion (in animals and humans).There was no increase in convulsive disorders at any dose in the group exposed during the first seven weeks postconception or after the 25th week postconception.

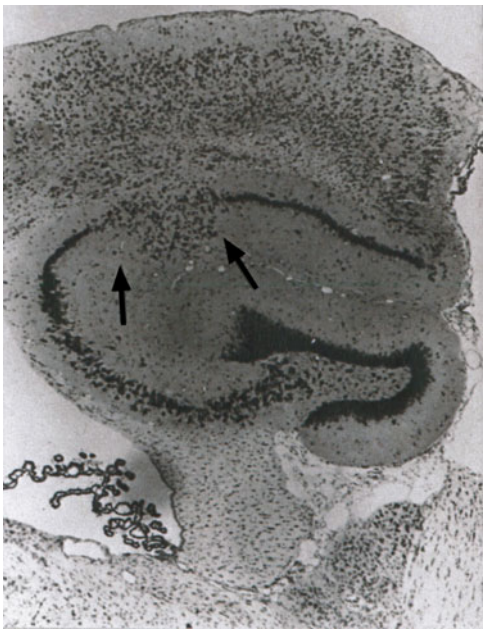

Fig. 5.9. Histological photo of the brain of an offspring following 1 Gy (whole-body dose) to a pregnant rat irradiated on the 17th day postconception (Jensh *et al*., 1986). The arrows are pointing towards an ectopic focus of neuronal cells that failed to migrate to their proper location, thus depleting the cortical layers of this population of cells. This is referred to as heterotopia.

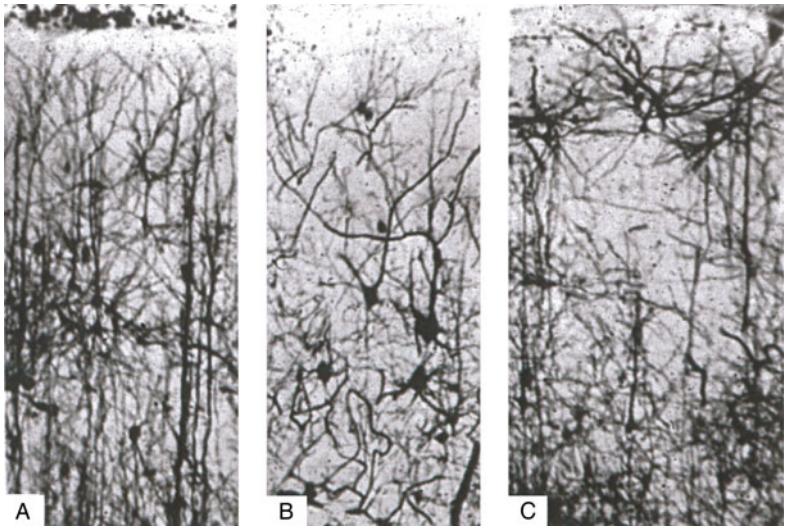

Fig. 5.10. The figure has three panels (A, B and C) (Hicks and D'Amato, 1966). All have been stained with the Cox Golgi stain. (A) shows the synaptic connections of the outer cortex in a normal adult rat brain. (B) shows the abnormal synaptic connections and abnormal neurons of an adult rat brain that had been exposed to a dose of 2 Gy (whole body) on the 17th day of rat pregnancy. (C) exhibits the abnormal outer neurons in an adult rat exposed to a dose of 2 Gy on the 22nd day postconception. While one cannot translate this pathology to specific abnormal human behavior, one could postulate that these abnormalities could account for decreased intellect and an increased risk for convulsive disorders.

5.2.1.4 *Mechanisms and Related Animal Studies*. Mechanisms to explain the depletion of neurons in the cerebral cortex that results in microcephaly and mental retardation include:

- radiation-induced cell killing of the ependymal cells or the migrating neuronal cells that were destined to find their proper place in the cerebral cortex; and
- heterotopia (Figure 5.9), which is a cluster of misplaced neuronal cells that persist in the cerebral cortex and never reach their proper position in the cerebral cortex, creating an ectopic cluster of cells as well as depleting the cortical layers of these cells (Jensh *et al*., 1986). Heterotopia was found in human brains from subjects with very low IQ following high doses of radiation (Brent, 1979; Cohen-Kerem *et al*., 2006; ICRP, 2003; Jensh *et al*., 1986; 1995; Otake and

Schull, 1984; 1998; Otake *et al*., 1987; 1988; 1996; Schull and Otake, 1986a; 1986b; Schull *et al*., 1988; 1991).

During organogenesis a dose of 1 Gy (whole body) on the 9th day postconception in the rat can produce a high incidence of malformations (Wilson *et al*., 1953b). When the brains of the irradiated rats that received a whole-body dose of 0.01 to 0.1 Gy on the 9th day postconception were examined, the irradiated brains were difficult to differentiate from the brains of the control rats, and there was no heterotopia (Hicks and D'Amato, 1966) (Figure 5.11).

This observation in humans and the negative results in the animals irradiated early in pregnancy are supported by the known resiliency of the CNS early in pregnancy. At doses below the no-adverse-effect level for the production of major malformations, the CNS cortical neuronal primordial cells are readily replaced. This does not happen in the human in mid-gestation or in the rat in late pregnancy.

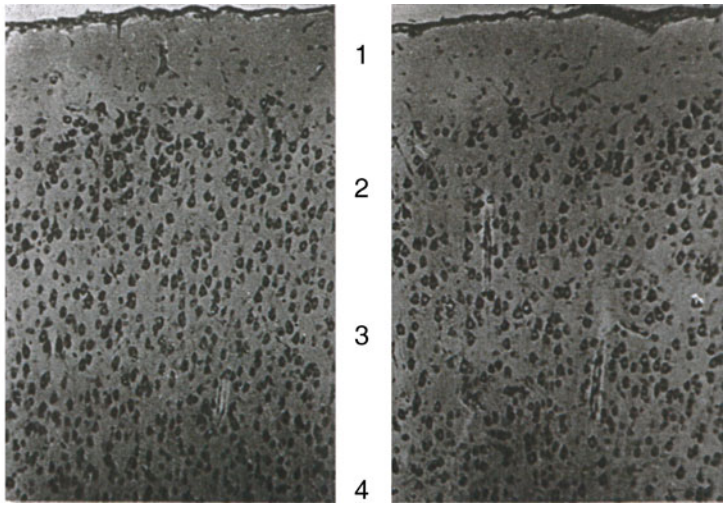

Fig. 5.11. The cerebral cortex of a 3.5 week old rat that was exposed to a dose of 0.2 Gy (whole body) on the 18th day postconception. The control rat is on the left and the irradiated rat is on the right. There is a reduction in the number of neurons in the outer cortical layers (Hicks and D'Amato, 1966). Similar studies that examined the effect at a dose of 0.01 Gy did not demonstrate a reduction in the number of cortical neurons (Kameyama and Inouye, 1994). Thus, there are no observable neuropathological effects that would indicate that mental retardation could be produced from doses <0.1 Gy.

Table 5.10 (Jensh *et al*., 1987) indicates that irradiation of the rat during late pregnancy does result in neurobehavioral or developmental effects at low doses with no-adverse-effect levels for growth and development at 0.4 Gy and for one reflex at 0.2 Gy. No neurobehavioral effects were observed in adult rats irradiated on the 9th day postconception (early organogenesis) at doses of 0.6 Gy or less and no neurobehavioral effects were observed at any stage <0.2 Gy.

The data with regard to mental retardation and other neurological effects pertaining to the children who were irradiated *in utero* in Hiroshima and Nagasaki is the most valuable set of data that we have dealing with the *in utero* effects of ionizing radiation. Animal studies in rodents cannot evaluate the risk of mental retardation from *in utero* radiation experiments. Jensh and Brent (1987; 1988a; 1988b; 1988c; 1999) and Jensh *et al*. (1986; 1987; 1995) investigated some aspects of behavior and neurological function and effects in adult rats. The results indicated that the stage of early organogenesis was resistant to radiation-induced neurobehavioral effects and neurological performance (*e.g*., Table 5.10). These results agreed with the findings for children who were irradiated *in utero* in Hiroshima and Nagasaki. During the later stages of pregnancy, when microcephaly can be readily produced in the rat, there were no-adverse-effect levels for all the neurobehavioral tests (Table 5.10).

In mid-gestation, it is not biologically plausible that mental retardation caused by irradiation of the brain could be a stochastic effect. A genetic alteration in one cell could not pathologically result in mental retardation (Brent, 1999a) (Table 5.11). Teratogenic (multicellular) effects are primarily threshold phenomena (Table 5.10). *In utero* exposure to ionizing radiation indicates that there is about a 25 point loss in IQ per gray (weighted uterine dose) during the most vulnerable period of human brain development (ICRP, 2003; Otake and Schull, 1998). The data on IQ loss of around 25 points per gray are difficult to interpret for low dose, however, even in the absence of a dose threshold, any IQ effects at low dose (*e.g*., 0.01 Gy) would be undetectable and therefore not of practical significance (ICRP, 2003). At <0.1 Gy (whole body) there are no observable histological effects in the developing rat brain that could account for severe CNS effects (Hicks, 1954; Hicks *et al*., 1953; Kameyama and Inouye, 1994) (Table 5.3). The current body of scientific data supports the view that radiation-induced mental retardation is a tissue reaction (deterministic effect) (Table 5.10) (Brent, 1999a; Jensh and Brent, 1987; 1988a; 1988b; 1988c; Jensh *et al*., 1986; 1987; 1995).

TABLE 5.10—*Effect on growth, reflexes, and developmental parameters for adult rats that were irradiated in utero (Jensh et al., 1987).*

	Postconception Day of Irradiation							
	Day 9				Day 17			
Dose (Gy) (whole body, x rays) →	0.1	0.2	0.4	0.6	0.1	0.2	0.4	0.6
Endpoint								
Growth retardation at term	0[a]	0	0	0	0	0	0	0
Growth retardation postpartum	0	0	0	0	0	0	+[b]	+
Four developmental parameters	0	0	0	0	0	0	+(2)[c]	+(2)
Five reflexes	0	0	0	0	0	+(1)[d]	+(1)	+(1)

[a]0 = no effect was observed
[b]+ = an effect was observed
[c]An effect was observed for two of the four developmental parameters.
[d]An effect was observed for one of the five reflexes.

TABLE 5.11—*Stochastic and deterministic dose-response relationships of health effects produced by environmental agents (adapted from Brent, 1987a; 1987b; 1990a; 1990b; 1999a).*

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

5.2.1.5 *Small Head Size (microcephaly)*. The discussion of microcephaly is an academic exercise that is meaningful from a statistical viewpoint but difficult to apply when evaluating a single case. Small head size includes subjects with microcephaly and craniosynostosis. Microcephaly is frequently associated with mental retardation, but not always. According to Otake and Schull (1984; 1993), Otake *et al*. (1987; 1988; 1996), Schull and Otake (1999), and Schull *et al*. (1988; 1991), small head size (less than two standard deviations below the mean) may or may not be associated with mental retardation and was increased in the 0 to 7th week postconception irradiated group. However, none of the children with small head size in this group were mentally retarded. Because of the nature of the small-head-size data, utilizing these data for counseling a pregnant woman regarding the risk of having a newborn with a small head size is problematic.

5.2.1.6 *Neuromuscular Function*. There were 888 individuals in the *in utero* population that were evaluated using two tests for neuromuscular function: grip strength and repetitive action (Otake and Schull, 1998; Yoshimaru *et al*., 1995). Grip strength measured strength and repetitive-action measured coordination. If the children with mental retardation were included in the evaluation, the populations in the 8th to 15th week postconception group and the 16th to 25th week postconception group demonstrated a statistically-significant difference. The strength test deficiency was absent if the retarded children were removed from the analysis. The repetitive-action performance tests were positively related to the IQ of the exposed subjects. While these reports do not specifically address the effect of low doses, it is apparent that neither the grip-strength test nor the repetitive-action test would be affected by doses <0.1 Gy (weighted uterine dose).

5.2.1.7 *Conclusions*. Studies on children who were irradiated *in utero* at Hiroshima and Nagasaki pertain to the effects of an acute irradiation of the developing embryo or fetus. The most vulnerable stage of pregnancy was from the 8th to 15th week postconception where a weighted uterine dose of 1 Gy resulted in an incidence of mental retardation in 40 % of the exposed pregnancies. From the 15th to 25th week postconception a weighted uterine dose of 1 Gy resulted in an incidence of mental retardation in 15 % of the exposed pregnancies. Before the 8th week and after the 25th week postconception mental retardation was not observed. School performance was not affected at any stage of pregnancy if the weighted uterine dose did not exceed 0.1 Gy (Figure 5.7).

For embryos and fetuses exposed to a dose <0.1 Gy during a pregnancy there is no evidence of an increased risk for microcephaly, mental retardation, lowered IQ, seizures, or impairment of neuromuscular performance (as exemplified by grip strength and repetitive action).

5.2.2 *Congenital Malformations (birth defects)*

High-dose radiation during early organogenesis in the rat (9th to 12th day postconception) (Figures 5.1 and 5.2) can produce anatomical congenital malformations of the brain, heart, craniofacial structures, viscera, and limbs (Table 5.12). A similar stage of development in the human theoretically should be similarly vulnerable to the induction of anatomical malformations (Table 5.12). There is not a great deal of available data dealing with acute high-dose radiation exposures during organogenesis in human pregnancies. Even the records of the pregnancies exposed to the atomic bombs in Hiroshima and Nagasaki in 1945 do not provide adequate clinical information on infants that were exposed to the atomic bombs during organogenesis. The embryonic LD_{50} during organogenesis is low and many embryos may not have survived to term, or the offspring may have died during infancy before the Radiation Effects Research Foundation (RERF) had developed accurate records in the late 1940s (Kato, 1971; Otake *et al*., 1996).

5.2.2.1 *Human Studies*. There have only been a few studies of adverse birth outcomes or infant mortality following accidents. Following the Chernobyl nuclear reactor accident, there were reports of a cluster of 12 cases (versus two to three expected) of trisomy 21 among children born in January 1987 in West Berlin (Sperling *et al*., 1991) and an increased frequency of neural-tube defects in hospital-based clinical series in Turkey (Mocan *et al*., 1990). It is very unlikely that these malformations reported by Mocan *et al*. (1990) and Sperling *et al*. (1991) were related to radiation exposures (*e.g*., Burkart *et al*., 1997). Observations of serious adverse birth outcomes were not confirmed in larger, population-based studies in Hungary (Czeizel, 1991), Norway (Lie *et al*., 1992), Austria (Haeusler *et al*., 1992), Sweden (Ericson and Kallen, 1994), or Finland (Auvinen *et al*., 2001). For the most part, the studies examined vital statistics, birth certificates, national databases (medical terminations of pregnancy), special registries (medical-birth registry, congenital-abnormality registry), survey data (germline mutations), and other sources. Radiation exposure data were derived from detailed measurements including soil-deposition patterns, measurements of radioactive cesium in meat and milk, and

TABLE 5.12—*Increased vulnerability for congenital malformations at various stages postconception (pc) of rat and human embryonic development during early organogenesis (human stages are estimated from the rat data) (Brent, 1955; 1999a; Konermann, 1969; 1982; 1987; Rugh, 1971; Russell, 1950; 1954; 1956; Wilson, 1954; 1973; Wilson and Karr, 1951; Wilson et al., 1952; 1953a; 1953b).*

Rat	8 d pc or less	9 d pc	10 d pc	11 d pc	12 d pc
Estimated for Human	18 d pc or less	21 d pc	27 d pc	31 d pc	34 d pc
Whole-Body Dose in the Rat (Gy)					
<0.1	0 %	0 %	0 %	0 %	0 %
0.25	0 %	6 % microphthalmia		0 %	
0.5	0 %	72 % eye,[a] 9 % brain, 3 % spinal malformations	11 % eye malformations[a]	0 %	
1	0 %	90 % eye,[a] 41 % brain, 27 % spinal cord, 20 % heart, 13 % situs inversus, 10 % aortic arch, 5 % urinary malformations	75 % eye,[a] 11% urinary, 3 % brain malformations	5 % mortality No data on malformations	95 % eye malformations[a]

TABLE 5.12—(*continued*)

Rat	8 d pc or less	9 d pc	10 d pc	11 d pc	12 d pc
Estimated for Human	18 d pc or less	21 d pc	27 d pc	31 d pc	34 d pc
Whole-Body Dose in the Rat (Gy)					
2	0 %	100 % eye,[a] 78 % brain, 67 % spinal cord, 55 % situs inversus, 22 % heart, 11 % craniofacial, 11 % aortic arch malformations	94 % eye,[a] 33 % limb, 19 % brain, 11 % urinary, 19 % urinary tract, 11 % aortic arch malformations	100 % eye,[a] 77 % urinary tract, 54 % brain, 31 % spinal cord, 23 % aortic arch, 23 % ear, 15 % heart, 15 % craniofacial, 7 % limb malformations	100 % eye,[a] 6 % aortic arch, 6 % right-sided diaphragmatic hernia, 20 % micrognathia, 4 % absent kidney, 2 % limb malformations
3	100 % lethal	100 % lethal	100 % lethal	100 % lethal	71 % lethal
4	100 % lethal	100 % lethal	100 % lethal	100 % lethal	100 % lethal

[a]Eye malformations consist of anophtalmia and microphthalmia.

other types of measurements carried out in many countries following the Chernobyl nuclear reactor accident. The adverse outcomes examined varied somewhat among the studies, but included rate of live births, Down syndrome, new mutations per 10,000 live births, a range of sentinel anomalies, microencephaly, microphthalmia, and other potential adverse birth outcome manifestations of radiation exposure. Based on the very low doses in the area where most of these reports were published, it is very unlikely that malformations anecdotally recorded are related to radiation exposure during pregnancy, since (except for the genetic diseases) the other abnormalities are tissue reactions (deterministic effects). Down syndrome and genetic mutations from preconception exposures are very low-risk phenomena and a causal relation cannot be determined from anecdotal reports.

There have been reports of hydatidiform mole (molar pregnancy)[6,7,8] among Marshall Islanders exposed to intense radioactive fallout from the 1954 BRAVO and other nuclear weapon tests (Yamada, 2004). The abnormality was called "jellyfish babies." While there is clear evidence linking thyroid abnormalities and cancer to the exposed Rongelap population, there are no definitive associations between stillbirth, miscarriages, and other adverse pregnancy outcomes (Cronkite *et al*., 1997). Conard (1984) states: "The general health of the exposed people appeared to be about the

[6]Hydatidiform mole, or molar pregnancy, is a type of gestational trophoblastic disease. It is an abnormal growth or mass that forms inside the uterus as a pregnancy begins and results from the over-production of tissue that was supposed to have developed into the placenta. A cancerous form of this growth is called choriocarcinoma. Hippocrates was likely the first to describe hydatidiform mole in 400 BC as dropsy of the uterus (Seckl *et al*., 2010; Slim and Mehio, 2007).

[7]There are two types of hydatidiform mole. A partial molar pregnancy is an abnormal placenta and some fetal development. A complete molar pregnancy is an abnormal placenta but no fetus. Both forms of hydatidiform mole are due to problems during fertilization.Complete hydatidiform mole most often occurs when an ovum without maternal chromosomes is fertilized by one sperm that then duplicates its DNA, resulting in a 46XX androgenetic karyotype, in which all chromosomes are paternally derived. About 10 % of complete moles are 46XY, arising from fertilization by two sperm. Partial hydatidiform moles are almost always triploid, and result from fertilization of an ovum by two sperm (Seckl *et al*., 2010). The cause or causes of these fertilization problems are unknown. Some studies suggest a diet low in protein, animal fat, and vitamin A may play a role (Altieri *et al*., 2003). One well established risk factor for trophoblastic disease is maternal age with increased rates occurring among teenagers and among those over 40 y of age.

same as that of the unexposed people. Vital statistics suggested that mortality and fertility rates were about the same. During the first 4 years, there appeared to be an increase in miscarriages and stillbirths in the exposed Rongelap women, but this observation was uncertain in view of the small numbers involved. Genetic studies and examinations of the newborn have not revealed any detectable abnormalities that might be related to radiation exposure. A slight increase in chromosomal aberrations in lymphocytes was noted in the exposed Rongelap people." There have been ecological (geographic) descriptive analyses linking gestational trophoblastic disease with low dose rate exposures in 11 prefectures in Japan (Ujeno, 1985), but the ecological nature of the analyses, including the selection of prefectures for inclusion and the heterogeneity of dose rate within prefectures, precludes etiologic interpretations. Genetic factors influence the risk of hydatidiform mole as indicated by the paternal origins (*i.e.*, only the chromosomes of the father are involved) (Kajii and Ohama, 1977). Women, however, who carry mutations in the gene NLRP7 are predisposed towards molar pregnancies (Slim and Mehio, 2007). The reported associations between molar pregnancy and childhood cancer (Schuz *et al.*, 2007) also suggest a possible common etiology, including epigenetic mechanisms (Roman *et al.*, 2006). In summary, hydatidiform mole is a common occurrence in pregnancy but there are no clear etiologic causes, other than possible genetic or epigenetic factors. Ionizing radiation has been purported to increase rates following environmental exposures to fallout or natural background, but the evidence is weak and additional study would be required to confirm a radiation etiology.

Most routine diagnostic radiological procedures in pregnant women expose the embryo to a dose <0.1 Gy. Since a 0.1 Gy dose is below the estimated no-adverse-effect level for producing anatomical congenital malformations (~0.2 Gy from animal studies), it is not surprising that the vast majority of these studies do not observe an increased risk for birth defects. A dose greater than ~0.2 Gy would be needed to yield positive results and the dose would have

[8]There are wide variations in the rates of hydatidiform mole which may be related in part to differences in diagnostic techniques, reporting, classifying, and other methodological difficulties. Rates of hydatidiform mole in North America, Europe, and Oceania are ~1 per 1,000 pregnancies in contrast to the rate in Indonesia of ~10 per 1,000 pregnancies (*i.e.*, a 10-fold difference) (Altieri *et al.*, 2003). There are limited data suggesting that lifestyle or environmental factors are associated with increased rates of hydatiditiform mole (Altieri *et al.*, 2003; Bracken *et al.*, 1984; McGee and Covens, 2012; Seckl *et al.*, 2010; Steigrad, 2003).

to occur after the 18th day postconception [32nd day (into the fourth week) of gestation]. It would be unlikely to be able to obtain an adequate sized population exposed to this dose range during the fourth to seventh week of gestation. Based on the animal studies, pregnancy loss, congenital heart defects, kidney anomalies, CNS anomalies, gastrointestinal (GI) malformations and skeletal anomalies could be produced if the acute doses were high enough.

Preston *et al*. (2008) reported that 2,452 atomic-bomb survivors of *in utero* irradiation were included in their long-term study. Eighty percent of the survivors of the *in utero* irradiated population were exposed to a weighted uterine dose of <0.2 Gy. There were 312 survivors in this group; however, only 36 of these embryos were exposed during early organogenesis. The embryos exposed during early organogenesis [18th to 40th day postconception (32nd to 54th day of gestation)] to doses >0.2 Gy are too few to evaluate teratogenic effects, because most of these embryos received <0.5 Gy and some of the affected embryos may have died *in utero*.

Dekaban (1968) identified 26 pregnant patients that had received high doses of radiation during their pregnancies for various purposes. The doses were fractionated over a period of days or weeks and no case received an acute high dose on a single day during organogenesis. Dekaban (1968) did report microcephaly, mental retardation, limb abnormalities, and growth retardation (weight and height reduction) in this small series of patients. The teratogenic syndrome associated with mid-gestation irradiation is microcephaly, mental retardation, convulsive disorders, decreased school performance, low birth weight, and decreased attained height (Blot and Miller, 1973; Goldstein and Murphy, 1929a; 1929b; Miller, 1969; Murphy, 1929; Murphy *et al*., 1942; Otake and Schull, 1998).

In a few epidemiological studies there was no increase in congenital malformations or growth retardation observed from diagnostic radiological examinations with fetal doses <0.1 Gy (Cohen-Kerem *et al*., 2006; Kinlen and Acheson, 1968; Nokkentved, 1968; Ornoy *et al*., 1996; Tabuchi, 1964; Tabuchi *et al*., 1967; Vilumsen, 1970); however, there was one study that observed an increase (Jacobsen and Mellemgaard, 1988). All the populations that were studied were small. Studies of such human populations where the embryo or fetus of pregnant patients received a dose <0.1 Gy are extremely difficult to evaluate.

5.2.2.2 *Animal Studies*. The animal data support a conclusion that gross congenital malformations will not be increased in the offspring of a human pregnant population when the embryo or fetus is exposed to a dose <0.2 Gy. The no-adverse-effect level in the rat

for congenital malformations is ~0.2 Gy (whole-body dose) at the most vulnerable stage of development (9th day postconception in the rat) [21st day postconception (35th day of gestation) in the human] (Brent, 1955; 1999a; Wilson, 1954; 1973; Wilson and Karr, 1951; Wilson *et al*., 1952; 1953a; 1953b). The no-adverse-effect level on the 10th day postconception is ~0.4 Gy (*i.e*., twice as high as for the 9th day postconception) (Brent, 1999a; Wilson and Karr, 1951). If this latter no-adverse-effect level could be applied to the human embryo, the embryonic age would be during the 27th to 29th day postconception (41st to 43rd day of gestation). While there can be no certainty of the human no-adverse-effect level on the 28th day postconception (42nd day of gestation), it is certain that the no-adverse-effect level for birth defects is much higher at later stages of pregnancy. During the preimplantation period (Figure 5.1) the embryos that survive to term are not growth retarded nor do the surviving fetuses have a higher incidence of malformations (Table 5.3) (Brent, 1969a; 1969b; 1970; 1999a; 1999b; Brent and Bolden, 1967a; 1967b; 1968; Friedberg *et al*., 1973; Hicks *et al*., 1953; Job *et al*., 1935; Mazur, 1984; Roux *et al*., 1983; Russell, 1950; 1954; 1956; Russell and Russell, 1950; Schlesinger and Brent, 1978; Wilson *et al*., 1953b).

Bruni *et al*. (1994) studied the effects of a dose of 0.5 Gy (whole body) administered to pregnant rats at 9.5 day postconception. This stage is one of the most vulnerable stages for demonstrating the reproductive and developmental effects of toxic agents. At term there was no difference in litter size or resorption rates. However, there was a higher incidence of congenital malformations of the eye, spinal column, and visceral anomalies in the fetuses that reached term.

From fertilization until 8th day postconception the rat embryo is not as susceptible to the teratogenic effects of radiation. The first two weeks postconception (second two weeks of gestation) in the human are considered to be a comparable stage and is referred to as the all-or-none stage. The 9th day postconception in the rat is considered to be the most vulnerable to the teratogenic effects of ionizing radiation. The following is a list of anatomical malformations that ionizing radiation produced in the rat in various studies previously cited:

- microphthalmia*;
- incomplete closure of the choroidal fissure*;
- failure of the optic nerve to connect to the retina*;
- radiation-induced rosette formation*;
- abnormalities of the spinal cord*;
- middle ear abnormalities*;

- retardation of the aorticopulmonary septum*;
- absent left kidney*;
- micrognathia*;
- common cloaca*;
- hydrocephalus*;
- anencephaly*;
- right-sided diaphragmatic hernias;
- hypoplastic choroid plexus; and
- absent bones and limb-reduction defects.

At 9th day postconception, the rat embryo was most vulnerable to induction of 12 of these abnormalities [those indicated by an asterisk (*)]. Although stages of rat and human embryonic development can be compared, it is not possible to infer that the human embryo has the same vulnerability for the induction of various malformations that were produced in the rat embryo at the comparable stage of human development. Nor can we infer that the no-adverse-effect level is identical in the two species.

5.2.2.3 *Summary for Congenital Malformations*. The risk of congenital malformations from exposure to ionizing radiation can be summarized briefly in the following tentative conclusions:

- During early organogenesis, the susceptibility and vulnerability of the human embryo and fetus varies with the postconception stage, just as in the rat embryo and fetus.
- As the embryo and fetus develop, the dose necessary to malform the embryo and fetus increases. Therefore the no-adverse-effect level for producing malformations increases during the stages of organogenesis.
- At all stages of organogenesis the risk of radiation-induced anatomical malformations with a dose of <0.5 Gy is very low. In fact, on the most vulnerable stage in the rat, at 9th day postconception, a dose of 0.25 Gy resulted in a 6 % risk of microphthalmia (Table 5.12).

5.2.3 *Growth Retardation*

Many experimental animal studies have evaluated the effect of *in utero* irradiation on the growth of the irradiated embryo:

- during various stages of embryonic and fetal development;
- at term by removing the newborns by Cesarean section or allowing the pregnant animal to deliver; or
- allowing the newborns to reach adult maturity.

Note that Table 5.6 (Section 5.1.5) indicates that 0.3 Gy (whole body) is the no-adverse-effect level for growth retardation in newborn mice irradiated on the day of conception (one- or two-cell stage). However, in the studies of Rugh *et al*. (1964) (Figure 5.12), mouse embryos irradiated with 1 Gy at the one- or two-cell stage were normal weight at maturity.

Publications dealing with the effect of *in utero* irradiation on growth may be concerned with different endpoints. For human studies, the investigators may be concerned with the height of the *in utero* irradiated population, not the birth weight (Otake and Schull, 1998). Most animal studies dealing with *in utero* irradiation are concerned with fetal weight reduction measured at a particular stage of pregnancy or at term. The animal experiments can vary because of the:

- species or strain of rat or mouse;
- energy and type of ionizing radiation; and
- embryonic or fetal stage at time of irradiation.

It is not surprising that the animal experiments may not have uniform results.

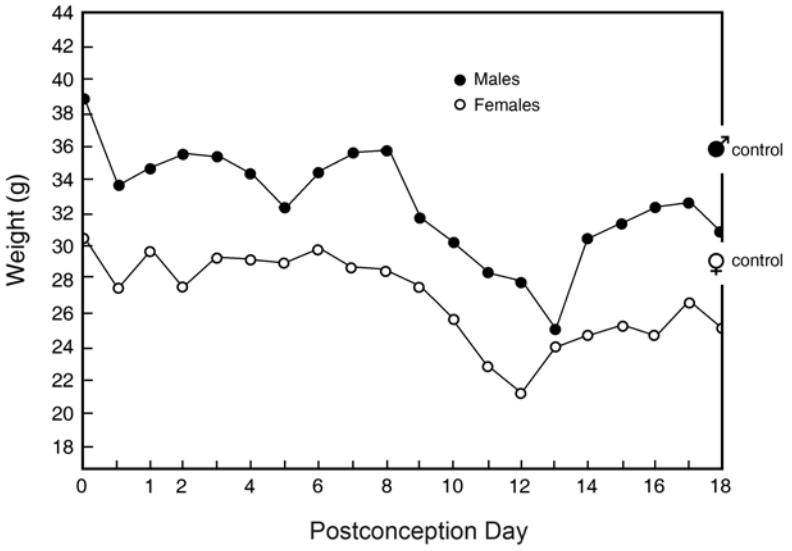

Fig. 5.12. Adult weights of offspring of pregnant mice irradiated at 1 Gy (whole body), as a function of postconception day irradiated (Rugh *et al.*, 1964).

ICRP (2003) lists the lowest range of dose for the production of growth retardation in offspring of animals irradiated *in utero* as 0.1 to 0.25 Gy (whole body). Information is not provided for what stage of pregnancy these results were obtained. Russell (1950), using doses of 2 to 4 Gy, reported that the most vulnerable stage for growth retardation in mice was on days 10.5 to 11.5 postconception. The newborn weight reduction was 0.22 g Gy^{-1}. These results agree with Rugh *et al*. (1964) (Figure 5.12), except that Rugh *et al*. (1964) studied postnatal growth retardation at three months of age. Kriegel (1965) found that the same days were the most vulnerable to growth retardation as did Russell (1950). While newborn weights may be reduced most by irradiation on the 10th to 11th day postconception of mouse pregnancy, permanent growth retardation is greatest with irradiation in later fetal stages (Sikov *et al*., 1969).

Growth retardation has been reported following high doses to the fetuses that were exposed from the atomic-bomb detonation and from embryos or fetuses exposed to radiation therapy (Blot, 1975; DeKaban, 1968; Goldstein and Murphy, 1929a; Greulich *et al*., 1953; Miller, 1969; 1970; 1990; Nakashima *et al*., 1995; 2002; Otake and Schull, 1998; Otake *et al*., 1993; 1994; Wood *et al*., 1967a). There is not enough information to definitively document effects in the human at doses to the embryo or fetus <0.3 Gy.

Rugh (1962) and Rugh *et al*. (1964) irradiated pregnant mice in separate experiments on each day of pregnancy. All pregnant mice were irradiated as a group on one particular day of pregnancy with 1 Gy (whole body) and the newborns were allowed to reach adulthood. Therefore, there were 18 groups of offspring that had been irradiated with 1 Gy on one particular day of pregnancy. The adult weights of these animals illustrated in Figure 5.12 and Table 5.3 (Section 5.1.2) and Table 5.6 (Section 5.1.5) indicated the information in the next paragraph.

The mouse embryos in Rugh *et al*. (1964) that were irradiated with 1 Gy before the 7th or 8th day postconception were not growth retarded as adults. From the 9th to 12th or 13th day postconception there was an increased reduction in weight of the adult mice that were irradiated with 1 Gy. Thus, the severest stage for permanent growth retardation after irradiation was in mid-pregnancy. The growth retardation that results at this stage is present in the postpartum period and for the rest of the life of the mouse or rat. Irradiation of the fetuses with 1 Gy for the remainder of pregnancy also resulted in permanent growth retardation, but not as severe as the mid-pregnancy irradiations. There are no human data to confirm or refute whether the Rugh *et al*. (1964) mouse data are applicable to the human, although the Otake and Schull (1998) data are

consistent with the Rugh *et al*. (1964) mouse data. However, it is reasonable to conclude that the extent of human growth retardation cannot be determined following *in utero* irradiation until the irradiated population has reached maturity (Otake and Schull, 1998), since the ability to recuperate from the growth-retarding effects of *in utero* irradiation varies with the actual stage of the exposure. The preimplanted embryo and the embryo during early organogenesis have better ability to recuperate than the older embryos and fetuses that probably have no-adverse-effect levels for adult growth retardation at a dose between 0.25 and 0.5 Gy.

Before implantation, the embryo is a multicellular organism with a varying proportion of pluripotential stem cells. Therefore, these early embryos have a decreased vulnerability to the teratogenic and growth-retarding effects of radiation and a greater degree of vulnerability to the lethal effects of irradiation at this early stage (Brent, 1999a; Brent and Bolden, 1967a; 1967b; Jensh and Brent, 1988a; 1988b; Jensh *et al*., 1986; Konermann, 1969; Rugh, 1971; Rugh *et al*., 1964; Russell and Russell, 1950) [Figure 5.12, Table 5.3 (Section 5.12), and Table 5.6 (Section 5.1.5)]. Irradiation of the embryo during the all-or-none period (*i.e*., conception to 8 d and 3 h postconception in the rat) results in a reduced litter size and more uterine surface available for the nourishment of each surviving embryo (Schlesinger and Brent, 1978). Thus, the surviving embryos may have average weights greater than embryos in control litters.

During early organogenesis (Figure 5.1) the embryo is very vulnerable to the growth-retarding, teratogenic, and lethal effects of irradiation, but these embryos have the ability to recover somewhat from the growth-retarding effects in the postpartum period if the dose was <0.5 Gy and the dose did not result in anatomical malformations (Rugh, 1962; Rugh *et al*., 1964; Russell, 1956; Russell and Russell, 1954).

Konermann (1982) irradiated mice on days 2 to 13 postconception in separate experiments utilizing a broad range of doses from 0.5 to 3 Gy (whole body). The fetuses were weighed at term and evaluated. Konermann (1982) reported that there was a linear relationship between dose and weight loss from 0.5 to 3 Gy. Konermann (1982) did not report a no-adverse-effect level, since there were no doses <0.5 Gy. He did confirm the existence of the all-or-none period since 0.5 Gy on 2nd through 8th days postconception did not manifest growth retardation at term. Konermann (1982) also reported that the most vulnerable stage for growth retardation in his extensive experiments was on the 13th day postconception, not during early organogenesis.

Investigators from RERF have spent over 20 y studying the children and adults who were exposed while *in utero* to radiation from the atomic bombs in Hiroshima and Nagasaki. Their publications regarding the effects of *in utero* irradiation on growth dealt primarily with small head size (microcephaly). Lengthy analysis and evaluation in their publications (*e.g.*, Otake and Schull, 1998) report that microcephaly is caused by radiation exposure, but these investigators can only hypothesize on whether radiation primarily affects skull growth or whether the growth of the skull is related to the effect of radiation on the size of the brain. Reduction of the height of the 10 to 11 y olds who were exposed *in utero* demonstrates a statistically-significant difference with increasing weighted uterine dose ($p < 0.1$). There are no data with regard to the no-adverse-effect level for linear growth in these publications.

In summary, the preimplanted embryo and the embryo during early organogenesis have better ability to recuperate from growth retardation than the older fetuses, where the latter probably have a no-adverse-effect level for adult growth retardation between 0.25 and 0.5 Gy.

5.2.4 *Embryonic and Fetal Death (miscarriage and stillbirth in humans)*

Of all the reproductive and developmental events, spontaneous abortion (miscarriage) is the most difficult to evaluate in epidemiological studies. Spontaneous abortions, frequently referred to as miscarriages by members of the public, are common occurrences during pregnancy. Fifteen percent of women (with a large standard deviation) spontaneously abort (miscarry) their pregnancies after the first missed menstrual period (WHO, 1970; Wilcox *et al.*, 1988). The true incidence of pregnancy loss is much higher, but undocumented pregnancies are not included in this particular risk estimate. A high percentage of embryos are aborted before the first missed menstrual period; before the mothers know that they are pregnant. It has been estimated that up to 30 to 40 % of all fertilized ova in humans are lost within the first three weeks of development (Hertig, 1967; Kline and Stein, 1985). The lay population and the news media are under the impression that many early spontaneous abortions are due to exposures to some type of environmental toxicant during the woman's pregnancy. This is an erroneous conclusion since most early spontaneous abortions (50 to 60 %) are due to chromosomal abnormalities that occurred before conception during the development of the sperm or the mother's ova or maternal disease states (Boue *et al.*, 1975; Simpson, 1980).

There are many causes of spontaneous abortions (Abenhaim and Lert, 1991; Beckman and Brent, 1986; Boue and Boue, 1974; Brent, 2009; Brent *et al*., 2011; Carr, 1971; Kline and Stein, 1985; Kline *et al*., 1977; Stein *et al*., 1975; Warburton *et al*., 1979; WHO, 1966; Wilcox *et al*., 1988), including:

- chromosomal abnormalities due to mutations during oogenesis or spermatogenesis, or inherited chromosome abnormalities (account for 50 to 70 % of spontaneous abortions) in early pregnancy;
- luteal phase hormonal deficiency;
- endometriosis;
- Lupus anticoagulant factor;
- cervicitis, or amnionitis due to bacterial or viral infections;
- uterine abnormalities such as: subserosal myoma, infantile uterus, bifid uterus, intrauterine device, multiple implantations;
- some teratogens, especially those with cytotoxic characteristics;
- maternal diabetes, alcoholism, drug abuse, phenylketonuria, hemorrhagic diatheses, and many other chronic and acute maternal diseases; and
- embryos and fetuses with severe congenital malformations or growth retardation, and many types of rare genetic traits that cause recurrent spontaneous abortion.

Epidemiological investigations dealing with the causes of spontaneous abortions have formidable problems:

- A majority of spontaneous abortions that occur early in pregnancy are due to chromosomal abnormalities that are unrelated to environmental exposures during pregnancy.
- The risk of spontaneous abortion changes with each day of pregnancy, so that it is essential to properly match controls, in order to eliminate the selection of two populations with different spontaneous abortion rates (Brent *et al*., 2011; Kline and Stein, 1985).
- Attempts to control for the hidden incidence of medical terminations of pregnancy have only limited success (Olsen, 1984; Susser, 1983). Susser (1983) stated that women not infrequently would report medical terminations of pregnancy as miscarriages.
- It is clear that there are numerous contributing factors to the incidence of spontaneous abortion, including environmental, genetic, mechanical, and maternal disease states,

and these all can affect the results and interpretation of spontaneous abortion studies.

The no-adverse-effect level for the lethal effects of radiation is lowest during the preimplantation and presomite stages (0 to 8th day postconception in the rat) [0 to 14th day postconception (14th to 28th day of gestation) in the human] and is estimated to be in the range of 0.15 to 0.2 Gy (based on studies in the mouse and rat) (Table 5.3). The no-adverse-effect level for increased risk of embryonic death increases throughout gestation. It is estimated to be in the range of 0.25 to 0.5 Gy during organogenesis and in late gestation is ~2 Gy (similar to the lethal dose for the mother). Doses <0.1 Gy do not represent an increased risk for pregnancy loss at any stage of gestation (Tables 5.3, 5.6, and 5.13).

An example of the excessive fear that can occur following low-dose ionizing radiation exposure to pregnant women is represented by the results of the Chernobyl nuclear reactor accident that occurred in 1986. While there were reports of an increase in the frequency of medical terminations of pregnancy in Russia following the disaster, this was not the case in northern and central Europe. The doses to the population were extremely low at great distances from the Chernobyl nuclear reactor and there was no increase in any reproductive effect studied, including congenital malformations, stillbirths, and spontaneous abortions in Austria, Finland, Norway and Sweden (Bengtsson, 1991; Haeusler *et al*., 1992; Harjulehto *et al*., 1991; Irgens *et al*., 1991; Knudsen, 1991; Odlind and Ericson, 1991). Yet in many countries in southeastern Europe and Ukraine, pregnant women were inappropriately encouraged to interrupt their pregnancies because of the perceived risks of radiation.

In summary, there is no evidence for any stage during pregnancy that the embryo or fetus is at an increased risk for spontaneous abortion if the dose to the embryo or fetus is <0.1 Gy. Except for the preimplantation stages the no-adverse-effect level for spontaneous abortion is estimated to be in the range of 0.25 to 0.5 Gy.

5.2.5 *Adult Diseases*

It is obvious that mental retardation, growth retardation, and cancer are diseases that have occurred because of intrauterine radiation exposure. However, there are many adult diseases that have their etiology from environmental events that occur during their postnatal or adult life. Unless the adult diseases have manifestations or signals related to these adult diseases at birth or in childhood, it is difficult to determine whether environmental factors (*e.g*., nutrition, drugs, or other life-style behaviors) or genetic

TABLE 5.13—*Increased radiation-induced mortality observed at term at various stages postconception (pc) of the rat compared to corresponding stages in human embryonic development (human stages are estimated from the rat data) (Brent, 1955; Konermann, 1969; 1987; Russell, 1950; 1954; 1956; Wilson et al., 1953a; 1953b).*

Rat	12 h pc	8 d pc or less	9 d pc	10 d pc	11 d pc	12 d pc
Estimated for Human	12 h pc	18 d pc or less	21 d pc	27 d pc	31 d pc	34 d pc
Whole-Body Dose in the Rat (Gy)			(%)			
<0.1	0	0	0	0	0	0
0.25	10	0	0	0	0	0
0.5	40	0	9	0	0	0
1	70	4	27	6	5	0
2	100	100	100	100	88	44
3	100	100	100	100	100	71.5
4	100	100	100	100	100	100

factors were etiologically related to the occurrence of the adult disease. RERF has evaluated some diseases to determine if there could be a relationship between *in utero* radiation exposure and the occurrence of these diseases. The two areas investigated are cardiovascular disease and thyroid disease.

5.2.5.1 *Cardiovascular Disease*. For the atomic-bomb survivors in Hiroshima and Nagasaki, Tatsukawa *et al*. (2008) investigated the association of hypertension, hypercholesterolemia and cardiovascular diseases in the adult populations that were exposed to radiation *in utero* and postnatally in children <10 y old. There were 506 adults who were exposed to radiation *in utero* and 1,053 children who were followed during 1978 to 2003 with biennial clinical examinations. There were no statistically-significant dose effects for any of these diseases in the entire *in utero* exposed cohort or in trimester-of-exposure subgroups. Statistically-significant dose effects were found for hypertension and cardiovascular disease in the childhood exposure cohort. One of the reasons for the negative findings in the *in utero* radiation cohort is that 94 % of the *in utero* doses were <0.5 Gy (weighted uterine dose). There were only 29 subjects in the *in utero* group that received >0.5 Gy. Since hypertension, hypercholesterolemia and cardiovascular diseases are so common in the adult population and there are so many known causes for these diseases in adults, it is unlikely that it is possible to determine a causal relationship between *in utero* irradiation and hypertension, hypercholesterolemia and cardiovascular diseases from these data.

5.2.5.2 *Thyroid Disease*. The association of an increase in thyroid disease with *in utero* exposure was studied by Imaizumi *et al*. (2008) for the population of atomic-bomb survivors in Hiroshima and Nagasaki. There were 328 survivors who were irradiated *in utero* with a mean age of 55.2 y. Examination of the subjects occurred between March 2000 and February 2003. The mean weighted uterine dose was 0.26 Gy. The dose range was 0.02 to 1.79 Gy. There were 229 subjects who received <0.1 Gy, 72 subjects who received 0.1 to 0.49 Gy, and 18 that received 0.5 to >1 Gy. There were 60 subjects exposed in the first trimester, 73 subjects exposed in the second trimester, and 48 subjects exposed in the third trimester. The investigators did not observe a statistically-significant dose-response relationship for the presence of thyroid nodules (p = 0.22). The prevalence of cysts and autoimmune thyroid disease was not associated with the radiation exposure. It was not possible to evaluate the relationship of radiation exposure with malignant tumors or benign nodules because of the small number of cases.

5.2.6 *Oncogenic Effects of In Utero Irradiation*

This section summarizes the epidemiologic literature on cancer risks in offspring associated with maternal exposures during pregnancy, including exposure to: diagnostic radiological examinations, radiation therapy for cancer, occupational sources, ubiquitous background, and various man-made environmental sources, including exposure of the Japanese atomic-bomb survivors. In addition, animal data on cancer risks in offspring associated with maternal radiation during pregnancy are reviewed.

Childhood malignancies represent <1 % of total cancer occurrence in the United States (Horner *et al*., 2009). Overall, the cumulative risk to 15 y of age for total childhood cancer ranges from 1 to 2.5 per thousand in most western countries (Stiller and Parkin, 1996). In contrast to the primarily epithelial origin of most common forms of adult malignancies (*e.g*., breast, colon, lung and prostate carcinomas), the originating tissues of most childhood cancers differ with leukemias, brain tumors and lymphomas accounting for close to 70 %. Risk factors for most childhood cancers are largely unknown, except for specific genetic and constitutional disorders, alkylating and other chemotherapy agents, and moderate-to-high radiation doses during the first few years after birth (Ross and Spector, 2006). The associations of postnatal radiation exposures and childhood cancer excesses are based on follow-up studies of the Japanese atomic-bomb survivors and cohort studies of children irradiated to treat benign or malignant medical conditions (Preston *et al*., 2008; Ross and Spector, 2006; UNSCEAR, 1994; 2000). Investigators often define childhood cancers as those diagnosed during 0 through 14 y of age (*i.e*., between birth and 15 y of age) (*e.g*., NCI, 2012b), but sometimes use other age categories. For this reason, care should be taken when making comparisons among studies.

A brief description of risk measures used in the description of findings from the epidemiologic studies in Section 5.2.6 is provided below. The risk measures also appear in the description of findings from other epidemiologic studies elsewhere in this Report.

- The *incidence rate* is the number of new cases per population in a given time period.
- The *relative risk* (RR) in a cohort study is the incidence rate of a disease in an exposed group divided by the incidence rate in an unexposed group. RR = 1 means that there is no difference in incidence rate in the exposed than in the unexposed group. RR < 1 means that the incidence rate in the exposed group is lower than the rate in the unexposed group.

RR > 1 means that the incidence rate in the exposed group is higher than in the unexposed group.

- The *excess relative risk* (ERR) is the ratio of the excess risk of a specified disease to the probability of the same effect in the unexposed population (*i.e.*, RR – 1).
- The *excess absolute rate* (EAR) is the excess rate of a specified disease in a specified population among exposed persons per unit dose. In radiation exposed populations, the EAR is designated as the number of excess cases of a specific disease in radiation-exposed persons per 10,000 person-years per gray [$(10^4$ PY Gy$)^{-1}$].
- The *odds ratio* is a measure of the odds of an event happening in one group compared to the odds of the same event happening in another group. Odds ratios are most often used in case-control studies to determine if being exposed to a certain substance or other factor increases the risk of a disease outcome. For case-control studies, the odds ratio is taken as an estimate of RR where the odds of being an exposed case are divided by the odds of being an unexposed control. For example, investigators study a group of cases with cancer and compare the cases to a group of controls without cancer. The investigators calculate the odds of exposure in both groups and compare the odds. An odds ratio = 1 means that there is no difference in the odds of exposure in both groups and therefore the exposure probably does not increase the risk of cancer. An odds ratio < 1 means that the exposure may reduce the risk of cancer. An odds ratio > 1 means that the exposure may increase the risk of occurrence of cancer. An odds ratio is a good measure of RR for rare outcomes such as childhood cancer.

If the confidence interval (CI) for either RR or an odds ratio contains the value one, then the risk is considered (by convention) not to be statistically significant, meaning that chance cannot be convincingly rejected as a possible explanation for the association. If the upper value of CI of a reduced risk is <1, then the risk is considered statistically-significantly reduced. If the lower value of CI of an increased risk is >1, then the risk is considered statistically-significantly increased. Statistical significance is related to the likelihood of ruling out chance as a possible explanation for an association between an exposure and a disease.

5.2.6.1 *Medical Exposures: Diagnostic*. Specific types of diagnostic radiological procedures and their associated doses to patients have

changed dramatically over the past 50 y. Some of these changes are due to the introduction of new equipment (*e.g.*, CT), the addition of new radiopharmaceuticals, or the reduction or elimination of some radiological procedures utilizing ionizing radiation (*e.g.*, due to the replacement of some procedures by ultrasonography or MRI).

During the late 1940s through the 1960s, obstetricians employed obstetrical abdominal x-ray procedures that utilized a large film to image the entire fetus, and pelvimetry x-ray procedures that provided images of the maternal pelvis and fetal structures within the pelvis to determine the method of delivery with the lowest risk. Nationwide surveys in the 1950s that employed phantom measurements and scaling factors to estimate doses to the maternal ovaries and the fetus (Bewley *et al.*, 1957; Clayton *et al.*, 1957) revealed that few x-ray machines had light-beam diaphragms to restrict the x-ray beam to the useful area of an x-ray film. For general diagnostic examinations, doses to the ovaries ranged over nearly five orders of magnitude (from 10^{-4} mGy to 5 mGy) with lowest doses when only scattered radiation reached the ovaries and highest doses if the ovaries were in the direct beam. For obstetrical examinations, doses to the maternal ovaries and fetus ranged over two orders of magnitude from obstetrical abdominal x-ray procedures and over 16-fold (ranging from 1.4 to 22 mGy per x-ray film) from pelvimetry depending upon the projection used (Matthews and Miller, 1969; MH, 1966; Mole, 1990). From a 1958 survey, the numbers of films for obstetric examinations varied; the average obstetrical abdominal examination included 1.2 films per examination and a fetal whole-body dose of 5 mGy, and a pelvimetry examination involved 1.5 films per examination and a fetal whole-body dose of 11 mGy (Mole, 1990).

Based on survey data from the Oxford Survey of Childhood Cancer (Oxford Survey) carried out in the United Kingdom, Mole (1990) found that the proportion of women undergoing obstetric radiological examinations rose from 5 % in the mid-1940s to 13 % in the mid-1950s, then declined temporarily to ~10 % in 1960 before gradually increasing to ~12 % in the late 1960s. With the advent of ultrasonography in clinical practice in the 1970s, obstetrical radiological examinations steadily declined from the mid-1970s onward as ultrasonography replaced obstetrical diagnostic procedures utilizing ionizing radiation. Patterns similar to those observed in the United Kingdom were observed in the United States (Shu *et al.*, 2002). Nevertheless, pregnant women still undergo clinically-important imaging procedures for pulmonary embolus, renal colic, urinary-tract diseases, appendicitis, injuries from trauma, and other examinations with typical doses shown in Table 3.2. A recent

report described notable annual increases in higher-dose imaging procedures in pregnant women (*e.g.*, CT examinations increasing by 25 % per year and nuclear medicine procedures increasing by 12 % per year) during 1997 to 2006 (Lazarus *et al.*, 2009).

As seen in Table 3.2, certain CT, fluoroscopic, and nuclear medicine procedures are characterized by higher doses to the embryo or fetus than other types of radiological examinations. Often, the dose for a procedure declines with increasing gestational age because the increase in body mass of the fetus is more dominant than the increase in radiation level to the larger fetus (Osei and Faulkner, 1999; Russell *et al.*, 1997). However, fetal dose may increase when the fetal uptake and placental transfer of radiopharmaceuticals such as ^{123}I sodium iodide increases with increasing gestational age (Russell *et al.*, 1997; Stabin *et al.*, 1991; Tran *et al.*, 2010; Watson *et al.*, 2005). Estimated doses to the embryo or fetus from multidetector CT protocols may be greater than doses from single-detector CT (Thornton *et al.*, 2003). The estimated range in dose to the embryo at zero months and the fetus at three months for implementation of the multidetector CT protocols for pulmonary embolus was 0.2 to 0.5 mGy and 0.6 to 0.7 mGy, respectively, and the dose was substantially higher at zero and three months for renal stone colic (8 to 12 mGy and 4 to 7 mGy) and appendicitis protocols (15 to 17 mGy and 20 to 40 mGy) (Hurwitz *et al.*, 2006).

5.2.6.1.1 *Epidemiologic case-control studies.* The relationship of *in utero* medical diagnostic radiation with increased risk of childhood cancer was first described more than 55 y ago (Giles *et al.*, 1956; Stewart *et al.*, 1958) in the Oxford Survey. Summarized in Table 5.14 are the Oxford Survey and subsequent reports from case-control studies in Canada, China, Finland, Germany, Italy, Japan, Sweden, The Netherlands, the United Kingdom, and the United States which include those with a minimum of 200 total childhood cancer cases, at least 100 cases of acute lymphoblastic leukemia, or at least 80 cases for each of the other types of childhood cancer.

- *Risk for all childhood cancers combined*: The Oxford Survey initially reported a statistically-significant twofold increase in total childhood cancer mortality risks in offspring (0 to 14 y of age) of mothers undergoing abdominal diagnostic x-ray procedures compared to mortality risks in total childhood cancer in children of women not undergoing radiological procedures during pregnancy (Giles *et al.*, 1956). That report generated skepticism in part because the results were

TABLE 5.14—*Risk of specific and total childhood cancers in offspring of women undergoing prenatal diagnostic x-ray procedures: Case-control studies (adapted from Little, 1999b).*[a]

Reference, Country, Birth Years	Number of Cases / Number of Controls	Type of Control	Source of X-Ray Procedure Information	Controls with Abdominal X-Ray Procedures (%)	Estimated RR (95 % CI)		
					Any X-Ray Procedure	Abdominal Procedure	Pelvimetry
Acute Lymphoblastic Leukemia							
Bithell and Stewart (1975)[b], United Kingdom, 1943 – 1967	2,007 / 8,513	Population	Interview, medical records, questionnaire	11.5		1.5 (1.3 – 1.8)	
Van Steensel-Moll *et al.* (1985), The Netherlands, 1959 – 1980	517 / 509	Population	Questionnaire	3.7		2.2 (1.2 – 3.8)	
Shu *et al.* (1988), Shanghai, China, 1960 – 1986	172 / 618	Population	Interview	7.1	1.6 (0.9 – 2.8)	2.0 (0.7 – 3.8)	
Magnani *et al.* (1990), Turin, Italy, years not provided	142 / 307	Hospital	Interview	5.5		1.1 (not provided)	
Naumburg *et al.* (2001), Sweden, 1973 – 1989	449 / 450	Population	Medical records	9.8	1.0 (0.6 – 1.7)	1.1 (0.8 – 1.6)	
Shu *et al.* (2002), United States and Canada, 1972 – 1992	1,842 / 1,986	Population	Interview	6 (before 1980) 2.3 (1981–1986) 1.8 (after 1986)		1.2 (0.8 – 1.7) (all ages) 2.4 (1.2 – 5.0) (ages 11 – 14 y)	
Acute Myeloid Leukemia							
Bithell and Stewart (1975)[b], United Kingdom, 1943 – 1967	866 / 8,513	Population	Interview, medical records, questionnaire	11.5		1.5 (1.2 – 1.8)	

Shu *et al.* (1988) Shanghai, China, 1960 – 1986	92 / 618	Population	Interview	7.1	1.4 (0.6 – 3.0)	0.6 (0.1 – 5.0)
Van Duijn *et al.* (1994) The Netherlands, 1969 – 1979	80 / 240	Population	Questionnaire	3		2.4 (0.8 – 7.0)
All Leukemias						
Kaplan (1958), California, United States, 1943 – 1967	150 / 150	Friends	Interview	16		1.7 (1.1 – 2.7)
Polhemus and Koch (1959), Los Angeles, California, years not provided	251 / 251	Hospital	Questionnaire	23.1		1.2 (0.8 – 1.8)
Graham *et al.* (1966) Baltimore, Minneapolis, New York State (Tristate Study), 1969 – 1979	313 / 854	Population	Medical records	23.4		1.4 (0.9 – 2.3)
Salonen and Saxen (1975) Finland, 1945 – 1968	373 / 373	Population	Medical records	49.3	1.0 (0.5 – 1.9)	
Hirayama (1979), Japan, 1969 – 1977	4,607 / 5,968	Other cancers	Not provided	10.6	1.6 (1.4 – 1.8)	
Monson and MacMahon (1984)[c], Northeast United States, 1947 – 1960	704 / 14,276	Hospital	Medical records	9.4		1.5 (1.2 – 2.0)[d]
Shu *et al.* (1994), Shanghai, China, 1986 – 1991	166 / 166	Population	Interview	7.1	2.4 (0.5 – 10.6)	
Infante-Rivard *et al.* (2000), Infante-Rivard and Deadman (2003), Canada, 1980 – 1993	701 / 701	Population	Interview			0.8 (0.6 – 1.3)
Rajaraman *et al.* (2011) United Kingdom, 1976 – 1996	1,253 / 4,857	Population	Medical records	1.2		1.4 (0.9 – 2.0)

TABLE 5.14—(*continued*)

Reference, Country, Birth Years	Number of Cases / Number of. Controls	Type of Control	Source of X-Ray Procedure Information	Controls with Abdominal X-Ray Procedures (%)	Estimated RR (95 % CI)		
					Any X-Ray Procedure	Abdominal Procedure	Pelvimetry
CNS Tumors							
Bithell and Stewart (1975)[b], United Kingdom, 1943 – 1967	1,332 / 8,513	Population	Interview, medical records, questionnaire	11.5		1.4 (1.2 – 1.7)	
Salonen and Saxen (1975) Finland, 1945 – 1968	245 /245	Population	Medical records	49.3			1.1 (0.3 – 4.2)
Preston-Martin *et al.* (1982), Los Angeles, California, 1948 – 1977	209 / 209	Friends, neighborhood	Interview	15.0		1.3 (not provided)	
Monson and MacMahon (1984)[c], Northeast United States, 1947 – 1960	298 / 14,276	Hospital	Medical records	9.4		1.2 (0.8 – 1.7)[e]	
Bunin *et al.* (1994) Greater Delaware Valley, 1980 – 1986	155 astro / 321 66 PNET / 321	Population	Interview			1.1 (0.3 – 3.9) 0.8 (0.3 – 2.3)	
Schuz *et al.* (2001) Germany, 1988 – 1993	466 / 2,458	Population	Interview			0.8 (0.4 – 1.4)	
Stalberg *et al.* (2007) Sweden, 1975 – 1984	512 / 524 (total CNS) 105 PNET / 524 191 astro / 524	Population	Medical records, registry	9.1		1.1 (0.7 – 1.6) 1.7 (0.9 – 3.2) 0.8 (0.4 – 1.5)	
Rajaraman *et al.* (2011) United Kingdom, 1976 – 1996	482 / 4,857	Population	Medical records	1.2		1.1 (0.6 – 1.8)	

Neuroblastoma					
Bithell and Stewart (1975)[b], United Kingdom, 1943 – 1967	720 / 8,513	Population	Interview, medical records, questionnaire	11.5	1.5 (1.2 – 1.8)
Bone Tumors					
Bithell and Stewart (1975)[b], United Kingdom, 1943 – 1967	244 / 8,513	Population	Interview, medical records, questionnaire	11.5	1.1 (0.7 – 1.7)
Ewing's Sarcoma					
Winn *et al.* (1992) United States, multicenter, years not provided	204 / 204 191 / 191	Population Siblings	Interview Interview	27.5 17.3	0.8 (0.5 – 1.2) 1.5 (0.8 – 3.2)
Rhabdomyosarcoma					
Grufferman *et al.* (2009) United States, multicenter, 1962 – 1988	319 / 319	Population	Interview	6.8	1.4 (0.7 – 2.9)
Total Childhood Cancer					
Bithell and Stewart (1975)[b], United Kingdom, 1943 – 1967	8,513 / 8,513	Population	Interview, medical records, questionnaire	11.5	1.5 (1.3 – 1.6)
MacMahon (1962)[c] Northeast United States, 1947 – 1954	556 / 7,230	Hospital	Medical records	10.6	1.5 (1.2 – 1.8)[d]

TABLE 5.14—(*continued*)

Reference, Country, Birth Years	Number of Cases / Number of. Controls	Type of Control	Source of X-Ray Procedure Information	Controls with Abdominal X-Ray Procedures (%)	Estimated RR (95 % CI)		
					Any X-Ray Procedure	Abdominal Procedure	Pelvimetry
Monson and MacMahon (1984),[c] Northeast United States, 1947 – 1960	1,342 / 14,276	Hospital	Medical records	9.4		1.3 (0.95 – 1.7)[d]	
Rajaraman *et al*. (2011) United Kingdom, 1976 – 1996	2,690 / 4,857	Population	Medical records	1.2		1.1 (0.9 – 1.4)	

[a]RR and CI values are presented to one decimal place (rounded), except one CI value is presented as 0.95 (rather than 1.0).

[b]Initial Oxford Survey of Childhood Cancer Case-Control Study (Stewart *et al*., 1958) was extended to include 12 additional birth years and an increase to 8,513 cancer cases from 1,299 in the original study (Bithell and Stewart, 1975). A third publication from the same investigation included cases born during 1948 to 1978 who died during 1953 to 1979 (Knox *et al*., 1987).

[c]Initial study by MacMahon (1962) was extended by Monson and MacMahon (1984) to include five additional hospitals, six additional birth years, seven additional years of childhood cancer deaths, and an increase to 1,429,400 children from 734,243 in the original study.

[d]Results for children who died from cancer before their 10th birthday.

[e]Results for children who died from cancer before their 20th birthday; CI computed from data in Monson and MacMahon (1984).

based on interview reports by mothers rather than medical records and the possibility of response bias could not be discounted (*i.e.*, mothers of children who died of cancer might have better memories of their prenatal circumstances than mothers of normal children). However, more notice was taken when the increase persisted after substantially larger number of cases and controls were accrued (Bithell and Stewart, 1975; Knox *et al.*, 1987) and a medical record-based investigation in the northeast United States reported a 1.5-fold statistically-significant increased risk of childhood cancer mortality (before 10 y of age) in offspring of mothers who underwent diagnostic radiographic examinations compared with cancer occurrence in children of women who had no radiological procedures during pregnancy (MacMahon, 1962). A lower 1.3-fold risk (95 % CI = 0.95 to 1.7) of all cancers in childhood (before 10 y of age) was subsequently reported in the combined extended northeast U.S. study (Monson and MacMahon, 1984) (Table 5.14).

Doll and Wakeford (1997) noted that efforts to derive estimates of the risk per gray from the case-control studies depend upon the estimated doses to the embryo and fetus from the diagnostic radiographic examinations. Estimated *in utero* doses ranged more than threefold for diagnostic radiographic procedures in the mid-1940s, close to 2.5-fold in the early 1950s, close to twofold in the late 1950s, and relatively little in the early 1960s (Bithell and Stiller, 1988; ICRP, 2003; Mole, 1990; Muirhead and Kneale, 1989; Stewart and Kneale 1970; UNSCEAR, 1972). Using calendar time-specific dose estimates from UNSCEAR (1972) or assumed mean doses ranging from 6 to 10 mGy, the corresponding EARs of cancer mortality under 15 y of age primarily modeled from the Oxford Survey ranged from 500 to 650 $(10^4 \text{ PY Gy})^{-1}$ (an excess absolute risk coefficient of 5 to 6.5 % Gy^{-1}) (Doll and Wakeford, 1997; ICRP, 2003). Although noting that the exact values of the risk coefficient for total cancer incidence under 15 y of age following low *in utero* doses of the order of 10 mGy was uncertain, Doll and Wakeford (1997) concluded that the excess absolute risk coefficient for total cancer incidence (essentially the same as for mortality for the Oxford Survey) was ~6 % Gy^{-1} (2.5 % Gy^{-1} for leukemia), which were the estimates adopted by the National Radiological Protection Board for childhood cancer incidence under 15 y of age (Muirhead *et al.*, 1993).

- *Risks for major categories of childhood cancer:*
  - *Leukemia*: A 2008 meta-analysis of 32 case-control studies of childhood leukemia (Wakeford, 2008) supported the statistical association originally reported in the 1956 report from the Oxford Survey. If the Oxford Survey and two others with methodological issues are omitted, the resulting estimated RR of 1.3 (95 % CI = 1.2 to 1.5) was similar although slightly lower than the estimated RR of 1.5 (95 % CI = 1.3 to 1.7) based on the 4,052 childhood leukemia cases in the Oxford Survey (Bithell and Stewart, 1975). In a hospital record-based large case-control study nested in a cohort of births identified in 42 hospitals in the northeast United States, Monson and MacMahon (1984) reported a statistically-significant increase in risk for total leukemia (RR = 1.5; 95 % CI = 1.2 to 2.0) among offspring of women who underwent abdominal x-ray examinations during pregnancy compared with nonexposed pregnant women, but a lower risk for all solid cancers in offspring of exposed versus unexposed pregnant women. This study had less potential for bias than most of the case-control studies of diagnostic x-ray procedures and risk of childhood cancer as well as substantially greater statistical power than the cohort studies. Similarly, Rajaraman *et al*. (2011), for a large population-based study from the United Kingdom that utilized medical records as the primary source of information, reported a similar elevated risk, albeit not statistically significant among offspring of women undergoing abdominal x-ray procedures during pregnancy compared with nonexposed pregnant women, although the percentage of mothers of cases and controls undergoing abdominal x-ray procedures during pregnancy was much smaller (Table 5.14). Compared with the 1.5- to 2.2-fold increased risks of childhood acute lymphoblastic leukemia in offspring of mothers undergoing abdominal or pelvic diagnostic x-ray procedures reported in earlier studies (Bithell and Stewart, 1975; Shu *et al*., 1988; van Steensel-Moll *et al*., 1985), risks were substantially lower or not increased in more recent studies (Magnani *et al*., 1990; Naumburg *et al*., 2001; Shu *et al*., 2002). The Swedish study is of note because it was nationwide with complete ascertainment of both leukemia cases (n = 652) and medical x-ray procedures abstracted from hospital records (Naumburg *et al*., 2001). Naumburg *et al*. (2001)

speculated that the likely lower fetal doses from x-ray procedures in the then modern era were lower than in years past and thus was a possible reason for the absence of a statistically-significant association. Risks of childhood acute myeloid leukemia were increased 1.5- to 2-fold among offspring in two (Bithell and Stewart, 1975; Van Duijn *et al*., 1994) but not a third study (Shu *et al*., 1988) comparing mothers undergoing versus those not undergoing diagnostic radiographic examination of the abdomen (Table 5.14).

- *Central nervous system tumors*: In the Oxford Survey, the estimated RR for all solid tumors was 1.5 (95 % CI = 1.3 to 1.6) and was similar to that for leukemia (RR = 1.5, 95 % CI = 1.3 to 1.7). The RR in the Oxford Survey for CNS tumors was 1.4 (95 % CI = 1.2 to 1.7) (Bithell and Stewart, 1975). For the large studies based on medical records, the initial and extended northeast U.S. studies combined did not find a statistically-significant increase of CNS tumors based on 298 cases who died up to 20 y of age (RR = 1.2; 95 % CI = 0.8 to 1.7) (Monson and MacMahon, 1984). Except for the Oxford Survey, all other studies of brain tumors did not find statistically-significant increases (Bithell and Stewart, 1975; Bunin *et al*., 1994; Monson and MacMahon, 1984; Preston-Martin *et al*., 1982; Rajaraman *et al*., 2011; Schuz *et al*., 2001) (Table 5.14).
- *Other childhood cancers*: A limited number of case-control studies have assessed risks of other childhood tumors, but most did not attain the minimum population size required for inclusion in Table 5.14. One matched case-control study of 104 cases of neuroblastoma was of interest, given the rarity of this condition, and reported a nonstatistically-significant odds ratio of 1.17 for pelvic or abdominal x rays during pregnancy (Kramer *et al*., 1987). Unfortunately, there were insufficient details for further evaluation. However, the Oxford Survey did evaluate practically all childhood tumors and analyses of each cancer type were statistically robust, specifically for cancers of the CNS, neuroblastoma, Wilms tumor, lymphoma, bone tumor, and all other solid tumors combined (Bithell and Stewart, 1975). Except for bone tumor, all the leukemia subtypes (myeloid and lymphatic), lymphoma and all the individual solid cancers had statistically-significant increased risks of approximately the

same magnitude (*i.e.*, RRs of the order of 1.4 to 1.5). The initial and extended northeast U.S. studies combined did not find a statistically-significant increase of solid cancers excluding CNS tumors based on 340 cases who died up to 20 y of age (RR = 1.1; 95 % CI = 0.8 to 1.7) (Monson and MacMahon, 1984).

- *Risk by trimester, reasons for examination, and number of x-ray films used*: Only a few epidemiologic studies have assessed risks in relation to the timing of diagnostic radiological examinations during pregnancy. Approximately 90 % of the diagnostic x-ray procedures in the Oxford Survey were performed in the third trimester compared with ~1 % in the first trimester of pregnancy, although virtually all of the former were obstetrical examinations whereas most of the latter were for other clinical conditions. Based on small numbers of cancer cases (n = 38) occurring among offspring who were exposed during the first trimester compared with the numbers among offspring exposed during the third trimester, the estimated RR was 8.4 (95 % CI = 3.5 to 22.7) compared with 1.4 (95 % CI = 1.3 to 1.6) in the third trimester (Bithell and Stewart, 1975). The data from the northeast U.S. study were noninformative as only 10 cases had exposures in the first or second trimester (Monson and MacMahon, 1984). The types of radiographic procedures in the Oxford Survey varied by the time period (given in the survey as postconception), since nonobstetric examinations comprised 82 % of examinations in the first seven weeks postconception (with a substantial fraction involving fluoroscopy), 27 % in 8th to 24th weeks postconception, but only 4 % in 25th to 38th weeks postconception (Mole, 1990). Data from the Oxford Survey also revealed that the ratio of total films (*e.g.*, the number of offspring exposed *in utero* times the mean number of x-ray films per exposed offspring) was higher in cases compared with controls in the first trimester (case-control ratio = 2.45) than in the third trimester (case-control ratio = 1.38) (Gilman *et al.*, 1988). Data from the Oxford Survey on the number of x-ray films used in third trimester radiological examinations, which were derived from hospital records (and when this did not exist on an estimate by the hospital of the likely number of films), were reported to show an increasing risk of childhood cancer associated with increasing number of films per examination (Bithell, 1989; Wakeford, 2008). The number of films per examination depended in part on recall of past events (not

only the mother, but by hospital personnel) that could not be checked (Mole, 1990). Retake examinations because of poor film quality or incorrect machine settings were usually not recorded or recalled.

- *Geographic variation and time trends in risk*: Detailed review of the case-control epidemiologic studies revealed geographic differences in the proportions of mothers undergoing pelvimetry or abdominal x-ray procedures within and among countries (Linet *et al*., 2009) and over time (Shu *et al*., 2002; Totter and MacPherson, 1981). In the Oxford Survey, there was a general decline in risks of childhood cancer in relation to *in utero* radiation exposure from the mid-1940s to the more recent birth cohorts. Introduction of faster films and other technical changes in the late 1950s likely led to a reduction in doses.
- *Confounding*: Confounding can result in a distortion in the level of association between an exposure and an outcome in an epidemiologic study. Similar to bias, confounding can lead to a systematic error and may result in incorrect conclusions. A confounder is an exposure or factor that is associated with the exposure under study, is an independent risk factor for the outcome, is *not* an intermediate step in the causal chain between the exposure under study and outcome, and must be present to a lesser or a greater extent in the study group versus the comparison group. As an example of a confounder, cigarette smoking has been linked with increased risk of motor vehicle injuries in some studies. To evaluate the association between cigarette smoking and injuries from motor vehicle accidents, it is important to consider potential confounding exposures. Cigarette smoking is associated with alcohol consumption. Alcohol drinking is a well-known risk factor for motor vehicle injuries. To evaluate the role of cigarette smoking in occurrence of motor vehicle injuries, it is important to consider confounding by alcohol consumption. Concerns that the observed associations between *in utero* diagnostic x-ray procedures and elevated childhood cancer risk in offspring might be confounded by medical indication led to analyses according to the reasons for the x-ray tests. The associations were still apparent when the data were separately assessed according to the reason for the diagnostic radiological examination (Knox *et al*., 1987). In the medical record-based northeast U.S. study, there was no evidence of confounding by the factors that were evaluated (Monson and MacMahon, 1984).

5.2.6.1.2 *Epidemiologic cohort studies*

- *Singletons*: Cohort investigations to assess childhood cancer risks among those undergoing diagnostic x-ray procedures *in utero* included radiation-exposed populations ranging in size from <200 to close to 40,000 children. As shown in Table 5.15, the point estimates for RRs for total cancer ranged from 0.7 (95 % CI = 0.3 to 1.8) to 4.6 (95 % CI = 0.9 to 25.1) and for leukemia ranged from 0.4 (95 % CI = 0.1 to 2.6) to 1.6 (95 % CI = 0.6 to 4.6). There were 61 total childhood cancers, including 24 leukemias in all cohorts combined. Confidence intervals (CI) for the RR estimates for total cancer or for the subset of leukemias for each of the studies included the value 1.0. All of the estimates were based on small numbers; there were 13 or fewer total exposed cancer cases in each cohort.

  Doll and Wakeford (1997) evaluated most of the studies shown in Table 5.15 (including Diamond *et al*., 1973; Griem *et al*., 1967; Hagstrom *et al*., 1969; Lejeune *et al*., 1960; Lewis, 1960; Magnin, 1962) and calculated an estimated composite RR for total childhood cancer of 1.2 (95 % CI = 0.7 to 2.0). Subsequently, ICRP (2003) estimated a composite RR for total childhood cancer of 1.1 (95 % CI = 0.8 to 1.5). The CIs from both estimates are compatible with the composite risk estimate of a 30 % increase from the case-control studies and with a composite risk estimate compatible with no evidence of an increase in risk, but cautious interpretation of the likely magnitude of the risk is needed in view of the small number of childhood cancer cases, the likely heterogeneity among studies, the variation in types of childhood cancer outcomes, and the failure to take into consideration in one study (Hagstrom *et al*., 1969) the use of a radionuclide and known familial and genetic factors.

  For comparison, only one cancer death (a liver cancer) occurred among the 1,292 children who were *in utero* at the time of the atomic bombings of Hiroshima and Nagasaki and were followed up for mortality for 10 y. This result was similar to the expected mortality of 0.75 deaths from cancer. There were no leukemia deaths in this group (ICRP, 2003; Jablon and Kato, 1971). In a later follow-up of mortality during 1950 to 1984 of 1,630 offspring of atomic-bomb survivors who were *in utero* at time-of-exposure, there were 18 deaths from cancer including the child who died from liver cancer at 6 y of age, a child who was diagnosed with Wilms tumor at 14 y of age, and two young persons diagnosed with

TABLE 5.15—*Cancer mortality rates in cohorts of children whose mothers underwent diagnostic x-ray procedures during pregnancy.*[a]

Reference, Location	Number of Cancer Deaths;[b] Number of Children Exposed *In Utero*	Total Cancer [RR (95 % CI)]	Leukemia [RR (95 % CI)]
Murray *et al*. (1959) (Rochester)	3 (L); ~6,740[c]		0.9 (0.3 – 3.1)
Court Brown *et al*. (1960) (Edinburgh)[d]	9 (L); 39,166		0.9 (0.4 – 1.6)
Lewis (1960) (London)	1 (L); 11,443		0.4 (0.1 – 2.6)
Griem *et al*. (1967) (Chicago)	4 (1 L, 3 O); 982	1.2 (0.4 – 4.0)	
Oppenheim *et al*. (1974; 1975) (Chicago)[e]	1 (L); 939		0.7 (0.1 – 5.0)
Diamond *et al*. (1973) (Baltimore)	13 (6 L, 7 O); 19,889	1.1 (0.5 – 2.1)	1.6 (0.6 – 4.6)
Shiono *et al*. (1980) (United States, multicenter)	7; ~5,000[f]	1.1 (0.5 – 2.4)	
Golding *et al*. (1990) (United Kingdom, national)	12; ~3,000[g]	1.2 (0.6 – 2.5)	

TABLE 5.15—(*continued*)

Reference, Location	Number of Cancer Deaths;[b] Number of Children Exposed *In Utero*	Total Cancer [RR (95 % CI)]	Leukemia [RR (95 % CI)]
Combined small cohorts (ICRP, 2003)	7	4.6 (0.9 – 25.1)	
Dempster (1958)	[0; 148]		
Milis *et al*. (1958)	[0; 190]		
Lejeune *et al*. (1960)	[2; 491]		
Magnin (1962)	[1; 5,353]		
Nokkentved (1968)	[0; 152]		
Hagstrom *et al*. (1969)[h]	[4; 649]		
Ray *et al*. (2010) (Ontario, Canada)	4; 5,590	0.7 (0.3 – 1.8)	

[a]Adapted from Doll and Wakeford (1997) and ICRP (2003).

[b]The number of leukemias (L) and other cancers (O) are given when available.

[c]A total of 140,438 children under 20 y of age were included; ~6,460 of the 6,740 exposed mothers had pelvimetry or other abdominal x-ray procedures during pregnancy.

[d]Doll pointed out his concerns about the adequacy of the identification of irradiated women that arose when he tried to extend the Court Brown *et al*. (1960) study. Doll indicated that as a result some of the findings may be unreliable (Doll and Wakeford, 1997).

[e]Subsequent follow-up study of Griem *et al*. (1967).

[f]A total of 55,908 live births were studied; ~10 % of the mothers had abdominal x-ray procedures during pregnancy.

[g]A total of 16,193 live births were studied; ~18 % of the mothers had abdominal, nonabdominal or dental x-ray procedures during pregnancy.

[h]Exposure in Hagstrom *et al*. (1969) was to radioactive iron (^{59}Fe) administered during pregnancy. The RR and 95 % CI for this small cohort was 6.1 (1.7 to 15.8).

leukemia at 18 and 29 y of age; the remaining 14 cancers were all of types generally occurring in adults (Yoshimoto *et al*., 1988). A radiation dose-related increase in cancer mortality before 15 y of age could not be demonstrated due to the small number of cancers. A more comprehensive assessment and the latest results of follow-up of the offspring who were *in utero* are given in Section 5.2.6.6.

More recently, a record linkage of more than 1.8 million pregnant women from Ontario, Canada compared occurrence of childhood cancer in offspring of 5,590 mothers exposed to major radiodiagnostic testing in pregnancy with that in offspring of 1.83 million mothers not exposed and found a nonstatistically-significant reduction in risk (RR = 0.7; 95 % CI = 0.3 to 1.8) based on four childhood cancers (Ray *et al*., 2010). In addition to the small number of cases, the study is difficult to interpret because 68 % of the women received CT examinations of the head which would have resulted in negligible dose to the developing child.

- *Twin studies*: Because the association between *in utero* diagnostic x-ray procedures and childhood cancer risk could be confounded by maternal or fetal medical conditions prompting the diagnostic x-ray procedures, epidemiologic studies of twins were recommended to clarify whether confounding factors could explain the association since a high proportion of twins underwent pelvimetry to determine fetal positioning rather than for medical conditions (NA/NRC, 1980). The level of childhood leukemia risks associated with fetal diagnostic x-ray procedures in three important case-control twin studies (Harvey *et al*., 1985; Mole, 1974; Rodvall *et al*., 1990) was comparable with the risks observed in the case-control studies of singletons, with RRs for leukemia ranging from 1.7 to 2.2, although only the risk estimate from the study of twins in the Oxford Survey was statistically significant. Cancer risks have also been investigated in twin cohorts ranging in size from 13,000 to more than 125,000 (Hewitt *et al*., 1966; Inskip *et al*., 1991; Jackson *et al*., 1969; Murphy *et al*., 2001; 2008; Neale *et al*., 2005; Norris and Jackson, 1970; Rodvall *et al*., 1992; Windham *et al*., 1985). The observed number of total childhood cancers ranged from 14 to 166, and the number of childhood leukemias from 3 to 55. Risk ratios ranged from 0.7 to 1.0 for total cancer and from 0.7 to 1.1 for leukemia. The variation in results might reflect differences in study design, methods of analysis, or chance due to the rarity of childhood cancer. The

lower risk of childhood leukemia observed in twins (a substantial proportion of whom were exposed to radiation *in utero* from pelvimetry) compared with risks found in singletons should be interpreted with caution since other biological explanations (*e.g.*, low birth weight, intrauterine growth retardation, fivefold higher mortality in the first year of life, genetic factors) (Murphy *et al.*, 2001; Puumala *et al.*, 2009) conceivably may explain the decreased childhood cancer risk in twins compared with singletons in light of the increased frequency of prenatal x-ray exposure among twin pregnancies. Cancer risks in twins have not changed over time as pelvimetry has been replaced with ultrasonography (Inskip *et al.*, 1991).

5.2.6.1.3 *Other issues.* Data on early childhood exposure to diagnostic x-ray procedures and childhood cancer risks are more limited and results inconsistent (Bartley *et al.*, 2010; Hammer *et al.*, 2011; Linet *et al.*, 2009; Rajaraman *et al.*, 2011; Schulze-Rath *et al.*, 2008) with few exceptions. Pearce *et al.* (2012) found that use of CT scans in 174,604 children in the United Kingdom was associated with statistically-significant increases in radiation dose response for leukemia [ERR mGy^{-1} (active bone marrow) = 0.04; 95 % CI = 0.005 to 0.1; $p = 0.01$; $n = 74$ cases] and brain tumors [ERR mGy^{-1} (brain) = 0.02; 95 % CI = 0.01 to 0.05; $p < 0.0001$; $n = 135$ cases]. A substantial proportion of the cases (41 % for those developing leukemia and 47 % of those developing brain tumors) underwent more than one CT scan. Compared with patients who received an active bone marrow dose of <5 mGy, the RR of leukemia for patients who received a cumulative dose of 30 mGy was 3.2 (95 % CI = 1.5 to 6.9) and the RR of brain tumors for patients who received a cumulative mean dose (brain) of 60 mGy was 2.8 (95 % CI = 1.3 to 6.0). Ongoing studies of cancer risks following administration of pediatric CT scans (particularly if long-term monitoring is undertaken) will be helpful for identifying childhood and adult cancer risks and clarifying the existence of dose-response relationships.

Repeated diagnostic x-ray procedures in adolescents and young women monitored for scoliosis have been associated with increased breast cancer risks later in life (mean dose to the breast was 0.12 Gy and the ERR Gy^{-1} for breast cancer incidence was 2.9; $p = 0.06$) (Ronckers *et al.*, 2008; 2010). The studies found no evidence of excess lung cancer or leukemia. A slight excess of cancer (RR = 1.6; 95 % CI = 0.4 to 4.1) occurred in 4,891 Canadian children with congenital heart disease who underwent cardiac catheterization during 1946 to 1968, and a nonstatistically-significant increase of leukemia was observed on additional follow-up of a subset. The

findings were based on five total childhood cancers, including three leukemias (McLaughlin *et al*., 1993; Spengler *et al*., 1983). Among 675 Israeli children who underwent cardiac catheterization for congenital anomalies during 1950 to 1970, there was a statistically-significant cancer excess (RR = 2.3; 95 % CI = 1.2 to 4.1), due to increased risks of lymphomas and melanomas (Modan *et al*., 2000), cancers that have not clearly been linked to ionizing radiation in other studies (UNSCEAR, 2011). Larger and pooled studies in children undergoing cardiac catheterization would be helpful in clarifying cancer risks associated with these radiation exposures. Recent and ongoing advances in genomics and other molecular work will hopefully identify the genetic basis of the increased susceptibility or resistance to radiation-related leukemia and other cancers in children and adults, clarify the biological basis and functional nature of genetic characteristics associated with cancer risks, and ascertain potential interactions of genes and other host factors with radiation.

5.2.6.2 *Medical Exposures: Therapeutic*. There is limited information on cancer risks in offspring of mothers undergoing radiation treatment for cancer during pregnancy (de Wildt *et al*., 2009; Jacobs *et al*., 1981; Spitzer *et al*., 1991; Woo *et al*., 1992). The paucity of data is likely due to clinical recommendations to avoid or limit use of radiation therapy in pregnant women (Scarth *et al*., 2002) and/or to the subsequent fetal loss associated with sufficiently high doses to the developing fetus. Compared to women not receiving radiation therapy during pregnancy, those undergoing radiation treatment when pregnant had higher rates of medical terminations of pregnancy because of fear of possible injury to the fetus (Fenig *et al*., 2001; Green *et al*., 2002) and greater fetal loss in pregnancies (Chiarelli *et al*., 2000). Some patients undergoing radiation therapy also experience problems with fertility and other reproductive disorders. The literature on cancer risks in offspring generally provides descriptive case report information only on small numbers of outcomes that preclude accurate quantitative estimates of childhood cancer risks (*e.g*., Mulvihill *et al*., 1991). For example, in a series of 775 women treated for Hodgkin's lymphoma at a single large referral institution, 25 (3.2 %) were pregnant at diagnosis, including seven who were in the first trimester, 10 in the second trimester, and eight in the third trimester (Woo *et al*., 1992). The investigators reported that none of the offspring had developed a malignancy, but the length of follow-up varied from 1 y to as many as 35 y. More importantly, statistical power was limited for evaluating even the most common types of childhood cancer.

5.2.6.3 *Occupational Exposures: Nuclear Industry.* A few case-control studies investigating risks of cancer in young persons living in proximity to nuclear plants have observed increased incidence of leukemia and non-Hodgkin's lymphoma, particularly in relation to the Sellafield Nuclear Fuel Reprocessing Plant, the Dounreay Nuclear Energy Plant, and the Aldermaston and Burgfield Nuclear Weapons Producing Plants in the United Kingdom (Gardner *et al*., 1990; Urquhart *et al*., 1991). To evaluate reasons for the sustained excesses of childhood leukemia and lymphoma that were observed in the village of Seascale near Sellafield, Gardner *et al*. (1990) conducted a case-control study and reported an association between leukemia and lymphoma in young persons and paternal preconception exposure. To further evaluate the potential relationship between leukemia in persons under 25 y of age and parental occupational exposure to ionizing radiation, the Nuclear Industry Family Study was undertaken which examined cancer risks in 39,557 children of male workers and 8,883 children of female workers. The offspring ranged from less than one month to 58 y of age. The median length of follow-up was ~23 y for both groups. Of the 111 children who developed a malignancy before 25 y of age (28 diagnosed with leukemia), standardized incidence ratios were not increased for offspring of mothers (or fathers) and there was no leukemia in children of women who were monitored for external sources of ionizing radiation (Roman *et al*., 1999). Relatively few children in this very large study had mothers whose work in the nuclear industry required monitoring and thus even this very large study could not contribute dose-response information about occupational radiation exposures during pregnancy and risk of childhood leukemia.

5.2.6.4 *Occupational Exposures: Medical Radiation Workers.* Childhood cancer in offspring of medical radiation workers has been investigated in two cohort studies. In the United Kingdom, Roman *et al*. (1996) obtained information from a high proportion of female and male members 30 to 64 y of age of the College of Radiographers and observed little difference in adverse reproductive events between women (n = 4,847) and men (n = 662). Overall, the difference in risk was not statistically significant [observed to expected (O/E) ratio = 1.2; 95 % CI = 0.7 to 2.0] based on the 16 cancers (11 in offspring of women, five in offspring of men) diagnosed in the 7,607 live-born children. There was no excess risk in offspring of women (O/E = 1.0; 95 % CI = 0.5 to 1.8) and a nonstatistically-significant increase in men (O/E = 2.7; 95 % CI = 0.9 to 6.5) based on small numbers. The dose response could not be evaluated because dose records could not be accessed.

Cancers diagnosed prior to 20 y of age were examined among 105,950 offspring born during 1921 to 1984 to members of the U.S. radiologic technologists' cohort (Johnson *et al*., 2008a). There were 145 childhood hematopoietic and lymphoproliferative malignancies (111 diagnosed in offspring of female radiologic technologists, 34 in offspring of male radiologic technologists) and 149 childhood solid tumors (115 diagnosed in offspring of female radiologic technologists, 34 in offspring of male radiologic technologists). The mean estimated *in utero* doses in the offspring of both male and female radiologic technologists declined about four- to sixfold from the 1930s through the 1970s and 1980s. Among female radiologic technologists, there was no statistically-significant increase in risk or dose response for leukemia, lymphoma, all solid tumors combined, or childhood cancer in their offspring overall in relation to *in utero* radiation exposure (*in utero* dose ranged from 0 to 13 mGy). Based on 48 cases of lymphoma in offspring of female radiologic technologists, risks ranged from two- to threefold, elevated in all dose categories, but there was no statistically-significant linear trend. Overall, there was no convincing evidence of an increased risk of childhood cancer in the offspring of radiologic technologists in relation to the estimated maternal *in utero* doses.

5.2.6.5 *Environmental Exposures: Ubiquitous Background Radiation*. To address concerns raised in ecologic studies showing statistically-significant positive correlations between county radon levels in the United Kingdom and mortality from acute lymphoblastic leukemia in children (Mole *et al*., 1990), case-control studies were carried out in which radon detectors were placed in children's residences (Lubin *et al*., 1998; Steinbuch *et al*., 1999). Kendall and colleagues have been evaluating the possible role of exposure to low-level natural background ionizing radiation and have developed risk models and used age-specific active bone marrow dose estimates to calculate the proportion of childhood leukemia incidence in Britain resulting from this exposure (Kendall *et al*., 2009; Little *et al*., 2009; Wakeford *et al*., 2009). Recently these investigators reported findings from a large record-based case-control study including 27,447 childhood cancer cases (9,058 total leukemias) (children 0 to 14 y of age) and 36,793 matched controls. Using the mother's residence at the time of birth to estimate radiation exposure, the investigators calculated cumulative risks from birth to diagnosis and found a statistically-significant ERR mGy^{-1} (cumulative active bone marrow, gamma rays) for total childhood leukemia (RR = 1.1; 95 % CI = 1.03 to 1.2), but nonstatistically-significant increases for other childhood cancers (Kendall *et al*., 2013).

The possible role of radiation exposure in occurrence of childhood cancer in offspring of mothers exposed to background radiation during pregnancy has not been specifically evaluated, although it would be almost impossible to ascertain prenatal exposures separately from postnatal exposures since the exposures are ubiquitous.

5.2.6.6 *Environmental Exposures: Man-Made (Japanese atomic-bomb survivors, nuclear reactor accidents, weapons tests, and residential proximity to radionuclide contaminants or nuclear plants)*. As early as 1966, the Atomic Bomb Casualty Commission (now RERF) reported on mortality and cancer incidence among Japanese survivors who were *in utero* at the time of the bombings of Hiroshima and Nagasaki (Kato and Keehn, 1966). Although there was no evidence of a dose-related increase in cancer mortality at ages prior to 15 y among the ~2,500 persons who were *in utero* at the time of the bombings (Kato, 1971), as the cohort has grown older, a statistically-significant ERR of solid cancers became apparent (ERR = 2.1 Gy^{-1}; 90 % CI = 0.2 to 6.0), based on 10 deaths among those with weighted uterine doses >0.01 Gy (Delongchamp *et al*., 1997). In a follow-up of cancer mortality risks during 1950 to 1992 comparing risks among a subset of persons who were *in utero* versus those who were 0 to <6 y of age at the time of the bombings, there were only two deaths from leukemia (both exposed to relatively low doses and none during childhood) in the *in utero* cohort versus 24 among children <6 y of age at exposure (Delongchamp *et al*., 1997). The small numbers of deaths from leukemia in the *in utero* cohort and the absence of a dose-response relationship complicate efforts to compare the leukemia mortality risks in the *in utero* versus the early childhood cohort. Subsequently, Preston *et al*. (2008) compared solid cancer incidence risks among *in utero* cohort members 12 to 55 y of age during 1958 to 1999 (based on 94 cancers) with risks among survivors who were younger than 6 y of age at the time of the bombings (based on 649 cancers) (Table 5.16). Increasing ERRs with increasing weighted uterine dose were apparent in both groups. Using an effect modification statistical model to describe variation in the ERRs with attained age, the ERRs for both the *in utero* and the early childhood cohorts decreased with increasing age when a common attained age was used for both cohorts and no sex effect was incorporated. Allowing for this temporal trend, the ERR at 50 y of age was 1.0 Gy^{-1} (95 % CI = 0.2 to 2.3) for the *in utero* cohort, while ERR at 50 y of age was 1.7 Gy^{-1} (95 % CI = 1.1 to 2.5) for the early childhood cohort (data not shown in Table 5.17). Using a different, more general statistical model that allowed different attained age effects for each cohort

TABLE 5.16—*Number of subjects, person-years, and numbers of solid cancers by weighted organ dose[a] for atomic-bomb survivors (in utero and early childhood cohorts) (adapted from Preston et al., 2008).*

Dose Category (weighted organ dose)[a,b] (Gy)	Cohort: Age at Exposure	Number of Subjects	Person-Years	Number of Cancers
<0.005	*In utero*	1,547	49,326	54
	Early childhood	8,549	247,744	318
0.005 to <0.1	*In utero*	435	14,005	16
	Early childhood	4,528	134,621	173
0.1 to <0.2	*In utero*	158	5,041	6
	Early childhood	853	25,802	38
0.2 to <0.5	*In utero*	172	5,496	8
	Early childhood	859	25,722	51
0.5 to <1	*In utero*	92	2,771	7
	Early childhood	325	9,522	21
≥1	*In utero*	48	1,404	3
	Early childhood	274	7,620	48
Total	*In utero*	2,452	78,043	94
	Early childhood	15,388	451,031	649

[a]Weighted organ doses are the estimated absorbed dose from gamma rays plus 10 times the estimated absorbed dose from neutrons. In this Report, the weighted organ dose is presented in gray; it has also been reported in the literature in sievert.
[b]For the *in utero* cohort, weighted uterine dose; for the early childhood cohort, weighted colon dose.

TABLE 5.17—*Parameter estimates and 95 % CIs for solid cancer excess risks for atomic-bomb survivors in the in utero and childhood cohorts (adapted from Preston et al., 2008).*

Risk Estimates (per unit weighted organ dose)[a,b]	Cohort: Age at Exposure	Male	Female	Sex-Averaged
ERR Gy^{-1} at 50 y of age	*In utero*	0.3 (0.0 – 2.0)	0.5 (0.0 – 2.4)	0.4 (0.0 – 2.0)
	Early childhood	1.3 (0.6 – 2.2)	2.2 (1.3 – 3.4)	1.7 (1.1 – 2.5)
EAR $(10^4$ PY $Gy)^{-1}$ at 50 y of age	*In utero*	4.3 (0.001 – 36)	9.2 (0.002 – 65)	6.8 (0.002 – 48)
	Early childhood	36 (16 – 63)	76 (49 – 100)	56 (36 – 79)

[a]Weighted organ doses are the estimated absorbed dose from gamma rays plus 10 times the estimated absorbed dose from neutrons. In this Report, the weighted organ dose is presented in gray; it has also been reported in the literature in sievert.
[b]For the *in utero* cohort, weighted uterine dose; for the early childhood cohort, weighted colon dose.

and included a sex effect, the sex-averaged ERR estimates at 50 y of age were 0.4 Gy^{-1} (95 % CI = 0.0 to 2.0) for the *in utero* cohort and 1.7 Gy^{-1} (95 % CI = 1.1 to 2.5) for the early childhood cohort, with a weak suggestion of a sex difference in the ERRs (p = 0.13) (Table 5.17). There was no variation in ERR by trimester of exposure. Excess absolute rates (EAR) increased markedly with attained age among those exposed in early childhood [the EAR at 50 y of age was 56 $(10^4 \text{ PY Gy})^{-1}$ (95 % CI = 36 to 79)], but showed little change with time for the *in utero* cohort [the EAR at 50 y of age was 6.8 $(10^4 \text{ PY Gy})^{-1}$ (95 % CI = 0.002 to 48) (Table 5.17)].

This important study demonstrates that radiation exposure *in utero* is associated with increased risks of adult-onset solid tumors. The investigation also confirms earlier results demonstrating a statistically-significant increased ERR for adult-onset solid cancers following radiation exposure in early childhood among atomic-bomb survivors (Preston *et al*., 1994). The difference in ERRs and EARs between the two cohorts suggests that lifetime cancer risks at 50 y of age following *in utero* exposure are lower than risks for early childhood exposure. However, the investigators state that "additional follow-up of this cohort is necessary before definitive conclusions can be made about the nature of the risks for those exposed *in utero*" (Preston *et al*., 2008). The investigators also note that "this study cannot provide information on the effect of radiation on the incidence of childhood cancers … because comprehensive data on solid cancer incidence are unavailable for the period from 1945 to 1957." Mortality follow-up for the *in utero* cohort, however, was available from 1950 and indicated no deaths from childhood leukemia (Delongchamp *et al*., 1997). Another limitation is the small numbers of cancers in each dose category in the *in utero* cohort. Nevertheless, this investigation is the only cohort study with long-term, continuous, active follow-up of a population with *in utero* radiation exposure and high-quality estimated doses for each subject.

Ostroumova *et al*. (2005) examined cancer mortality up to 49 y of age among 3,097 persons residing near the Techa River in the Southern Ural mountains who were exposed to radiation from radionuclide contamination of the river *in utero* and/or in early childhood before 5 y of age. Prenatal total-body doses (dose to the embryo or fetus) ranged from 0 to 0.2 Gy and postnatal total-body doses from 0 to 0.5 Gy. An excess, but not a statistically-significant excess of solid cancers (30 observed, 25.4 expected) was reported. Combining pre- and postnatal active bone marrow doses (the combined average was 0.3 Gy with individual values ranging up to 2 Gy), risk of leukemia rose modestly with dose (p = 0.09). On average, the

postnatal exposure to the population was twice as high as the prenatal exposure and the authors considered the radiation risk estimates as preliminary until the intrauterine do9se estimates were verified.

Imaizumi *et al*. (2008) carried out a cross-sectional screening study during 2000 to 2003 to identify thyroid nodules and assess thyroid function in 328 Japanese atomic-bomb survivors who were *in utero* at the time of the bombings. The mean estimated maternal weighted uterine dose was 0.26 Gy. The odds ratio for prevalence of thyroid nodules at 1 Gy was 2.8 (95 % CI = 0.5 to 11.8), and there was not a statistically-significant dose response ($p = 0.2$). There was no association of dose with elevated antibodies to thyroid peroxidase or thyroglobulin, antithyroid antibody positive or negative hypothyroidism, or with Graves' disease. Small numbers limited inferences and precluded assessment of dose response for thyroid cancer (Imaizumi *et al*., 2008).

Studies of reactor accidents in 1957 at Windscale, involving risk projections (NRPB, 1984), and in 1979 at Three Mile Island, involving an ecologic analysis (Hatch *et al*., 1990), suggested little evidence of a statistically-significant increase in childhood leukemia. An ecologic study (Petridou *et al*., 1994) compared leukemia rates among children *in utero* during an 18 month period of maximum fallout from Chernobyl nuclear reactor with those born before the exposure period or conceived after the exposure period in Greece. The study reported a statistically-significant elevated risk for leukemia diagnosed in infancy, but not at 1 to 3 y of age. However, that study was followed by inconsistent results from studies in Germany (Michaelis *et al*., 1997; Steiner *et al*., 1998) and Scotland (Gibson *et al*., 1988). In addition, data from 36 cancer registries representing 35 countries in Europe when combined with doses from UNSCEAR (1988) by time period showed no evidence of a statistically-significant increased risk of childhood leukemia or a dose-response trend (Parkin *et al*., 1996). In a cohort exposed *in utero* in Belarus, the region most highly exposed to radiation from the 1986 Chernobyl nuclear reactor accident, the RRs for infant leukemia were 1.5 (95 % CI = 0.6 to 3.6) for regions in Belarus with the highest doses and 1.3 (95 % CI = 0.8 to 2.1) for all of Belarus (Ivanov *et al*., 1998). Effective doses were low, with the highest dose from the Chernobyl nuclear reactor for the first year in Belarus (2 mSv) lower than the estimated dose from ubiquitous background (2.4 mSv).

From the population in Ukraine exposed to radiation from the Chernobyl nuclear reactor accident, Hatch *et al*. (2009) identified a cohort of 2,582 persons who were *in utero* in Ukraine at the time of

the Chernobyl nuclear reactor accident (April 1986) and conducted a screening study (using palpation, ultrasound scan, measurement of thyroid hormones, antithyroid antibodies, and, if indicated, fine needle aspiration) during 2003 through 2006 to evaluate thyroid cancer and other thyroid diseases in the offspring. The mean estimated cumulative thyroid dose to the fetus, which was derived from the estimated ^{131}I activity in the mother's thyroid gland, was 72 mGy (range was 0 to 3,230 mGy) (Likhtarov *et al*., 2011). The investigators identified seven cases of thyroid cancer and one case of Hurthle cell tumor all arising in offspring of the 1,494 mothers living in fallout-contaminated regions of Ukraine at the time of the accident versus no thyroid or Hurthle cell tumors occurring in offspring of the 1,088 mothers living in uncontaminated regions of Ukraine at the time of the accident. An increase in radiation-related risk was not statistically significant (excess odds ratio at 1 Gy = 11.7, 95 % CI was not evaluable; p-value for linear trend = 0.12). The excess odds ratios at 1 Gy for nonmalignant thyroid diseases [including diffuse goiter (n = 263 in contaminated areas versus 174 in the comparison group), ultrasound-detected nodules (100 versus 63), hypothyroidism (48 versus 38), hyperthyroidism (9 versus 6), elevated antibodies to thyroid peroxidase thyroglobulin (87 versus 87), and autoimmune thyroiditis (9 versus 14)] demonstrated no evidence of a radiation-related increase in risk (Hatch *et al*., 2009).

The relation between nuclear weapons testing and risk of childhood leukemia has been evaluated among populations:

- residing in proximity to the Nevada Test Site through record matching of deaths to the deceased membership files of the Church of Jesus Christ of Latter Day Saints (Stevens *et al*., 1990) or by an ecologic study (Machado *et al*., 1987);
- through time trends analysis to examine risks in Denmark, Norway, and the United Kingdom (Darby and Doll, 1987); in Denmark, Finland, Iceland, Norway and Sweden (Darby *et al*., 1992); and in New Zealand (Dockerty *et al*., 1996) in relation to fallout from atmospheric testing; and
- in Kazakhstan among persons living in proximity to the Semipalatinsk Test Site (Zaridze *et al*., 1994).

None of these investigations provide information specific to clarifying risks in offspring of women who were pregnant at the time of the nuclear testing. Similarly, the studies assessing risks of childhood leukemia, lymphoma, or other cancers among children residing in proximity to nuclear installations (Clarke *et al*., 1991; Cook-Mozaffari *et al*., 1987; 1989a; 1989b; Hill and Laplanche, 1990;

Jablon *et al*., 1990, 1991; Michaelis *et al*., 1992) also provide little insight about risks of cancer in offspring of pregnant women.

5.2.6.7 *Methodological Issues*. Given the rarity of childhood cancer, particularly when specific sub-types are considered, it can be difficult to assemble large studies with adequate power to detect small to moderate increases in risk. Furthermore, the absence of dose data is a major shortcoming of virtually all the studies of cancer risk in offspring of mothers undergoing diagnostic radiological procedures during pregnancy. Classification of radiation exposure status in mothers has generally been based on questionnaire data obtained from mothers or, in two instances, from medical reports. The accurate classification of disease, especially with regards to evaluation of histological sub-types and combining of distinct childhood cancer entities, poses a further challenge, as does the classification of radiation exposure status in study subjects, particularly when exposure assessment relies on interview data, or medical records or radiological reports are missing.

The majority of the evidence on cancer risks in offspring associated with maternal *in utero* diagnostic x-ray procedures comes from case-control studies, which have more cases and thus higher statistical power than cohort studies. The earlier studies evaluated risks in relation to childhood cancer mortality, whereas more recent studies have focused on childhood cancer incidence. Variation was also evident among the studies in the population targeted for study (population-based versus hospital-based), the methods for selecting controls, and the age range for inclusion of childhood cancer cases and controls. Case-control interview studies are more prone to reporting or recall bias if parents of cases differentially remember more diagnostic x-ray procedures than control parents, which could lead to inflated measures of risk. Assessment of the anatomic site of the x-ray procedures varied somewhat among the studies, and recall problems may have contributed to misclassification of exposure. Studies in adults that compared the numbers of x-ray examinations reported in interviews with numbers reported in medical records demonstrated disagreement and poorer reporting by control subjects (Berrington de Gonzalez *et al*., 2003). Underreporting of exposure was documented in the Oxford Survey (Gilman *et al*., 1989) and the U.S. Tristate Study (Graham *et al*., 1966), and medical case notes or x-ray reports were missing for 30 to 45 % of subjects in the Oxford Survey (Hewitt *et al*., 1966). For those subjects for whom medical case notes or x-ray reports were available, similar proportions were observed in cases and controls of false positives (27 % for cases and 25 % for controls) and false

negatives (0.6 % in cases and 1 % in controls) (Hewitt *et al*., 1966). Many of the false positives were maternal x-ray procedures of the chest or extremities rather than the abdomen, and some of the false positives may have represented missing x-ray reports. A second methodological study of false positives in the Oxford Survey also found similar rates of false positives by case (7.6 %) and control (7 %) mothers (Knox *et al*., 1987). For the large U.K. study, data were abstracted from medical records of 86 % of targeted case mothers and 78 % of targeted control mothers (Rajaraman *et al*., 2011). For the studies based on medical records, there is no way to determine the completeness of recording of x-ray procedures that were carried out but not reported in the medical records (MacMahon, 1962). As MacMahon noted, incompleteness of recording of diagnostic procedures would result in some underestimation of relative risk. Monson and MacMahon (1984) found that in a blinded re-review of a sample of medical records that had previously been searched, 10 % of all records were not found on re-review and a further 10 % of the initially recorded x-rays were not found. There was no difference in the information lost between the cases and the comparison group, however. Cohort studies, while less susceptible to recall bias, may have small numbers of outcomes of rare conditions such as childhood cancers which limits statistical power. The study size may therefore be inadequate to ascertain small increases or decreases in risks. Another subtle form of bias relates to publication of positive but not negative findings. For example, Carter *et al*. (1961) published the results of a study that did not show an association between Down syndrome and maternal radiation only after a positive report appeared in the literature.

It can be difficult to assess radiation-related dose response for childhood cancer in offspring exposed to protracted radiation, such as offspring exposed *in utero* or preconception of nuclear or medical radiation workers, residents with ubiquitous background exposures, or persons exposed to radiation from other environmental sources. Some of the difficulty arises because of the protracted, cumulative, and generally low-dose nature of these radiation exposures and the difficulty of disentangling exposures confined to the period of the pregnancy from those prior to the pregnancy. It is also important to consider additional sources of radiation exposure such as personal diagnostic radiological procedures.

Data from the follow-up of Japanese atomic-bomb survivors who were *in utero* at the time of the bombings (Preston *et al*., 2008) has demonstrated the need to continue follow-up of the exposed and unexposed offspring for decades after radiation exposures to quantify long-term risks of associated cancers.

As with all epidemiological studies, the relationship between radiation and childhood risk can be masked by confounding factors which are associated with both exposure and disease (Section 5.2.6.1.1). Further, models of radiation exposure and cancer risk are subject to a number of statistical uncertainties, and for accurate assessment of these risks, uncertainties should be taken into account. An important consideration from the clinical and radiation protection perspective is that adult women may be unaware that they are pregnant at the time of diagnostic radiological examination.

5.2.6.8 *Animal Studies*. Several studies have reported excess risks of various tumors in mice after *in utero* irradiation, mostly after whole-body doses higher than 2 Gy. Offspring of BC3F1 mice who received whole-body *in utero* doses (17th day postcoitus) ranging from 0.3 to 2.1 Gy (41 to 58 animals in each dose group) developed small increases in liver tumor occurrence (Di Majo *et al*., 1990). Offspring of B6C3F1 mice exposed to a whole-body dose of 3.8 Gy *in utero* (65 to 93 mice in each group exposed between 16th and 18th days postconception) developed increased risk of pituitary, ovarian, liver, and bone tumors; an increase in lung tumors was statistically significant after doses of 1.9, 3.8, and 5.7 Gy; and an elevation in malignant lymphoma, lymphocytic type, was statistically significant after 5.7 Gy (Sasaki, 1991).

A number of studies have examined the carcinogenic effects of gamma-ray irradiation (^{60}Co) on the fetal hematopoietic system. Whole-body doses of 0.5 to 3 Gy to B6D2F1 mice on 10.5 day postconception were associated with long-lasting effects of reduced spleen cellularity and perturbations in concentrations of hematopoietic progenitor cells in the bone marrow of young adult mice (Weinberg, 1983). Exposure of (C57BL/6J $\times$ BALB/c)F1 mice at late (but not early) stages of embryonic growth (*e.g*., 13th or 17th day postconception) to 0.5 Gy (x rays) as a single acute irradiation induced statistically-significant long-term changes in the proportion of granulocyte-macrophage colony-forming units (CFU-GM) in progenitor femoral bone-marrow cells. These changes were first manifest at nine months of age (Grande and Bueren, 1995). The investigators acknowledge that the relation of this relatively modest hematopoietic dysfunction to induction of leukemia was unknown. Irradiation of pregnant (C57BL $\times$ DBA2)F1 mice at mid-term with 1.8 Gy (gamma rays) (15 in each exposure group) caused a 40 % reduction in the spleen colony-forming units (CFU-S) which persisted at least 24 weeks, but grew normally after transplantation into normal recipients. But when the irradiated offspring were used as the recipients of bone-marrow transplants

from either normal or irradiated offspring, the offspring of the irradiated mothers were unable to support normal CFU-S growth, thus indicating that the fibroblastoid colony-forming units (CFU-F) were unable to compensate for the poor microenvironment in the irradiated offspring hosts (Yang *et al*., 1995). Exposure of pregnant Swiss mice to 0.1 to 1.5 Gy on 17th day postconception led to a statistically-significant reduction in the weights of fetal liver and spleen, and CFU-S of liver and spleen showed a dose-dependent decrease, but the spleen demonstrated a higher sensitivity than liver to doses <1 Gy. Chromosomal damage in liver increased linearly with dose, while the increase in spleen was linear-quadratic (Uma Devi *et al*., 1998). The investigators interpreted the results as suggesting that induction of cytogenetic damage by radiation appeared to be a nonthreshold effect.

Bone marrow in mice at 12 months of age that were exposed prenatally to a single 0.5 Gy dose of x rays on 14th to 17th days postconception showed a higher incidence of chromosomal aberrations and a dose-dependent increase in frequency of aberrant metaphases compared with unexposed mice (Uma Devi and Hossain, 2000). At 12 months, mice treated with a single dose (ranging from 0.4 to 1.5 Gy) of gamma radiation during the early or late fetal period had lower than normal postnatal blood counts (~15 to 20 % lower peripheral granulocytes and lymphocytes) compared with control mice (Hossain and Uma Devi, 1999), and animals with abnormal leukocyte counts appear to be at higher risk of developing polyploidy cells in the bone marrow (Uma Devi and Hossain, 2000). Genomic instability induced by radiation in fetal murine hematopoietic cells is transferred through cell migration to postnatal bone marrow, and seen subsequently as chromosomal abnormalities in adult bone marrow, but to date studies have not shown induction of leukemia from the prenatal irradiation (Uma Devi, 2003). Efforts to trace explicit aberrations from fetus to adult revealed that cells with these aberrations are eliminated during the early postnatal stage (Uma Devi *et al*., 2002).

Investigators have also found that *in utero* irradiation may serve as an initiator of carcinogenesis in two-phase experiments that include treatment with promoter agents. Offspring of 27 pregnant Wistar-MS strain rats treated with a whole-body intrauterine dose of 2.5 Gy on the 20th day postconception and then with diethylstilbestrol after maturation developed a small increase in mammary tumors (Inano *et al*., 1996). *In utero* irradiation [0.3 and 1 Gy (x rays, whole body) during day 10.5 postconception] of (PT × HT F1) mice induced a high incidence of coat-color genes (a mutation) but no neoplasms in the offspring; but statistically-significant

excesses of skin tumors and hepatomas were induced when the irradiated animals receiving 1 Gy were treated postnatally with 12-*O*-tetradecanoylphorbol-13-acetate (Nomura *et al*., 1990).

Studies have also evaluated the carcinogenic effects of lower-dose irradiation on other fetal organs. A summary of the effects of low-LET prenatal radiation in mice revealed variation according to mouse strain and anatomic site of cancer in the minimum dose at which a statistically-significant increase in cancer risk is detected (ICRP, 2003). Studies assessing tumor risks in different strains of mice demonstrate high susceptibility of the ovaries for radiation-related tumor induction during the fetal period, with 0.25 Gy the lowest dose associated with a statistically-significant increase although an increase that was not statistically-significant was seen at 0.1 Gy (Sasaki, 1991; Schmahl *et al*., 1980; Uma Devi and Hossain, 2000).

Other investigations found no excess cancer after *in utero* irradiation of mice with 3 Gy (Upton *et al*., 1960) or 2 Gy (Ellender *et al*., 2006), although each of these studies showed increased risks of cancer in the mice following administration of similar doses postnatally. Although investigators found no excess cancer in BC3F1 mice after *in utero* exposures to 0.3 Gy, increased risks were seen in mice given the same dose postnatally (Di Majo *et al*., 1990).

Rugh *et al*. (1966), in a very large study, irradiated mice with 1 Gy on each day postconception and observed the incidence of tumors in the offspring as adults. There was no statistically-significant increase in the incidence of tumors in adult animals from irradiation *in utero* on any day. Brent and Bolden (1968) exposed pregnant mice to doses of 0.3, 0.6, and 0.9 Gy at 0.5, 7.5, 8.5, 12.5, and 16.5 days postconception. They also did not observe an increase in the incidence of tumors. However, the presexually mature mouse was more vulnerable than the adult mouse to the leukemogenic effect of radiation.

Nitta *et al*. (1992) irradiated mice at 16.5 day postconception with 1 and 2.7 Gy and followed the offspring for 2 y looking for an increase in tumors. The results indicate that irradiation *in utero* during the late embryonic stage can induce tumors postnatally after a long latency. There was a low incidence of ovarian tumors and a high incidence of liver, lung and pituitary tumors. However, there were no groups receiving low doses.

Offspring of pregnant beagles treated with mean doses of 0.16 or 0.81 Gy at 8th, 28th, or 55th days postcoitus (120 dogs in each dose and treatment day group) experienced increases in mortality from total cancers that were not statistically significant, and statistically-significant elevated mortality risks from lymphoma

among those treated at 55th day postcoitus as well as statistically-significant increased risks of hemangiosarcomas associated with both dose levels at 8th day (statistically-significant dose response) and 55th day (borderline statistically-significant dose response) postcoitus (Benjamin *et al*., 1998a). Myeloproliferative disorders were increased among beagles irradiated from the mid-prenatal to the neonatal period, and CNS astrocytomas showed a statistically-significant increase in beagles irradiated at 28th day postcoitus. A statistically-significant dose response for all fatal neoplasms was seen in beagles irradiated at 2nd day postpartum. Detailed assessment revealed that the increased risk of fatal neoplasms was most pronounced in beagles irradiated in the neonatal period (Benjamin *et al*., 1998a). These data suggest that irradiation in both the fetal and neonatal periods are associated with an increase of early onset and lifetime cancer risk. However, the lower-dose group (0.16 Gy) did not have an increased incidence of tumors.

Benjamin *et al*. (1998b), for the same group of irradiated beagles, reported that chronic renal disease was a cause of mortality and irradiation in the late fetal or juvenile periods potentiated this disease resulting in an increased mortality due to renal failure. Hypothyroidism, associated with atrophic thyroiditis was increased by irradiation, a finding contrary to expectation and not easily explained. Diabetes mellitus was increased, a finding that is intriguing since a similar finding was present in the early reports on atomic-bomb survivors.

Kalter *et al*. (1980) and Warkany *et al*. (1976) studied the interaction of ethylnitrosourea and x irradiation in rats. The original goal of the investigators was to determine the effect of x irradiation administered on the 16th day postconception on the incidence of tumors following the administration of ethylnitrosourea on the 20th day postconception. Sixteen months after delivery 62.2 % of the rats that received only the ethylnitrosourea during the fetal period had neurogenic tumors. After fetal irradiation on the 16th day postconception followed by ethylnitrosourea 4 d later 16.7 % of the rats developed neurogenic tumors. The mechanisms of these unexpected findings, whereby irradiation before receiving an oncogenic drug reduced the incidence of cancer have not been determined.

Nakano *et al*. (2007) irradiated mice at various stages of pregnancy with 1 or 2 Gy. Translocation frequencies in the peripheral blood T cells, spleen cells, and bone-marrow cells were determined when the offspring were 20 weeks old. The translocation frequency was very low in the mice that were irradiated *in utero* (0.8 %). The mice that were irradiated during days to weeks after birth had translocation frequencies of 5 %. The authors suggested that the

abnormal cells in the fetus were replaced by normal fetal stem cells during the postnatal growth of the animal. If this phenomenon occurs in humans, it could explain why the fetus may be less vulnerable to the oncogenic effect of radiation than the child. Earlier research supporting the findings of Nakano *et al*. (2007) found that x irradiation of the rat embryo during early organogenesis resulted in the production of hundreds of small growths that resembled well differentiated ependymomas or retinoblastomas (Brent and Jordan, 1951; Wilson *et al*., 1952) (Figure 5.13). As the embryo developed, some of the tumors de-differentiated into more primitive growths (Photograph 4 in Figure 5.13). However, at term almost all the tumors had regressed similar to the result reported by Nakano *et al*. (2007) (Photographs 5a, 5b, and 5c in Figure 5.13).

5.2.6.9 *Summary for Fetal Exposure and Subsequent Cancer Risk*

5.2.6.9.1 *In utero diagnostic x-ray procedures*. Although the statistical association from case-control epidemiological studies is not generally debated, investigators have argued about:

- the etiologic significance (causality); and
- if the association is causal, the likely magnitude of the leukemogenic risk.

The arguments favoring and opposing causality are listed below.

Arguments favoring causality (adapted from Doll and Wakeford, 1997) include the:

- consistency of the estimated risks for all forms of childhood leukemia among the earlier case-control studies [particularly the medical record-based northeast United States (Monson and MacMahon, 1984) and United Kingdom (Rajaraman *et al*., 2011) studies];
- decline in risks in more recent birth cohorts (Totter and MacPherson, 1981) and more recent case-control studies as doses from diagnostic x-ray procedures decreased (Naumburg *et al*., 2001; Shu *et al*., 2002; Rajaraman *et al*., 2011); and
- comparable childhood leukemia risks associated with fetal diagnostic x-ray exposure in the case-control twin studies (Harvey *et al*., 1985; Mole, 1974; Rodvall *et al*., 1990) as in the case-control studies of singletons (Boice, 2006).

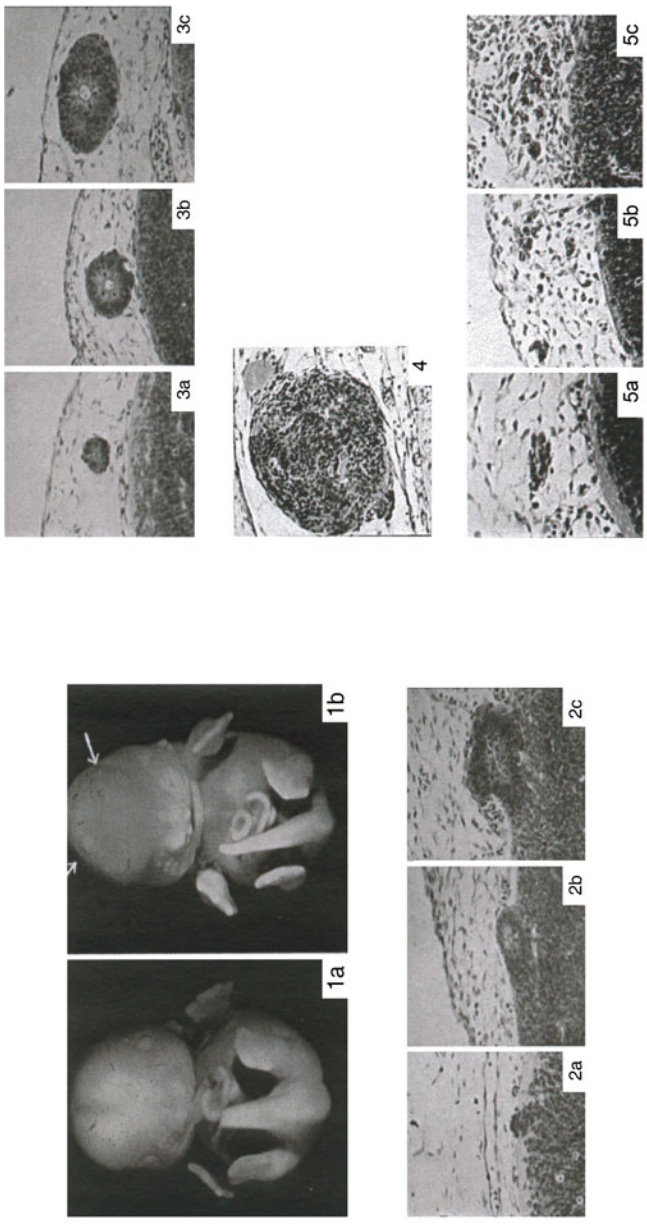

Fig. 5.13. Photographs 1A and 1B are of 15 d old rat fetuses that were exposed to 1.5 Gy at 9th day postconception. The arrows in 1b are pointing to tumors under the scalp that can be seen in histological sections in 3a, 3b, and 3c. The tumor growths are derived from outgrowths of the radiated neural tube as seen in 2a, 2b and 2c. Some of the growths de-differentiated into more aggressive appearing tissues (4). At the time of the birth of the fetuses almost all the growths had regressed except for a few remnants of pyknotic cells located between the brain and the scalp (5a, 5b, and 5c). All photographs are from Wilson *et al.* (1952).

Arguments opposing causality (adapted from Boice and Miller, 1999) include the:

- lack of clear confirmation of the statistical associations in cohort studies, although statistical power is limited;
- decreased risk of childhood leukemia and other childhood cancers in twin cohorts, which may reflect an intrinsic biologic difference between twins and singletons; and
- similarity of the RR estimates for almost all types of childhood cancers in the Oxford Survey.

Although further insights might be provided by large international studies of offspring of women who were treated for cancer with radiation during pregnancy, it may be challenging to assemble such large cohorts in light of the relatively small numbers of pregnant women undergoing radiation therapy for cancer. As noted in Section 5.2.6.7, risk of cancer per gray from case-control and most of the cohort studies of cancer risk in offspring of mothers undergoing diagnostic radiologic procedures are not based on actual dose reconstructions of case and control exposures but rather on general hospital surveys which may or may not be relevant to the pregnancy circumstances studied. Thus studies that can confirm the associations reported and improve upon fetal dose estimates would add appreciably to understanding. The animal data summarized in Section 5.2.6.8 on radiation-related effects on hematopoiesis and developing microenvironmental stromal cells have not provided strong evidence for leukemogenesis. Nonetheless, it would be useful to pursue further studies that provide biologically plausible mechanistic information.

5.2.6.9.2 *In utero exposure to occupational or environmental sources, and Japanese atomic-bomb survivors.* There was little evidence from epidemiologic studies of increased risks for childhood leukemia, other childhood cancers or adult cancers in offspring of mothers or fathers who were nuclear workers or medical radiation workers. These findings, however, were based on relatively few studies.

Epidemiologic studies of childhood leukemia have shown little evidence of association with exposure to natural background radiation, but the epidemiologic studies of the latter have not had sufficient statistical power to detect small risks.

A statistically-significant dose-related increased incidence of solid tumors in adulthood was observed among Japanese atomic-bomb survivors exposed to radiation *in utero* and those exposed in early childhood, although the EARs increased markedly with

attained age among those exposed in early childhood, but showed little change with time for the *in utero* cohort. This difference in EARs between the two cohorts suggests that lifetime cancer risks following *in utero* exposure may be notably lower than for early childhood exposures. The leukemia mortality among the atomic-bomb survivors exposed *in utero* was based on only two cases in adults, both exposed to low doses, thus precluding efforts to compare leukemia mortality risks of the *in utero* versus the early childhood cases (Delongchamp *et al*., 1997).

In follow-up to 49 y of age, residents living near the radionuclide-contaminated Techa River who were exposed to radiation *in utero* and/or in early childhood before 5 y of age experienced an excess of solid cancers that was not statistically significant, and a nearly statistically-significant increase in leukemia deaths (Ostroumova *et al*., 2005). Studies of nuclear reactor accidents have shown little evidence of an increase in childhood leukemia among offspring who were *in utero* at the time of the accident (Ivanov *et al*., 1998; Parkin *et al*., 1996). Investigations of fallout from nuclear weapons testing or from residing in proximity to nuclear installations provide little insight about risks of childhood leukemia or other childhood cancer in offspring of pregnant women (Darby and Doll, 1987; Darby *et al*., 1992; Dockerty *et al*., 1996; Machado *et al*., 1987). A screening study to evaluate thyroid cancer and other thyroid diseases in offspring of women who were pregnant at the time of the Chernobyl nuclear reactor accident identified seven thyroid neoplasms (a large, but not statistically-significant excess) in offspring of 1,494 mothers residing in fallout-contaminated regions (Hatch *et al*., 2009).

5.2.6.9.3 *Animal data*. Animal data reveal evidence of statistically-significant excesses of ovarian cancer (some strains of mice) (Sasaki, 1991; Schmahl *et al*., 1980; Uma Devi and Hossain, 2000) and lymphoma (beagles) (Benjamin *et al*., 1998a) at single doses of low-LET radiation of 0.25 and 0.18 Gy, respectively. A higher incidence of chromosomal aberrations (Uma Devi *et al*., 1998), dose-dependent increase in frequency of aberrant metaphases (Uma Devi and Hossain, 2000), and lower than normal granulocyte or lymphocyte counts (Uma Devi and Hossain, 2000) have been observed postnatally in mice from prenatal doses ranging from 0.4 to 1.5 Gy, but no clear progression to leukemia (Uma Devi, 2003). Other studies have demonstrated no excess of cancer in mice following *in utero* radiation exposures of 2 to 3 Gy, but observed increased risks linked with the same doses administered postnatally (Di Majo *et al*., 1990; Ellender *et al*., 2006; Upton *et al*., 1960).

5.3 Guidance for Diagnostic and Fluoroscopically-Guided Interventional Procedures

The risk for the effects discussed in Section 5.2 to an embryo or fetus from an absorbed dose of 0.1 Gy or less at any time during gestation is small (or possibly nonexistent); therefore, medically-justified and properly performed procedures using ionizing radiation need not be withheld because of concern for such doses. For doses to the embryo or fetus from diagnostic and fluoroscopically-guided interventional procedures >0.1 Gy the benefit-risk ratio should be evaluated in deciding whether to perform the procedure. In the great majority of such cases, the potential medical benefit will greatly exceed the potential risk (Table 5.3). However, in all cases, the dose to the embryo or fetus should be maintained as low as feasible while obtaining the necessary diagnostic information or performing a necessary fluoroscopically-guided interventional procedure.

6. Radiation Risk to the Nursing Infant

6.1 Radiopharmaceuticals Administered to the Mother

If the mother has received a radiopharmaceutical, the nursing infant may be exposed, either as a result of transfer of the material to the infant by the mother's milk or by exposure to radiation from the mother's body. In the first case, the transferred amount will depend on the concentration of the radionuclide in the milk. With few exceptions, <10 % of the administered activity is excreted in the breast milk, and typical estimates range from 0.3 to 5 % of the administered activity to the mother (Stabin and Breitz, 2000). With the objective of maintaining an effective dose to the infant <1 mSv, many radiopharmaceuticals commonly used in nuclear medicine do not require interruption in breast-feeding.

In the United States, NRC (2007b) requires that licensees provide instructions on the discontinuation or interruption of breast-feeding and the consequences of failing to follow the instructions. Advice on counseling and interruption of breast-feeding was provided by Stabin and Breitz (2000). The most current recommendations on interruption of breast-feeding are found in ICRP (2008) and are provided in Table 6.1, which gives the actions that should be taken for various radiopharmaceuticals so that the amount of radiopharmaceutical secreted into the milk is estimated to give an effective dose no greater than 1 mSv to the child. The milk expressed during the interruption period should be discarded.

It should be noted that if a nursing mother requires a myocardial-perfusion study, ^{201}Tl should be avoided and ^{99m}Tc agents (sestamibi or tetrofosmin) or ^{82}Rb-chloride should be employed instead. Iodine-131, especially at therapeutic levels, is a special case and serious consideration is necessary before deciding to proceed. Diagnostic tests that would normally utilize ^{131}I should be undertaken with either ^{123}I or ^{99m}Tc if possible. Clinical studies of cumulative breast milk activity following administration of ^{131}I for thyroid uptake studies have shown significant absorbed doses (Weaver *et al*., 1960), and use of ^{131}I therapy for treatment of thyroid tumors or nonmalignant thyroid diseases is contraindicated while breast-feeding (Woeber, 2000).

TABLE 6.1—*Recommendations for breast-feeding interruption (adapted from ICRP, 2008).*

Radiopharmaceutical[a]	Interruption
^{14}C-labeled	
Triolein	No
Glycocholic acid	No
Urea	No
^{99m}Tc-labeled[b]	
DISIDA	No[b]
DMSA	No[b]
DTPA	No[b]
ECD	No[b]
Phosphates (MDP)	No[b]
Gluconate	No[b]
Glucoheptonate	No[b]
HMPAO	No[b]
Sulphur colloids	No[b]
MAA	12 h
MAG3	No[b]
MIBI	No[b]
Pertechnetate	12 h
PYP	No[b]
RBC (*in vivo*)	12 h
RBC (*in vitro*)	No[b]
Technegas	No[b]
Tetrofosim	No[b]
WBC	12 h
Iodine-labeled	
^{123}I-BMIPP[c]	>3 weeks[d]
^{123}I-HSA[c]	>3 weeks[d]
^{123}I-iodo hippurate	12 h
^{123}I-IPPA[c]	>3 weeks[d]
^{123}I-MIBG[c]	>3 weeks[d]
^{123}I-NaI[c]	>3 weeks[d]
^{125}I-HSA	>3 weeks[d]
^{125}I-iodo hippurate	12 h
^{131}I-iodo hippurate	12 h
^{131}I-MIBG	>3 weeks[d]
^{131}I-NaI	>3 weeks[c]

Others	
^{11}C-labeled	No[e]
^{13}N-labeled	No[e]
^{15}O-labeled	No[e]
^{18}F-FDG	No
^{22}Na	>3 weeks[d]
^{51}Cr-EDTA	No
^{67}Ga-citrate	>3 weeks[d]
^{75}Se-labeled agents	>3 weeks[d]
^{81}Kr-gas	No
^{82}Rb-chloride	No[e]
^{111}In-octreotide	No
^{111}In-WBC	No
^{133}Xe	No
^{201}Tl-chloride	48 h

[a] BMIPP = beta-methyl iodophenyl pentadecanoic acid
DISIDA = diisopropyl iminodiacetic acid
DMSA = dimercaptosuccinic acid
DTPA = diethylenetriamine pentaacetic acid
ECD = ethyl cysteinate dimer
EDTA = ethylenediamine tetraacetic acid
FDG = fluorodeoxyglucose
HMPAO = hexamethylpropylene amine oxime
HSA = human serum albumin
IPPA = para-iodophenyl pentadecanoic acid
MAA = macroaggregated albumin
MAG3 = mercaptoacetyltriglycine
MDP = methylene diphosphonate
MIBG = meta-iodobenzylguanidine
MIBI = methoxyisobutyl isonitrile
PYP = pyrophosphate
RBC = red blood cells
WBC = white blood cells

[b] Interruption not essential for most of the ^{99m}Tc-labeled compounds, under the circumstance that no free pertechnetate exists in the radiopharmaceutical. An interruption of 4 h during which one meal is discarded can be advised to be on the safe side.

[c] All substances labeled with ^{123}I (except iodo hippurate): more than three weeks due to the risk of contamination of other iodine isotopes.

[d] Three weeks (504 h) at least. However, difficulty to maintain the milk supply may lead to cessation.

[e] For ^{11}C, ^{13}N, ^{15}O, and ^{82}Rb-labeled substances, interruption not essential due to short physical half-life.

In one well known case, a patient was administered ~185 MBq (5 mCi) of ^{131}I and resumed breast-feeding 11 h later. The amount of ^{131}I taken in by the two-week old infant was enough to ablate the infant's thyroid (Marcus, 1990a; 1990b). Iodine-131 therapy should not be administered unless breast-feeding is terminated. In the case described above, the fact that the patient was breast-feeding was discovered when she was imaged 2 d after receiving the 185 MBq administered activity. All that was visible on the scan were her breasts which had taken up most of the radiotracer. It is known that lactation causes the up-regulation of the sodium iodide symporter in breast tissue, thereby leading to significant uptake of ^{131}I. Consequently, it is important to have women discontinue breast-feeding at least three to four weeks prior to planned^{131}I therapy (NCRP, 2006).

In addition to the potential internal dose to the child from radionuclides in the breast milk, there is also the potential for external dose to the child from radionuclides in the mother. Using a general method to estimate the effective dose to an infant held in close contact to a radioactive parent, Mountford (1987) concluded that effective doses to infants from adults who have undergone diagnostic radiopharmaceutical procedures can be kept <1 mSv without imposing restrictions on close contact. When concerns arise, estimates can be made of the effective dose to the infant while nursing based on the absorbed-dose rate on the surface of the mother. As is the case whenever one is evaluating methods to reduce exposure from a source of radiation, the basic principles of time, distance and shielding should be considered. The dose to the child will be lower if the amount of time that the mother spends with the child is limited and the distance between the mother and child is maximized. If the radionuclide is uniformly distributed in the mother, the dose rate at the mean distance of the child (~10 cm) is about one-fifth of the maximum dose rate in the mother's body. Thus the dose rate to the child would be approximately equal to the mother's whole-body dose rate divided by five. Assuming the fraction of time the infant spends nursing is approximately one-tenth of the day, the total dose to the infant would be approximately one-fiftieth of that received by the mother (NCRP, 1994). The mother should, however, be advised not to hold the infant unnecessarily during the period of highest dose. For most technetium agents this time period would last for 12 to 18 h from the time of administration.

6.2 Brachytherapy

Brachytherapy is a form of radiation therapy wherein a source of radiation is placed in close proximity to the tissue to be irradiated. For interstitial brachytherapy, the radioactive source or sources are

implanted directly into or around the target location. Depending on the source that is used and the area being treated, the sources may be permanently implanted or they may be temporarily implanted and then removed after a prescribed period of time.

In the event that the patient receiving brachytherapy is the mother, the infant could be exposed to a significant amount of radiation if efforts to minimize the dose are not implemented. Each individual situation has to be evaluated separately. In the case of temporary implants (*e.g.*, intracavitary sources in the uterus and/or cervix or an interstitial ^{192}Ir implant), the mother will be hospitalized and under the supervision of a physician. Depending on the implant site and radionuclide, absorbed-dose rates in close proximity to the mother can exceed several milligray per hour (Papin *et al.*, 1990). Since temporary implants are routinely held for 1 to 5 d, contact between the mother and infant should be avoided during this period, as was previously recommended in NCRP Report No. 37 (NCRP, 1970).

In the case of a permanent, low dose-rate brachytherapy implant such as for the treatment of lung cancer with ^{125}I or ^{131}Cs seeds or for breast cancer with ^{103}Pd seeds, the patient will generally be released from the hospital within several days following the implant. The hospital will provide specific radiation safety instructions to minimize the dose to other persons, in particular the infant during breast-feeding and routine care. Radionuclides used for permanent implants emit radiation of low energy which is more easily attenuated or blocked; therefore, except for implants close to the body surface, minimal external dose results. In the case of implants close to the surface, shields can be fashioned from a thin lead sheet or other attenuating material to reduce the external dose from the mother during her contact with the child.

In the case of a permanent implant in an individual other than the mother who may come in contact with the infant, specific radiation safety instructions should be provided to the individual to minimize the dose to the infant. A permanent brachytherapy implant in a father, grandfather, or other adult will typically utilize ^{125}I, ^{103}Pd, or ^{131}Cs seeds. As noted, these radionuclides all emit low-energy photons, so short periods of contact between an infant and the individual are not a concern. However, instructions should include guidance to the individual to not hold an infant or small child in the lap for prolonged periods of time (*e.g.*, hours) based on the initial total source strength and half-life of the implanted radionuclide. Each individual situation has to be evaluated separately, and the individual's radiation oncologist should set a patient-specific plan to address lifestyle issues while minimizing dose to the infant.

6.3 Environmental Exposure to Radioiodine

When there is evidence that the mother has inhaled or ingested radioiodine, typically ^{131}I, from an accident or other incident, lactating women should be administered potassium iodide for both their protection as well as to potentially reduce the radioiodine content of their breast milk (FDA, 2001). If the radioiodine burden in the mother is significant or if repeated doses to the mother of potassium iodide are required, the infant should be evaluated for hypothyroidism and discontinuation of breast-feeding may be warranted. In such rare instances, breast-feeding should be replaced by packaged feedings which are known to be free of contamination. Intake of ^{131}I by the infant from breast-feeding can be estimated using ICRP (2004).

Because radioiodines pass into breast milk, the American Academy of Pediatrics has recommended that pediatricians caution lactating mothers to temporarily cease breast-feeding their infants after the release of radioiodines in a radiation disaster, unless no alternatives are available (COEH, 2003). COEH (2003) advises that public health authorities will declare when it is safe to go back to breast-feeding after a radiation disaster.

7. Mitigation of Ionizing Radiation Risk for Pregnant or Potentially-Pregnant Women

7.1 Pregnancy Testing and Documentation

7.1.1 *Introduction*

Radiation exposure during pregnancy or potential pregnancy is a source of great anxiety (ACOG, 2004; ACR, 2008; Berlin, 1996; Brent, 1989; 2006b; 2009; 2010; Lowe, 2004). There is potential concern on the part of the mother and other individuals involved, including family members, as well as those who have a responsibility for managing radiation exposure. Medical exposure of patients is the largest source (48 %) of radiation exposure to the U.S. population after that from ubiquitous background (50 %) (Mettler *et al*., 2008; NCRP, 2009).

In the medical setting, individuals who share responsibility for the performance or interpretation of an imaging procedure using ionizing radiation include technologists, medical and health physicists, radiation safety officers, physician extenders, and physicians such as radiologists and cardiologists. Despite their medical expertise, many health professionals disseminate much misinformation regarding the effects of radiation exposure on the embryo or fetus and on the advisability of recommending medical termination of pregnancy (Brent, 2009; Ratnapalan *et al*., 2004). Experienced counselors understand that their primary task is to educate the pregnant women or family members concerning the risk of radiation exposure. The counselor should advise them on the options available, but not on which option to select. On the contrary, in one survey, up to 6 % of all physicians would recommend medical termination of pregnancy for women who had undergone a single CT at six weeks gestation and 27 % of all physicians surveyed were uncertain if they would recommend a medical termination of pregnancy (Ratnapalan *et al*., 2004) (Table 7.1).

TABLE 7.1—*Survey of obstetricians and family physicians from Ontario, Canada on medical termination of pregnancy in women who underwent radiography or CT during early pregnancy (Ratnapalan et al., 2004).*

Medical Termination of Pregnancy Recommended	Percentage of Respondents			
	Family Physicians (n = 208)		Obstetricians (n = 65)	
	Radiography	CT	Radiography	CT
Yes	1	6	0	5
Not sure	25	39	6	25
No	74	55	94	70

In addressing these issues it is first necessary to determine if the woman is pregnant, or if there is the possibility that she may be pregnant. The conventional methods of inquiry range from verbal communication about potential pregnancy to the use of a highly-sensitive biochemical assay of human chorionic gonadotropin (HCG) produced by the developing placenta. In addition to obtaining the details of pregnancy assessment, it is important to document the potential benefits and risks, including dose estimates, of the procedure or examination and the discussion of this information with the patient and appropriate healthcare providers. Discussion should also include a review of the procedure, including duration of the radiation exposure, and estimated total dose. It may be useful to emphasize, although it may seem obvious, that radiation exposure only occurs when the equipment is energized, which is a small fraction of the examination time.

Examination time also includes patient positioning, examination set-up (*e.g.*, parameter setting on the console in the technologist control room), and image review to assure adequate study quality.

The following section discusses methods for assessment of pregnancy, including sensitivity, and reasons for false positive and false negative results. It will provide information on the components for documentation by personnel involved in radiation exposure or planned exposure in the pregnant or potentially-pregnant individual.

7.1.2 *Assessment of Pregnancy*

There are several points about assessment of pregnancy that should be clarified. First, pregnancy needs to be defined. For the purposes of this Report, the pregnancy must be viable or likely to

be viable (*i.e.*, capable of success). For example, an ectopic pregnancy, while still a pregnancy, would not merit the same considerations for radiation exposure as an intrauterine pregnancy. There may be other medical conditions (*i.e.*, uterine anomalies) for which a viable pregnancy is either extremely unlikely or not possible. The range of these types of conditions is outside the scope of this Report and information will deal predominantly with the implantation of the fertilized egg or eggs within the endometrial cavity and embryological and fetal development that will result in a live birth. Views regarding actual *onset* of pregnancy vary from the time of conception to the time of implantation. Implantation follows conception by ~5 to 7 d (rarely, up to 10 d). However, gestational age is typically defined from the first day of the last menstrual period. This date precedes ovulation and fertilization by 10 to 14 d, and therefore precedes implantation by about three weeks. Finally, material is primarily focused on radiation exposure to any pregnant or potentially-pregnant women. However, appropriate precautionary measures should also be taken for accompanying individuals such as family members who are or may be pregnant.

Discussion of radiation exposure of the embryo or fetus subsumes identification of those women who are pregnant or potentially pregnant. There is essentially no risk of pregnancy for girls in the first part of the first decade and a very low risk in young females who have not yet began to ovulate and menstruate, and no risk for those women who are actually postmenopausal. Also those with hysterectomy, or oophorectomy, irreversible loss of viable reproductive organs or syndromic or other systemic diseases which preclude pregnancy are at no risk. In addition, pregnancy cannot occur without intercourse or other form of insemination. History of sexual activity, especially in the adolescent, however, may be unreliable and decisions about additional testing may be necessary. In addition, contraception may affect the probability of being pregnant. It is worth noting that nonabstinence forms of contraception can substantially reduce, but not altogether eliminate the risk of pregnancy. In the setting of potential radiation exposure, the effectiveness of contraceptive use in the prevention of pregnancy will have to be considered based on a combination of institutional or organizational, regional or national policies, guidelines, or standards of care.

The onset of reproductive capability is dependent on a functional menstrual cycle. The onset of menses is variable and may occur in otherwise healthy females before 10 y of age throughout teenage years. It is reasonable to establish an age range for normal female fertility. In the absence of a history of earlier menses or

menopause, this range is generally between 12 and 55 y of age (ACR, 2008; El-Khoury *et al*., 2003).

In conclusion, a woman should be considered potentially pregnant if she:

- is between 12 and 55 y of age (with no history of menopause), younger than 12 y of age and has started menstrual cycles, or older than 55 y of age without a history of menopause;
- has no reliable history or documented condition which results in sterility; and
- has not had a menstrual period beginning within the last three to four weeks.

7.1.3 *Methods for Pregnancy Assessment*

Methods for assessment of pregnancy consist of medical history including menstrual status and sexual history, signs and symptoms of pregnancy, physical examination (later in pregnancy), biochemical markers (urine and serum), or imaging evaluation, consisting predominantly of sonography. Assessment for pregnancy may include information obtained from a personal file, including medical history. This can include, in the medical setting, information from the imaging requisition. Information about potential pregnancy can also be obtained prior to the imaging or therapeutic procedure through interview or from a form completed by the individual or a responsible party, such as a parent. If potential pregnancy information is obtained through interview, then the details of this exchange should be adequately documented. Discussion with individuals who are under 18 y of age and not an emancipated minor should be discreet (ACR, 2008) in order to protect confidentiality. Some states provide for minors to get a pregnancy test without parental knowledge and, as recommended by the American College of Radiology, it is important to be familiar with the requirements in the applicable state (ACR, 2008). Professionals who interact with pregnant or potentially-pregnant women should be familiar with and use strategies to determine pregnancy status in minors, such as bringing an individual into the room prior to her parent or guardian. For example, this strategy can be used while introducing her to the examination procedure when first entering the room. In addition, there should be readily visible on-site signage and other potential information (*e.g*., with email or paper appointment information) to urge patients to notify the appropriate personnel about pregnancy or potential pregnancy *prior* to the examination or treatment. If the patient cannot report on pregnancy or potential pregnancy, this information may be obtained

from the family, guardians, or in the case of medical imaging, the requesting healthcare provider. If this information cannot be reliably determined, then routine biochemical assessment, such as a serum β-human chorionic gonadotropin (β-HCG) should be considered (El-Khoury *et al*., 2003).

Institutional or organizational policies should define those situations, including medical examinations, where doses to the embryo or fetus present an increased risk for potential health effects. Radiography which provides negligible uterine exposure, such as cervical spine, skull, distal extremity, or upper body, may not necessarily warrant adherence to a strict policy of pregnancy assessment through biochemical assay or comprehensive discussion including signed informed consent. However, individualized policies for what constitutes a negligible exposure should be determined based on available guidelines and standards for the individual practice, institution or organization.

Biochemical tests for pregnancy consist of quantitative and qualitative measures of β-HCG in the urine or blood. The use of quantitative testing of urine is becoming increasingly rare in preference for quantitative assay of blood. HCG is a glycoprotein dimer comprised of both alpha and beta subunits. There are several forms of HCG present in pregnancy and in women who are not pregnant. Biochemical methods for HCG assay in pregnancy detect elevated levels of the β subunit. Laboratory and over-the-counter tests may differ in the types of HCG they detect.

A brief review of embryology is necessary to begin to understand the basis for quantitative and qualitative pregnancy testing, as well as potential false-negative and false-positive examinations. It is important to realize that conception occurs before production of HCG, which is not produced until attachment of the fertilized egg to the endometrium. Prior to implantation, the zygote has divided into blastomeres through the morula stage to the blastocyst stage at ~5th day postconception (during the third week of gestation). Implantation in the endometrium occurs 5th to 10th day postconception (during the third or fourth week of gestation). This is the earliest time that the cellular elements of the trophoblast would form. HCG is produced by this trophoblastic tissue which is developed from an outer layer of cells of the blastocyst stage of the embryo. This tissue will eventually form the placenta so β-HCG does not become elevated until after implantation. β-HCG is measured in milli-international units per milliliter (mIU mL^{-1}). Normal β-HCG is <5 mIU mL^{-1}. β-HCG levels typically double about every 2 to 3 d initially, and eventually, about every 4 d, to a peak at ~12 to 16 weeks following the last menstrual period (gestational

age). Peak β-HCG is ~200,000 to 300,000 mIU mL^{-1}. HCG levels subsequently decline during the remainder of pregnancy but remain elevated until falling to normal levels in the postpartum period.

A pregnancy is considered present with a level of β-HCG ≥ 25 mIU mL^{-1}. Qualitative assessment of β-HCG is performed in either the urine or blood and the test results are either positive or negative. The home pregnancy test is a qualitative urine pregnancy test for β-HCG. The level of β-HCG required for a positive urine test is 20 to 50 mIU mL^{-1}. It is important to realize that a single β-HCG level of 5 to 20 mIU mL^{-1} should not be used to determine pregnancy. In addition, single β-HCG levels should not be used to ascertain the age of the conceptus. This estimate is better obtained with multiple quantitative β-HCG levels separated by several days. The accuracy of qualitative urine pregnancy test will depend on factors, including the gestational age, concentration in the urine, and expertise in performing the examination (Bastian *et al*., 1998). A quantitative blood test or sensitive urine test can detect HCG 6 to 12 d after ovulation, depending on the timing of implantation. Some sensitive home pregnancy tests can demonstrate gestational β-HCG levels as early as 10 d postovulation if ovulation indicators (such as urine luteinizing hormone ovulation levels) are being tracked.

The accuracy of home urine pregnancy tests approaches 90 % but can decrease to ~75 % (operator error range 24 to 32 % of users) with test inexperience (Bastian *et al*., 1998). Accuracy is higher with positive tests than negative tests. Reasons for a false-positive in a qualitative test include incorrect use of the test (Bastian *et al*., 1998), maternal use of medications which cross-react with the assay, and production of β-HCG by nongestational tissue, such as trophoblastic disease, and some liver and germ-cell tumors. In addition, with a very recent missed spontaneous abortion, β-HCG levels will be initially elevated and a single test could be positive whereas serial tests will show a rapid decline in β-HCG levels. A false-negative test can result from incorrect use of the test kit, testing too early in pregnancy, or, in rare cases, in ectopic pregnancy where there is some disorganization or absence of trophoblastic tissue to generate sufficient β-HCG.

Qualitative β-HCG testing of either serum or urine is more commonly performed to confirm pregnancy. Quantitative serum β-HCG testing is generally used for complications in pregnancy or potential pregnancy, including ectopic pregnancy, or uncertain dates. Qualitative urine or blood β-HCG assessment is more reliable beginning ~10 d after a missed menstrual period (during the first or second week of gestation), rather than before this time. This would be ~14 to 20 d after implantation (about three weeks after

ovulation). Since the lower level of β-HCG at this time is going to be >25 mIU mL^{-1}, then false-negative rates will be minimized.

Serum β-HCG is obtained *via* phlebotomy. Because this is a laboratory assay, obtaining results will take longer than the rapid (home) urine pregnancy test where the test results are essentially immediately available. False-positive and false-negative reasons will be the same as with qualitative assessment. Serial quantitative measures, however, will provide information as to whether the pregnancy is failing (poor growth or fall in sequential β-HCG levels), ectopic, or in some other way disordered to suggest nongestational β-HCG production (such as trophoblastic disease).

Sonography, using both transabdominal and endovaginal techniques, can also be used to assess for intrauterine pregnancy. Endovaginal sonography is usually reserved for evaluation of ectopic pregnancy, but would be more sensitive than a transabdominal scan early in gestation. The sensitivity in detecting very early pregnancies may also depend on the body type of the women (the transabdominal scan may be limited with obesity) and the expertise of the sonographer. In comparison with serum or urine pregnancy testing, sonography is expensive, and not expeditious. Sonography is used for such fetal surveys and for gestational complications. Ultrasound is considered reliable for a diagnosis once the β-HCG levels reach ~2,000 mIU mL^{-1}, which usually occurs by six weeks after the last menstrual period and sometimes as early as five weeks. This level is well beyond the lower threshold of β-HCG for biochemical assays for pregnancy assessment. When an unsuspected pregnancy is identified prior to an abdominal or endovaginal examination, a qualified expert should evaluate the potential dose to the embryo or fetus prior to the examination.

7.1.4 *Documentation of Pregnancy and Pregnancy Policy Considerations*

Assessment for pregnancy or potential pregnancy should be documented in the patient's medical record (Berlin, 1996; Jaffe *et al*., 2007a). This includes the method used to test for pregnancy and the results (ACR, 2008; Jaffe *et al*., 2007a). The policies and procedures for assessment and documentation vary however. Considerations for the establishment of a policy for radiation exposure in potentially-pregnant patients consist of several elements.

First, the responsibility for developing such a policy should be multidisciplinary (ACR, 2008; El-Khoury *et al*., 2003). Representation should consist of medical imaging expertise (radiologist or other imaging physician expert, medical physicist, radiation safety officer), obstetricians, and members of the local risk management

community (ACOG, 2004; Berlin, 1996; El-Khoury *et al*., 2003). For medical imaging, radiologists are one group of imaging experts in radiation effects for diagnostic and interventional procedures and should be invested in the development of the policy, particularly since it impacts management of patients in clinical practice. In addition, the policy should be consistent across all areas of exposure or potential exposure in the institution. At this time, while there are some guidelines available regarding establishment of a policy, such as through ACR (2008), within the imaging community there is still variability in imaging strategies for potentially-pregnant individuals (Jaffe *et al*., 2007a). For example, Jaffe *et al*. (2007a) in a survey of academic institutions noted that 74 % of those surveyed had a policy in place, while 25 % did not. Twenty-seven percent of those returning surveys did not have written consent available for imaging with CT. Twenty-seven percent of respondents did not have a policy for imaging of the acute abdomen in the pregnant individual (Jaffe *et al*., 2007a). The minority (14 %) of practices surveyed obtained urine or serum beta β-HCG evaluations in the setting of the acute abdomen, and most assessment of pregnancy was based on patient report.

Assessment of pregnancy is variable and there are currently no national requirements (ACR, 2008). Pregnancy assessment ranges from documentation based on a patient's report, obtaining a pregnancy test on all potentially-pregnant patients, or some combination of both. An example is given in Section C.1 in Appendix C. While many health workers in the imaging setting may have the opportunity to inquire about pregnancy status, the technologist will often be the individual who obtains this information (ACR, 2008). This may vary within an institution depending on whether it is an urgent care setting, such as the emergency department, versus the outpatient clinic. Finally, any qualitative or quantitative pregnancy test on all potentially-pregnant patients obviously incurs additional cost and may be inefficient in terms of examination performance.

The need for verbal informed consent, written informed consent, or signed informed consent also varies. (ACR, 2008; Jaffe *et al*., 2007a; Lowe, 2004). For each of these, the standard components include the potential benefit of the procedure (*i.e*., imaging examination), the potential risks and alternatives, and provide the individual an opportunity to ask questions. In addition, the information should use language understandable to the patient.

7.1.5 *Summary of Pregnancy Assessment*

Radiation exposure during pregnancy or in a potentially-pregnant female may add an additional risk factor due to fetal exposure.

Appropriate patient assessment requires an understanding of methods, and limitations of pregnancy screening and testing ranging from patient history to quantification of serum β-HCG. This screening information, as well as pregnancy assessment, and discussion with the patient or other responsible individuals or parties about the procedure, potential doses, procedural benefits and risks (*i.e.*, fetal risks), and alternate imaging or therapy strategies should all be documented in the medical record. The use of signed informed consent varies in clinical practice. An example is given in Section C.2 in Appendix C. Development and periodic review of, and accountability for a policy for evaluation of the pregnant or potentially-pregnant female should be interdisciplinary and be based on a combination of practice, institutional, organizational (including professional societies), as well as local, regional or national policies, guidelines and standards, when available.

7.2 Managing Dose and Mitigating Exposure

7.2.1 *Medical Diagnostic Imaging*

7.2.1.1 *Introduction*. Two considerations that need clarification when discussing management of dose from medical diagnostic imaging procedures are:

1. Understanding what diagnostic imaging entails, and how diagnostic imaging differs from other sources of medical radiation exposure, especially radiation therapy and interventional procedures, and other sources of environmental or occupational exposures.
2. Understanding how the fundamental radiation protection principles of justification of practices and optimization of radiation protection are applied to diagnostic imaging.

With these foundations, the techniques and technology, and strategies to effectively manage dose in diagnostic imaging of the pregnant or potentially-pregnant individual can be addressed.

With regard to Consideration 1, medical diagnostic imaging in this Report refers to methods that use ionizing radiation modalities or nonionizing modalities to depict anatomic or functional information, usually in a visual format. Ionizing radiation modalities include the use of x rays (*e.g.*, radiography, fluoroscopy and CT) and emissions from radioactive (or radiolabeled) compounds that interact with organs or areas in the body. Nonionizing modalities include ultrasound and MRI. Diagnostic imaging implies that the information will be used for the potential diagnosis of illness or

injury, as opposed to therapeutic procedures that consist of either therapy for treatment of cancer (radiation oncology) or interventional procedures (usually done under fluoroscopic guidance) such as angiography, central venous catheter placement, abscess drainage, or vertebroplasty.

A large proportion of diagnostic imaging involves ionizing radiation exposure. In addition, diagnostic imaging options for imaging evaluation in known or suspected pregnancy are either not subject to consensus standards or when consensus standards exist they may be variably utilized (Jaffe *et al*., 2007a). CT is often utilized (Lazarus *et al*., 2007) and its use has been increasing in the patient population (Lazarus *et al*., 2009). There is a direct and recognized real and potential benefit to the individual from a medical exposure as opposed to an exposure from environmental or occupational sources, where the benefit to the individual is indirect (*e.g*., salary compensation in occupational exposures), minimal or absent. The frequency of diagnostic imaging procedures is far in excess of that from therapeutic procedures. Diagnostic imaging will therefore be much more likely to occur in the setting of potential or known pregnancy, or occur in individuals in whom pregnancy was not known before the procedure. In addition, pregnancy itself can present additional medical complexities which prompt diagnostic imaging. For example, signs and symptoms secondary to pregnancy (such as vomiting or occasionally abdominal pain) may mimic those presenting in conditions in nonpregnant patients such as renal calculi, appendicitis, bowel obstruction, or inflammatory bowel disease. Pregnancy may predispose to disorders which may necessitate diagnostic imaging and clinical management (*e.g*., venous thrombosis, pulmonary thromboembolism). Finally, imaging findings secondary to pregnancy may overlap those in disease states such as gestational hydronephrosis versus an obstructing ureteral stone (Jaffe *et al*., 2007a).

Variable levels of dose to the embryo or fetus, some of which approach the range of dose that is associated with an observed increase in cancer risk to the offspring later in life, are often of concern to individual women undergoing diagnostic evaluation who are or may be pregnant as well as other family members and healthcare providers, such as referring physicians. This is unlike radiation therapy or interventional procedures, where given the more invasive nature and inherently higher risks, procedures are often more clearly weighted towards reducing maternal morbidity or mortality (versus fetal risk). In these latter circumstances, discussions should proceed on a case-by-case basis and will likely necessitate more involvement of a qualified expert in radiation

dosimetry than with diagnostic imaging (*e.g.*, see guidance in Dauer *et al.*, 2012). When a pregnant woman has radiation therapy at a site distant from the uterus (*e.g.*, the head, chest or extremities) careful evaluation of the dose to the embryo or fetus may reveal a low dose of protracted radiation administered over a period of weeks. In many such cases dose evaluation will indicate no increased risk for tissue reactions (deterministic effects) in the embryo or fetus. The potential risk of cancer to the embryo or fetus for protracted low doses and the uncertainties associated with the risk are discussed in Section 5.2.6.

With regard to Consideration 2, the fundamental radiation protection principles can be expressed as justification of the medical procedure (in particular, whether the imaging procedure is indicated for the individual patient), and optimization of radiation protection (*i.e.*, whether the dose from the procedure is commensurate with the medical purpose).

ICRP (2007a) states that the principle of justification applies at three levels in the use of radiation in medicine.

- *First level*: The proper use of radiation in medicine is accepted as doing more good than harm to the patient.
- *Second level*: A specified procedure with a specified objective is defined and justified (*i.e.*, judged to improve the diagnosis or treatment, or provide necessary information).
- *Third level*: The application of the procedure to an individual patient should be justified (*i.e.*, judged to do more good than harm to the individual patient).

Justification that a given type of diagnostic imaging procedure is appropriate for a given medical task (the second level), including in the pregnant patient, is a complex topic (Sistrom, 2009; Wall *et al.*, 2006), and is generally beyond the intent of this Report. Some of the complexities impacting justification are discussed in Section 7.2.1.2. The assumption here is that the procedure is appropriate for the clinical purpose and has already been deemed to be beneficial for a given patient.

Optimization of radiation protection then requires proper conduct of the procedure, in particular, techniques should be emphasized that manage the dose and thus manage the radiation risk to the individual. The imaging strategy (type of study or sequence of studies) and the technique for the modality should be appropriate. Implicit in this discussion is that imaging strategies that may be more appropriate for evaluation of the pregnant individual should be considered (Jaffe *et al.*, 2007a). With respect to technique, the desirable study quality has often been equated to maximal image

or examination quality (Frush, 2006). For example, multiple additional projections in radiography or increased x-ray tube current in CT may increase confidence that a fracture is present. Prolonged fluoroscopic evaluation may best define a dynamic or anatomic abnormality in the GI tract. At some point, however, the associated dose is not justified in the context of the potential benefit. While this point is impossible to define for all modalities and in all settings (as well as for all healthcare providers or individual patients), the stance that the highest image quality should be the goal is not appropriate when radiation exposure is involved. Image quality should be adequate for the indication (Frush, 2006). Acceptable study quality, then, entails a balance of image quality and radiation dose. The technical parameters for the examination should be predetermined as much as possible, and selected to provide adequate diagnostic information while managing the dose to the patient.

ICRP (2007a) recommends the use of the diagnostic reference level to implement optimization of radiation protection for procedures performed for medical imaging. Diagnostic reference levels are expressed as a readily measurable patient dose-related quantity for the specified procedure. If in routine conditions the levels of patient dose from a specified x-ray imaging procedure (or administered activity for a radiopharmaceutical) are unusually high or low for that procedure, a local review should be initiated to determine whether radiation protection has been adequately optimized or whether corrective action is required. Detailed discussions on the appropriate patient dose-related quantities and implementation of diagnostic reference levels are available from ICRP (2001; 2007b) and NCRP (2012).

7.2.1.2 *General Considerations*. An estimated 30 to 40 % of diagnostic imaging examinations have questionable indications (Cascade *et al*., 1998), and there is an increased focus on such issues that lead to overutilization of imaging in healthcare (Emanuel and Fuchs, 2008). This may be in part due to the practice of defensive medicine and self referral in the United States (Levin *et al*., 2008; Studdert *et al*., 2005). Additional factors that influence the utilization of diagnostic imaging for clinical evaluation are complex (Frush *et al*., 2009; Sistrom *et al*., 2009) and include:

- availability of resources (*i.e*., critical shortages in certain subspecialties may render a different decision process than the process used when there is adequate resources);
- time of service (*e.g*., availability of MRI or sonography after-hours in place of CT) (Doria *et al*., 2005);
- local, regional or national standards of care;

- prior experience and familiarity with specific patient populations or disease processes;
- patient population (*e.g.*, cultural, demographic and socioeconomic variation) (Fortier *et al.*, 2009);
- legal implications;
- marketing pressures;
- discrepancies in decision making as a result of medical training (Frush *et al.*, 2009); and
- patient and patient family requests or preferences.

The healthcare environment can also influence imaging evaluation. For example, in a high-stress environment such as the emergency department, decisions may need to be made urgently and without the benefit of data from physical examination or laboratory evaluation, changing the decision-making process for diagnostic imaging assessment. The availability of consultants may be limited and this may also affect decision making for obtaining diagnostic imaging (Frush *et al.*, 2009).

A single clear strategy for imaging, therefore, will almost certainly not be applicable in all situations. However, general guidelines and recommendations such as the American College of Radiology's Appropriateness Criteria®, and Practice Guidelines and Technical Standards (ACR, 2008) may be helpful in providing information for diagnostic imaging experts. In addition, evidence-based information will continue to provide guidance in terms of improving imaging algorithms, including consideration of risk factors such as radiation exposure in the pregnant patient. For the pregnant or potentially-pregnant patient, some of the general factors to consider when pursuing diagnostic imaging include the stage of pregnancy, the benefits of the procedure (*i.e.*, nonemergent evaluation versus a lifesaving imaging procedure), and the potential dose delivered to the embryo or fetus. In order to influence the balance towards the side of benefit and away from risk, individuals responsible for the imaging decisions should be familiar with strategies for dose management, such as:

- waiting to perform the examination in the postpartum period;
- use of other modalities that do not involve ionizing radiation; or
- modification of the technique (*e.g.*, lower tube current or limited scan range for CT, decreased number of projections for radiography).

A few additional points need to be considered. First, the information in the following material will deal predominantly with

methods that the user can employ to manage dose to the pregnant or potentially-pregnant individual undergoing diagnostic imaging. While cooperation between science, medicine and industry will continue to provide opportunities for technologic developments that may require less dose, discussion here will focus on more pragmatic steps that may be taken currently in the setting of diagnostic imaging by technologists, radiologists, and other imaging experts.

For diagnostic imaging, there are very few imaging pathways that do not entail some judgment and decision making based on the myriad of factors outlined above. Elements that should be taken into consideration when designing imaging strategies have been recently discussed in greater depth (Frush *et al*., 2009). These include:

- acceptance of responsibility by diagnostic imaging experts as major stakeholders in designing appropriate imaging strategies for pregnant or potentially-pregnant individuals;
- development of strategies or modification of current practice to be in line with available guidelines, standards and policies for imaging evaluation;
- investment of multiple disciplines in developing, implementing, reviewing and modifying imaging protocols that includes pertinent clinical expertise (*i.e*., emergency room physicians, surgeons, obstetricians); and
- review of established policies to assess the impact of the decision process on quality, safety and appropriate resource utilization.

7.2.1.3 *Radiography.* In general, settings used in radiography for the pregnant or potentially-pregnant patient will not change for those examinations performed for regions outside of the abdomen and pelvis, such as extremity or cervical spine evaluation. If it is necessary to obtain radiography which exposes the embryo or fetus, exposure factors should not be decreased below those values that have been determined to be appropriate for individuals who are not pregnant, and exposure factors may be greater dependent on the increased penetration that the gravid uterus may require. However, the least number of projections needed to obtain sufficient diagnostic information should be performed. Shielding of the abdomen or pelvis for radiography will eliminate only a minimal amount of externally-scattered radiation from the direct beam for an appropriately collimated examination. Shielding will not reduce internally-scattered radiation which is relatively low. Whether or not shielding of the abdomen and pelvis is routinely applied during radiography of extra-abdominal or pelvic areas will need to be

determined based on institutional practice or policy. However, the act of shielding may be viewed by the mother or family as giving careful attention to radiation protection.

7.2.1.4 *Fluoroscopy.* For fluoroscopy, the abdomen and pelvis should be shielded for procedures performed in regions outside of these truncal regions. Shielding would decrease the minimal amount of radiation from the primary beam which extends beyond the area of coverage, and may be useful to reduce anxiety in the pregnant or potentially-pregnant individual or their family members. It is exceptionally rare to need to do fluoroscopic evaluation of the abdomen or pelvis in the known pregnant or suspected pregnant patient (Lazarus *et al*., 2009). For example, GI tract luminal tract evaluation by MRI has been increasing (Hammond *et al*., 2008). During fluoroscopic evaluation, the use of magnification should be minimized. The image intensifier should be as close to the patient as is reasonable for performance of the procedure. For example, a 38 % increase in dose can result from an air gap of 10 cm as opposed to no air gap (Dixon, 2006). In addition, the distance of the x-ray source to the patient should be maximized. The exposure-rate setting should be as low as possible consistent with the need to provide sufficient diagnostic information. Fluoroscopic time should be minimized with frequent indicators for lapsed time (*e.g*., alarm every 1 to 3 min). Image-store archive rather than spot films should be performed as the former does not add any additional dose during the examination, and video recording can be utilized for review rather than incurring additional fluoroscopic time. Pulsed-fluoroscopic technology with low frame rate will also result in reduced dose (Hernanz-Schulman, 2006). Other modalities should be considered in place of fluoroscopy such as sonography or MRI. In addition, if ionizing radiation is requisite for diagnosis, then often a CT examination may provide superior anatomic detail at doses which may be similar to or lower than overall fluoroscopic doses (Gaca *et al*., 2008; Jaffe *et al*., 2007b).

7.2.1.5 *Computed Tomography.* For computed tomography (CT) in the pregnant or potentially-pregnant patient, the dose to the uterus resulting from examinations that are remote from the abdomen and pelvis (*e.g*., CT of the brain) is negligible (Table 3.2). This includes chest CT evaluation for the patient in the first trimester and first portion of the second trimester (Hurwitz *et al*., 2006). As with radiography and fluoroscopy, lead shielding would decrease the minimal amount of radiation from the primary beam which extends beyond the area of coverage (over-ranging) and is not useful in image formation. This amount of over-ranging will depend

partly on the number of detector rows. A larger number of rows (*e.g.*, 256 slices versus 16 slices) results in a larger effective beam width and more over-ranging (van der Molen and Geleijns, 2007). Current multidetector CT technology is being developed which will collimate this portion of the beam at the beginning and end of the examination, reducing over-ranging dose contributions. As with radiography and fluoroscopy, shielding of the abdomen and pelvis may be useful to reduce anxiety in the pregnant or potentially-pregnant individual or their family members. In-plane shielding of surface structures has been shown to reduce CT dose in both adults and children (Fricke *et al.*, 2003; Hopper *et al.*, 1997). However, there are currently no data on dose reduction or effect on image quality from in-plane shielding of the gravid uterus. With tube current modulation, which adjusts the tube current based on body geometry, tissue density, in addition to user preferences (Kalra *et al.*, 2004; McCollough *et al.*, 2006), the use of in-plane shielding becomes complicated, and *could conceivably increase dose if the manufacturer-specific modulation technology is not adequately understood* (Coursey *et al.*, 2008). General approaches to lowering dose to the pregnant or potentially-pregnant individual include: minimizing the scan coverage; avoiding multiple scan phases; adjusting tube current and peak tube potential to the indication (Paulson *et al.*, 2008), region scanned and size (*e.g.*, cross-sectional area) of the patient; and using tube current modulation technology (Kalra *et al.*, 2004; McCollough *et al.*, 2006).

7.2.1.6 *Nuclear Medicine*. Most diagnostic nuclear medicine procedures are performed using short-lived radionuclides (such as ^{99m}Tc) which typically do not impart high doses to the embryo or fetus, though this may not be the case for very early-stage embryos for which there is little data. For radionuclides that do not cross the placenta, the dose arises mostly from the radionuclides in the maternal tissue. For a number of radiopharmaceuticals that are rapidly eliminated by the maternal kidneys, the kidneys and bladder become a predominant source of irradiation. Maternal hydration and frequent voiding can reduce the dose in this situation. When feasible, using lower administered activities and longer imaging times can also lower the dose. If this approach is taken, it is important that the diagnostic quality of the images not be compromised as that would result in a dose to the embryo or fetus without the desired clinical information being obtained. It is also important to assess the ability of the mother to lie still, usually in a supine position, for the longer scan period before deciding on the reduced-dose approach. One example of using a reduced dose is in

a ventilation perfusion study; if pulmonary embolus is suspected, the perfusion study can usually be performed with 75 MBq rather than the typical 110 to 150 MBq.

The choice of radiopharmaceuticals is also important. The risks to the embryo or fetus should be discussed with the patient and the referring physician. For certain thyroid assessments, ^{123}I can be used in place of ^{131}I. Due to the ability of iodine to cross the placenta and accumulate in the fetal thyroid, and the fact that the fetal thyroid dose from ^{131}I is much higher than from ^{123}I due to the longer physical half-life and the decay scheme of ^{131}I, the use of ^{131}I in pregnant women should be carefully evaluated. Generally speaking, ^{131}I should not be used during pregnancy unless it is required as a lifesaving measure for the mother. The fetal thyroid begins concentrating iodine at 8th to 10th weeks postconception (10th to 12th weeks of gestation). Therapy with ^{131}I during pregnancy has been shown to have negative consequences including hypothyroidism and thyroid ablation in infants (Fisher *et al*., 1963; Goh, 1981; Green *et al*., 1971). If the pregnancy is discovered within 12 h of iodine administration, giving the mother 60 to 130 mg of stable potassium iodide will partially block the fetal thyroid and reduce thyroid dose. After 12 h post radioiodine administration, this intervention is not very effective (ICRP, 2000).

Another technique to lower dose to the embryo or fetus is to consider the sequence of multi-part examinations. In the case of a myocardial-perfusion study, if the mother receives the stress portion of the study first and it is normal, there is no need to proceed with the rest portion of the study thereby reducing the dose by up to 50 %.

In the case of studies using positron-emission tomography with CT, or single-photon emission computed tomography with CT, the dose from the CT portion of the study also needs to be considered. During single-photon emission computed-tomography studies, a low-dose CT scan is performed for attenuation and scattered radiation correction. Though positron-emission tomography with CT studies are not commonly ordered for pregnant women, particular consideration should be paid to the CT acquisition parameters of the CT component when a study is ordered. In some cases, a diagnostic-quality CT may be required. In other cases, the CT may only be needed for attenuation correction thereby leading to a lower dose to both the patient and the embryo or fetus.

7.2.1.7 *Modifications of Diagnostic Imaging Strategies for Pregnant Patients*. In addition to technical modifications, strategies for imaging evaluation of the pregnant patient may be modified to reduce dose to the embryo or fetus; however, any adjustments

should not be made at the expense of a loss of necessary diagnostic information. Imaging pathways which may be modified in pregnancy are best clarified prior to the examination or should exist as a protocol so that the medical staff is in agreement, and the decision process can be explained to and discussed with the patient succinctly, clearly, and in a consensus fashion. Modifications of existing protocols for pregnancy should be based on a combination of available literature, local resources including experience, and be in agreement with available policies, guidelines, and standards of care (*e.g.*, Goldberg-Stein *et al.*, 2011; Wang *et al.*, 2012b). Information obtained from surveys will also be helpful as this establishes needs, and current practice patterns, as well as potentially-identifying challenges in policy development (Jaffe *et al.*, 2007a). For example, in one survey of academic centers, MRI tended to be used more often in the first trimester for suspected appendicitis versus the second and third trimester where CT was used more frequently. With possible appendicitis, 48 % of respondents chose CT over MRI in the second trimester, and 58 % in the third trimester. In the first trimester, 46 % chose MRI versus 32 % for CT (Jaffe *et al.*, 2007a).

7.2.1.8 *Image Gently® and Image Wisely® Philosophy.* Because of the growing concern with radiation from medical imaging and potential risks, there has been an increasing call for measures to address radiation protection of individuals through organizations such as professional societies, cross-disciplinary national and international organizations, and regulatory groups. One such organization for children, the Alliance for Radiation Safety in Pediatric Imaging, was founded by four organizations: the Society for Pediatric Radiology, the American Association of Physicists in Medicine, the American College of Radiology, and the American Society of Radiologic Technologists (Goske *et al.*, 2008a). The fundamental philosophy of this organization, now comprised of ~55 affiliate professional organizations, including 15 international organizations, is on advocacy through education regarding dose management, rather than taking an alarmist approach. The model for the various campaigns is social marketing where behavior is altered through communication strategies (Goske *et al.*, 2008b). The chief strategies for this successful program have been representation by reputable organizations, commercial (or special interest group) independence, orchestrated rollouts of the campaigns (such as the Image Gently® CT Campaign in 2007) (Goske *et al.*, 2008a), reliance on affiliates for dispersion of information originally vetted through media experts, electronic media, content control, identified spokespersons staying on message, and controlled access (*e.g.*,

spokespersons). The impact of the CT Campaign was discussed in light of reduced use of CT at 39 U.S. children's hospitals in one recent publication (Townsend *et al*., 2010), and the Image Wisely® Campaign, addressing similar radiation protection issues in the adult population, was recently formed modeled on the success of the Alliance. Among objectives of this new focus on adult radiation protection will be radiation management in medical imaging of the pregnant or potentially-pregnant patient.

7.2.1.9 *Summary of Dose Management in Diagnostic Imaging*. Outside of ubiquitous background radiation, the likeliest source of radiation exposure to the pregnant or potentially-pregnant individual is from medical sources. Of the medical sources, diagnostic imaging is a much greater proportion of examinations and a larger collective dose than interventional procedures, especially in the pregnant or potentially-pregnant population. Given the high frequency of pregnancy, and current U.S. trends in medical imaging, diagnostic evaluation in this population is inevitable. For any patient, the decision to conduct diagnostic imaging should balance the benefit and risk to the patient. While justification of the procedure is an important consideration, this decision process is quite complex and variable. However, understanding some elemental radiation-reduction strategies in radiography, fluoroscopy, CT, and nuclear medicine will help to achieve the goal of dose management in the application of diagnostic imaging to the pregnant or potentially-pregnant individual.

7.2.2 *Radiation Therapy*

When a pregnant woman is diagnosed with cancer for which radiation therapy is the standard treatment, or part of the standard treatment, a benefit-risk assessment is generally needed. Consultations among the team of cancer specialists as well as the woman's obstetrician are necessary to formulate a treatment plan that takes into consideration the risk of the disease to the woman and the risk to the embryo or fetus. If the cancer is in an early stage, is not progressing rapidly, and is not immediately life-threatening, it might be possible to postpone radiation therapy until after delivery. Alternatively, some other forms of therapy, including the use of certain chemotherapeutic agents after the first trimester can be considered until after delivery of the baby. The risk of teratogenicity from these chemotherapy agents has been reported to be 10 to 25 % in the first trimester (Doll *et al*., 1988; Nicholson, 1968; Selig *et al*., 2012). However there has been no evidence of increased risk of teratogenesis during the second and third trimesters (Berry

et al., 1999; Lishner and Koren, 2001; Zemlickis *et al*., 1996), although there have been reports of higher rates of stillbirth and low birth weight (Bachanova and Connors, 2008; Doll *et al*., 1989; Zemlickis *et al*., 1992; 1996).

If radiation therapy has to be used and the pregnancy is early, a detailed discussion on the potential risk to the embryo or fetus and on the option of termination of the pregnancy would be prudent. If radiation therapy is necessary, it would be prudent to consider measures that would minimize the dose to the embryo or fetus. In summary:

- Avoid the use of radiation therapy, whenever possible, on pregnant woman diagnosed with cancer without jeopardizing the woman's life. Consider the use of alternative treatment such as surgery and or chemotherapy after the first trimester, and postpone radiation therapy until after delivery.
- If radiation therapy is necessary, avoid directions of the radiation beam that would be incident on the gravid uterus, and minimize the field size as well as the dose.
- Whenever irradiating a pregnant woman, use appropriate shielding over the abdomen and pelvis to reduce dose to the embryo or fetus from external leakage and scattered radiation. For irradiation of the brain, head and neck, upper chest, and breast, phantom studies using external shields have shown that the dose to the embryo or fetus is generally small, in the range of 0.01 to 0.72 Gy, depending on the gestational age.
- For intensity-modulated radiation therapy, consider adjusting the scanner settings to minimize treatment-planning cumulative dose to the embryo or fetus.

7.2.2.1 *Treatment Simulation*. The dose to the embryo or fetus from simulation procedures is very low and likely similar to simple diagnostic procedures if the x-ray beam is not directed toward the gravid uterus (Fenig *et al*., 2001). If a conventional fluoroscopic simulator is used, it is advisable to keep the number of fluoroscopic exposures to a minimum. If a CT simulator is used, it is also advisable to keep the CT volume to a minimum. The use of a lead apron over the abdomen and pelvis of the patient is sometimes used but is not absolutely mandatory as it would in theory reduce only the already very low externally-scattered radiation from these procedures. However, it may provide reassurance for the patient and indicate care on the part of the operator.

7.2.2.2 *Radiation Treatment Delivery*. It is important to avoid any therapeutic radiation beam being directly incident on the gravid

uterus. When irradiating a tumor some distance from the gravid uterus, considerations should be made to minimize the radiation exposure to the embryo or fetus. There are several sources of radiation exposure to the embryo or fetus, including externally-scattered radiation, internally-scattered radiation and leakage, or partially transmitted radiation through beam shaping devices such as a Cerrobend block or multileaf collimator. It is not possible to shield radiation scattered internally (inside the body). However, externally scattered radiation can be shielded. One reported method when irradiating tumors of the head and neck or upper chest region is to use four to five half-value layers of lead shield on top of a special table placed over the abdomen and pelvis of the patient during radiation therapy (Woo *et al*., 1992). Methods of estimating dose to the embryo or fetus using phantoms have been described (Cygler *et al*., 1997; Karacam *et al*., 2009; Mazonakis *et al*., 2003), as well as a method using Monte-Carlo simulations (Bednarz and Xu, 2008; Han *et al*., 2009). Several estimated fetal doses from radiation therapy of cancers during pregnancy are listed in Table 7.2. For radiation treatment of brain tumors during pregnancy where the tumor dose was 68 to 78 Gy, phantom measurements in one report estimated the total fetal dose to be 0.03 to 0.06 Gy (Sneed *et al*., 1995). Leakage contributed 20 to 74 % of the fetal dose, internally-scattered radiation 13 to 20 %, scattered radiation from the collimator 9 to 33 %, and scattered radiation from the wedge 4 %. For breast cancer irradiation using tangential beams to 50 Gy (treatment dose), the estimated maximum dose to the embryo or fetus ranged from 0.03 to 1.43 Gy depending on the stage of the pregnancy (Fenig *et al*., 2001; Van der Giessen, 1997). The use of appropriate external shielding could reduce the dose to the embryo or fetus ~50 % (Greskovich and Macklis, 2000; Van der Giessen, 1997). For irradiation of the neck or neck and mediastinum to 35 to 40 Gy (treatment dose) in early Hodgkin's lymphoma, phantom measurements have yielded a range of fetal doses from 0.014 to 0.245 Gy using ^{60}Co and a 6 MV linear accelerator (Mazonakis *et al*., 2003; Woo *et al*., 1992). In one report where 16 pregnant women with Hodgkin's lymphoma were irradiated using external shielding over the abdomen and pelvis, all 16 women subsequently delivered full-term normal infants (Woo *et al*., 1992). For irradiation of brain tumors to 54 Gy (treatment dose) the estimated fetal dose was from 0.022 to 0.59 Gy and lead shielding reduced the dose by 26 to 71 % depending on the distance from the isocenter, field size, and gestational age (Haba *et al*., 2004).

Devices such as external wedges that are attached to the head of the linear accelerator can scatter the radiation beam before it

TABLE 7.2—*Estimated dose to the embryo or fetus for radiation therapy of cancers during pregnancy.*

Site	Tumor Dose (Gy)	Dose to the Embryo or Fetus (Gy)	Reference
Brain	54	0.022 – 0.59 (26 – 71 % reduction with shielding)	Haba *et al.* (2004)
Brain	68 – 78	0.03 – 0.06	Sneed *et al.* (1995)
Head, neck, mediastinum	35 – 40	0.014 – 0.245	Mazonakis *et al.* (2003), Woo *et al.* (1992)
Breast	50	0.03 – 1.43 (50 % reduction with shielding)	Fenig *et al.* (2001), Van der Giessen (1997)

enters the patient and can thereby increase the radiation exposure to the embryo or fetus; therefore, their use should be avoided or minimized. Multileaf collimators from different manufacturers have different amounts of leakage radiation through them. Whenever possible, it would be prudent to use a collimator with the least amount of leakage when treating a pregnant woman. The absolute quantity of leakage radiation is also a function of the number of monitor units used to deliver a desired dose to the target. Modern radiation-therapy techniques such as intensity-modulated radiation therapy could require up to several-fold more monitor units than conventional radiation-therapy techniques to deliver the same dose to a tumor, and therefore could increase the dose to the embryo or fetus (Hall, 2006). It would be prudent to avoid the use of intensity-modulated radiation therapy for a pregnant woman, although a method to reduce the fetal dose by a factor of 3.5 when using intensity-modulated radiation therapy in a pregnant patient has been proposed (Josipovic *et al*., 2009). Image-guided radiation therapy would expose a pregnant patient to additional doses of radiation before each fraction of radiation therapy and should be avoided.

Photon beams with energy >10 MeV lead to production of neutrons (which have a higher RBE than x rays) by nuclear interaction, and a benefit-risk assessment in the use of high-energy photons in treating pregnant women would be advisable.

One advantage of proton-beam therapy over photon-beam therapy is a reduction of the integral dose with proton therapy. A lower integral dose from proton-beam therapy for a pregnant woman would theoretically decrease the dose to the embryo or fetus from scattered radiation. However, proton beams also produce a small amount of neutrons when they strike materials with high atomic mass in the proton treatment machine before they exit the machine. In addition, a small quantity of neutrons is produced by interaction of protons with the tissues within the patient. The quantity of neutrons thus produced is proportional to the energy of the protons. Measurements in an anthropomorphic phantom of neutron-scattered dose equivalent to an embryo or fetus from proton-beam therapy of the mother have been reported (Mesoloras *et al*., 2006). Suggestions have also been made to use high-density materials with low atomic mass (such as tungsten and tungsten alloy) to make collimators and external shields for proton-beam therapy to reduce the neutron exposure to the patient (Taddei *et al*., 2009). Nonetheless, in a pregnant woman, the potential advantage of lower integral dose with proton-beam therapy should be weighed against the potential adverse effect of neutrons on the

embryo or fetus. There have not been sufficient clinical data in humans to allow a definite opinion regarding the use of proton-beam therapy in pregnant women.

7.2.3 *Occupational Exposure*

Every employer has an obligation to provide hazard information to its employees and to establish mechanisms to maintain a safe and healthful work environment. The U.S. Department of Labor has standards that call for Workplace Injury Illness Prevention Programs. As ionizing radiation has long been identified as a workplace hazard, policies and procedures should be in place for anyone who routinely works around sources of ionizing radiation. In addition, NRC (1995) requires that all individuals likely to receive an annual effective dose of 1 mSv or more from working around radioactive material in the course of their employment be instructed in the health protection issues associated with exposure to radiation. In addition to establishing dose limits for workers and the requirement that licensees use procedures and engineering controls to the extent practicable to achieve the ALARA principle, NRC (1998) has also established the equivalent dose limit for the embryo and fetus of an occupationally-exposed woman. If worker activities are such that an individual could receive >1 mSv (annual effective dose) from external sources or occupational intake of radioactive material, the occupational radiation protection program is required to have a fetal assessment program (NRC, 1999). Upon formal written declaration of pregnancy by a woman, the employer is required to provide counsel that includes the potential effects of radiation exposure to the embryo and fetus and is required to limit the equivalent dose to the embryo and fetus (for the entire gestational period) to 5 mSv. It is important to realize that the assessment of dose conducted as part of the radiation safety program is meant to demonstrate regulatory compliance with the established limits, not to calculate the true equivalent dose received by the embryo or fetus. It is most common to assess the dose through the use of a dosimeter worn at the woman's waist. External dosimeters are typically calibrated to provide the dose at 1 cm depth. Therefore, utilizing the value from a dosimeter worn at the waist is usually an overestimate of the actual dose received. Keeping the monthly value <0.5 mSv (equivalent dose) is the most conservative and common method utilized to demonstrate regulatory compliance. More detailed descriptions of monitoring programs for equivalent dose to the embryo and fetus can be found in Stabin *et al*. (2008).

Methods for implementing the ALARA principle for external doses include time, distance and shielding. Reducing the amount of

time spent in close proximity to radiation sources reduces exposure but may not be practical or possible. If an individual cannot reduce the time spent in an area, the person's distance from the source may be increased. The inverse square law applies when the source of radiation is generated from a defined point or small area. The strength of the radiation field is inversely proportional to the square of the distance from the source. So practically speaking, each time a person's distance is doubled from the radiation source, the dose rate for the person drops by a factor of four. Lastly, depending on the type of ionizing radiation an occupational worker is exposed to, shielding may be very helpful in lowering dose.

For those whose occupations involve flying on a regular basis, reducing the amount of time spent in flight is the only practical way to reduce dose. The average annual effective dose for air travel crew is on the order of 3 mSv (NCRP, 2009; UNSCEAR, 2000).

In the medical environment, it is common practice for radiologic technologists to wear lead aprons in order to keep their dose to a minimum. In nuclear medicine, lead aprons do not afford as much protection as they do in an x-ray environment but they can be employed to lower a technologist's dose by 20 to 40 % under certain circumstances, which may allow them to continue to perform some tasks while pregnant. Shielding for radiopharmaceuticals is critical. Lead or tungsten syringe shields are an essential tool in maintaining occupational exposures as low as possible. Manipulations behind lead L-block shields and the use of lead pigs are commonplace as should be the practice of maintaining as great a distance as possible from the source of radiation consistent with providing good medical care.

Staff at nuclear power plants receive an average annual effective dose of 1.9 mSv, although 5 % of plant staff receive annual effective doses >5 mSv (NCRP, 2009). There has been a steady decline in both the number of individuals with recordable doses and the annual collective dose at power plants since the mid-1980s. This decline can be accounted for because of increased efficiency of reactor operations with fewer and shorter outages, improvements in reactor coolant chemistries and materials, careful planning for outages, increasing emphasis on the ALARA principle and radiation safety, improved tools and procedures, and a renewed emphasis on cleanliness of the work environment. Careful review of the work duties of the pregnant power plant worker should allow for continued work while remaining well below the dose limit.

Any risks from occupation exposure are considered minimal as long as the regulatory dose limits are met. Additional restrictions may be imposed when an occupationally-exposed woman declares

a pregnancy, depending on the evaluation of the job functions and her typical pre-pregnancy dosimeter values. In the case of a nuclear medicine technologist, who historically may have received >0.5 mSv per month on her whole-body dosimeter (personal dose equivalent), there may be a need to modify the work schedule or duties. A few examples of such modifications are: restricting the number of cases the technologist is involved in each day, restricting the technologist from administering radiopharmaceuticals, or assigning the technologist to scheduling patients and administrative duties such as ordering doses and postacquisition image processing.

7.2.4 *Accidental or Deliberate Exposure*

Detailed recommendations for management of terrorist incidents involving radioactive material can be found in NCRP Report No. 138 (NCRP, 2001b). Key aspects of particular relevance to pregnant women are summarized below.

7.2.4.1 *Dose Estimation*. A critical requirement following accidental or deliberate release of radionuclides is the need for area measurements of radiation levels at a wide array of local heavily-populated sites outdoors and indoors following an accident or a terrorist radiological incident. Identification of the types and levels of radionuclides generated is important, as is assessment of a pregnant woman's distance from the source(s), shielding by natural and man-made structures, time since exposure (to determine duration of exposure), and behavior to assist in estimating inhaled and ingested amounts. Absorbed dose from a single accident or deliberate release may vary by organ. For an external source, the variation may be more notable if there is nonuniform or partial-body irradiation when an individual is very close to the source or when part of the body is shielded from the source. For internal sources, the absorbed dose distribution will reflect the route of intake, and the kinetics of the radionuclide (*e.g.*, ^{137}Cs is generally uniformly distributed, whereas ^{131}I and ^{123}I are deposited in the thyroid and ^{90}Sr/^{90}Y in the skeleton). A pregnant woman's risk of illness and her prognosis will be reflected by the organ dose, and treatment recommendations will be based on the dose range.

The absorbed dose to the embryo or fetus depends on the physical and chemical nature of the radionuclide. For example compounds that are soluble in water and in ionic form, such as iodides, can easily cross the placenta whereas other compounds may be affected by the placental barrier (NCRP, 2001b). Effects on the embryo or fetus depend not only upon absorbed dose, but also on

RBE (Jiang *et al*., 1994; Narra *et al*., 1991), and often depend on the time of exposure relative to conception (CDC, 2005; ICRP, 2000; 2003; NCRP, 2001b). The dose should be estimated to determine the potential for health effects. Physicians should seek assistance from qualified experts, such as hospital medical physicists or health physicists, for estimating the dose to the embryo or fetus (CDC, 2005). The Radiation Emergency Assistance Center/Training Site (Oak Ridge Institute for Science and Education), the Health Physics Society, and the Conference of Radiation Control Program Directors, Inc. are major resources for expert advice or lists of available experts.

7.2.4.2 *Immediate Clinical Requirements and Recommendations to Limit Exposure*. Radiation injury can result from external irradiation, external contamination with radioactive material, and internal contamination by inhalation, ingestion, or transdermal absorption. Thermal burns and traumatic injuries may also accompany radiation injury (Waselenko *et al*., 2004). A detailed description of appropriate medical management of all persons in the event of accidental or deliberate incidents involving radioactive material (applicable also for pregnant women) can be found in NCRP Report No. 138 (NCRP, 2001b), and Waselenko *et al*. (2004).

Detailed methods for decontamination are also described in NCRP Report No. 138 (NCRP, 2001b). Hospital management of radiation casualties is described in several texts and articles (*e.g*., Waselenko *et al*., 2004). Current medical advice can be obtained from the Radiation Emergency Assistance Center/Training Site at Oak Ridge Institute for Science and Education and from the Medical Radiobiology Advisory Team at the Armed Forces Radiobiology Research Institute.

7.2.4.3 *Countermeasures Recommended*. Countermeasures recommended for all persons are outlined in Table 7.3. Some of these countermeasures (*e.g*., sheltering and respiratory protection) are effective (reducing exposure from external sources and internal contamination up to fivefold) and are associated with relatively little negative impact if carried out for relatively short periods of time. Other measures (*e.g*., evacuation) may avert exposures from all pathways, but may be quite disruptive. Personal decontamination may be as simple as undressing, showering and changing clothes, or may involve the need for use of special agents under medical oversight for extremely high levels of contamination. Measurement of radionuclides in water and food will likely occur before restricting consumption of contaminated water or food. Administration of

TABLE 7.3—*Countermeasures recommended after accidental or deliberate release of radionuclides, for each route of exposure.*

Exposure Pathway	Available Countermeasures
External: radiation from radionuclides in plume	Sheltering, evacuation, control of access
Internal: contamination from radionuclides in plume	Sheltering, respiratory protection (cover nose and mouth), administer stable iodine, evacuate, control access
External: contamination from surface deposited contamination and activation products	Sheltering, evacuation, control of access, decontamination
External: radiation from surface deposited contamination and activation products	Sheltering, evacuation, relocation, control of access, decontamination
Internal: contamination due to resuspension	Evacuation, relocation, control of access, decontamination
Internal: contamination due to personal contamination	Control of access, decontamination
Internal: radiation due to ingestion of contaminated water and food	Control of food and water and use of stored animal feeds

potassium iodide can reduce or block uptake of radioactive iodine in the thyroid of exposed individuals. Because the risk of thyroid cancer decreases with increasing age at exposure, the value of administration of potassium iodide to most adults is limited. Because the thyroid of the fetus and child is quite sensitive to induction of thyroid cancer from an internal source of radioiodine, administration of potassium iodide to pregnant women, neonates, and young children is recommended, if administration is done as soon as possible (NCRP, 2001b).

7.2.4.4 *Long-Term Follow-up*. Long-term follow-up studies of atomic-bomb survivors exposed *in utero* have shown statistically-significant excesses of cancers developing decades after a single acute exposure (Preston *et al*., 2008). Based on a screening study

carried out during 2003 to 2006 following the April 1986 Chernobyl nuclear reactor accident, an increase in radiation-related risk of thyroid cancer (that was not statistically significant) was seen in offspring of mothers living in contaminated areas of Ukraine at the time of the accident compared with the risk in offspring of mothers living in other noncontaminated regions of Ukraine at the time of the accident (Hatch *et al*., 2009). Despite the limited database and relatively small populations, the preliminary results on risk of thyroid cancer and other thyroid disorders (Hatch *et al*., 2009) and on estimated thyroid doses (with an arithmetic mean of 72 mGy and a range of <1 to 3,200 mGy) (Likhtarov *et al*., 2011) from these studies in Ukraine suggest that follow-up of the populations for cancer risks is important to increase understanding on the long-term health effects (Chen and Moir, 2009).

8. Nonionizing Modalities and Sources

When there is the need to image a pregnant patient, MRI and ultrasound are often the preferred modalities for the required diagnostic information.

8.1 Risks to the Embryo or Fetus During Magnetic-Resonance Imaging

8.1.1 *Introduction*

Since its introduction as a clinical imaging modality in the early 1980s magnetic-resonance imaging (MRI) has become a widely used and indispensable diagnostic tool in medicine. There are ~28 million MRI examinations performed annually in the United States. Only small percentages are performed on pregnant patients. However, when there is the need to image a pregnant patient, MRI and ultrasound are often preferred modalities if the required diagnostic information can be obtained satisfactorily without using ionizing radiation. In most MRI examinations of pregnant patients the exposure of the embryo or fetus is incidental to the woman's examination. However, in recent years there has been an increase in the use of MRI to image the developing fetus. Ultrasonography is the primary modality used in direct fetal imaging. However, MRI is indicated if ultrasound is inconclusive and there is a high suspicion of fetal anomaly, particularly those involving the CNS. While MRI is very sensitive to motion artifacts which had precluded its practical use in fetal imaging, the development of fast imaging techniques in the mid-1990s allowed MRI of the fetus to become an important adjunct to ultrasonography in the evaluation of a developing fetus.

During an MRI examination, the embryo or fetus is exposed to magnetic and electromagnetic fields from three sources:

- RF fields from the RF transmitter coil that oscillate at tens to hundreds of megahertz, depending on field strength (*e.g.*, for 1.5 T MRI systems, the RF magnetic field oscillates at 63.858 MHz);
- time-varying magnetic field gradients producing field changes on the order of 10 T s^{-1}; and

- static main magnetic field of the MRI system (the so-called "field strength"), which for clinical use is typically 1.5 or 3 T.

The magnitude of magnetic and RF electromagnetic field exposure of an embryo or fetus during an MRI examination of the mother depends, among other things, upon the body part being examined, the specific types of pulse sequences selected, and other scanning parameters used for the examination. The highest fetal exposure to the RF and static magnetic fields occurs when the embryo or fetus is imaged directly and is in the center of the imaging chamber (*i.e.*, isocenter of the magnet and RF transmitter coil). In contrast, higher exposure of the embryo or fetus to the time-varying magnetic field gradients occurs when the embryo or fetus is further away from the isocenter (*e.g.*, chest MRI examination of the mother). All of these sources of exposure, their risks, and safety guidelines will be discussed below.

8.1.2 *Effect of Radiofrequency Electromagnetic Fields*

The main concern regarding radiofrequency (RF) electromagnetic fields is direct heating of tissue, due to deposition of energy carried in the RF field. Excessive heating can overwhelm the thermoregulatory capacity of the body resulting in a variety of potential adverse health effects associated with the heat stress from a prolonged elevation of core temperature. Of special concern in this document is that sustained temperature elevation in the embryo or fetus may be teratogenic. As with all thermally-modulated injuries, the higher the temperature above normal, the shorter the exposure period before a detrimental effect occurs (Edwards, 2006). Intense localized RF fields are also capable of producing burns. About 100 MRI-associated skin or surface burns were reported to FDA from January 2005 to June 2009, many of which were not due to any extraneous leads or other conductors (FDA, 2009).

The RF fields utilized in MRI systems are produced by the RF transmitter coil. In the United States, FDA requires that all MRI manufacturers make an accurate estimate of the average specific absorption rate (SAR) for every pulse sequence and scanning prescription that will be used on a patient. The SAR is an estimate of the energy deposited by the transmitted RF field per unit time (*i.e.*, RF power) per unit mass of tissue expressed in units of W kg^{-1} and sometimes referred to as the energy density. The average SAR is calculated using the patient's total weight, and thus represents a whole-body average, rather than a localized SAR. The SAR limits imposed by FDA on the embryo or fetus are the same as those

imposed on the mother. Consequently, the automatic calculation of SAR by the MRI system does not estimate SAR for the embryo or fetus or even (except for the increased weight) depend on whether the patient is pregnant, or if the developing fetus is being directly imaged rather than the mother.

When a particular body part of the mother is being imaged, that body part is placed at the isocenter of the scanner where the RF exposure is greatest. While MRI systems do not estimate the average SAR that the embryo or fetus experiences, the SAR for the embryo or fetus will be at its lowest when physical distance of the embryo or fetus from the isocenter of the imaging chamber is greatest. When the developing fetus is being directly imaged, the mother will be positioned so that the womb is in the center of the imaging chamber, in which case, the SAR for the developing fetus will be at its highest. There is general agreement, however, that the maximum local SAR occurs in the mother, and the whole-body SAR to the embryo or fetus will likely be lower than the corresponding maternal whole-body or partial-body SAR.

For a given pulse sequence, the SAR depends on the number, shape, power and duration (as well as other aspects) of the RF pulses. The SAR generated by an RF pulse in the standard scan can be reduced by increasing the duration of the pulse while decreasing the magnetic field strength. While this can reduce the diagnostic capabilities of the scan, the scan may still be sufficient to resolve the clinical question while effectively reducing the SAR. The SAR generated by RF pulses can also be reduced by direct computer optimization of pulse shapes with lower peak amplitudes and longer duration to reach a desired excitation of the protons while achieving a desired SAR.

FDA limits the average whole-body SAR during MRI examinations to 4 W kg^{-1} for any 15 min period. By way of comparison, the Federal Communications Commission (Cleveland *et al*., 1997) limits the maximum RF exposure in the head from cell phones to 1.6 W kg^{-1} over any 1 g of tissue and limits the whole-body average SAR for continuous exposure of members of the public from all RF sources to 0.08 W kg^{-1}. The International Electrotechnical Commission (IEC) has established three levels of MRI system operation (normal mode, first-level controlled mode, and second-level controlled mode) (IEC, 2010). These levels have been incorporated into the software of the MRI systems of most major manufacturers. Each level specifies the maximum average whole-body SAR permitted during a specified interval of the scanning session. The normal mode permits whole-body SARs up to 2 W kg^{-1} during which the body's core temperature would not be expected to rise by more than

0.5 °C. The first-level controlled mode limits SAR to no more than 4 W kg^{-1}, and requires the approval by the radiologist responsible for the examination. Whole-body SAR of 4 W kg^{-1} would not be expected to raise the core temperature by more than 1 °C. The second-level controlled mode permits the SAR to exceed 4 W kg^{-1} during the examination, but stipulates that this level is to be used only under an approved Institutional Review Board protocol and signed patient consent.

The implicit conditions embedded in these SAR limits include assumptions that the adult imaged has normal thermoregulatory control mechanisms and is imaged in a favorable heat loss environment where temperatures in the scanner are maintained <24 °C and that the humidity is maintained <60 %. However, the embryo or fetus exists in a well insulated environment where the embryonic and fetal circulation is isolated from the maternal circulation and the normal heat loss mechanisms through the skin are not directly available to the embryo or fetus. Owing to its robust metabolism and more limited heat removal mechanisms, the embryo or fetus maintains a temperature slightly higher (~0.5 to 1 °C) than that of the mother (Adamson, 1966). Waste heat is primary removed by the large blood flow through the placenta in which the umbilical vein carries relatively cooler blood to the embryo or fetus. The amniotic fluid also helps to dissipate heat, and thus confers some additional protection against localized temperature increases.

Inhomogeneity of the RF field and complex interactions of the RF field in tissue leads to localized energy deposition with higher SAR values than are computed for the whole body. As noted by Gowland and De Wilde (2008), the mathematical modeling of local SAR or hot spots in the embryo or fetus during MRI procedures has been the focus of the recent literature concerning embryonic and fetal SAR (Dimbylow, 2007; Hand *et al*., 2006; Shamsi *et al*., 2006). FDA limits local SAR to 8 W kg^{-1} for any period of 5 min in 1 g of any tissue (other than the extremities for which higher SAR levels are allowed). The IEC SAR limit for local exposure averaged over any 10 g of contiguous tissue is 10 W kg^{-1} for the normal mode and first-level controlled mode during MRI examinations. Recent work with numerical models representing different stages of pregnancy utilized the Finite-Difference Time-Domain method to calculate the energy absorption inside pregnant woman exposed to MRI RF fields at 64 MHz (Shamsi *et al*., 2006). Their results indicated that, for a given set of imaging conditions, the 10 g averaged embryonic and fetal SAR increases during the pregnancy, with a peak around the fifth month. This same analysis indicated that, while imaging in normal mode did not violate any of the IEC SAR limits, imaging

in the first-level controlled mode may result in exceeding the 10 g averaged SAR limit of 10 W kg^{-1} in the fetus beyond the third month of pregnancy, reaching a peak of 60 % over the limit in the fifth month.

FDA does not provide special limits for imaging pregnant patients, or for direct imaging of the developing fetus. While no harm to the developing fetus has been identified as a result of the RF exposure during clinical MRI examinations, Gowland and De Wilde (2008) have recommended a number of precautions that can be taken to minimize the RF exposure risk to the developing fetus. Their recommendations are summarized below:

- Avoid scanning the embryo or fetus above the normal mode. If the clinical situation dictates the need for scanning in the first-level controlled mode then the high SAR sequences should only be applied for as short a time as possible, the mother's heat loss pathways should be optimized (*e.g.*, no blankets, good bore air flow, reasonable room temperature), and high SAR sequences should be interspersed with low SAR sequences if relevant.
- When scanning a pregnant woman, if the embryo, fetus, or maternal abdomen are not the target tissues of interest, then the embryo or fetus should be kept out of the transmit field of the RF coil if possible.
- Particular care is necessary when scanning fetuses with poor placental function, for instance in fetal growth retardation. It should be noted that maternal heat stress has been reported to reduce placental perfusion (NRPB, 2004).
- Particular care is necessary when scanning pregnant women with conditions leading to impaired thermoregulation. Unless the clinical situation dictates that the scan is urgent, it would be prudent not to scan pregnant women who are febrile [this is in line with advice for ultrasound (Church and Miller, 2007)].

Gowland and De Wilde (2008), conclude their discussion of this topic with the statement that the general arguments presented would also apply to embryonic and fetal heating with ultrasound and a recommendation that future models of RF energy deposition in the embryo and fetus should calculate the average SAR for the embryo or fetus and amniotic fluid.

8.1.3 *Effect of Time-Varying Magnetic Field Gradients*

The time-varying magnetic field gradients in an MRI system are used to encode the locations of the MRI signals emanating from the RF excited protons within the imaging volume. These magnetic fields are "magnetic field gradients," meaning that the strength of the magnetic field varies linearly with distance. During an MRI scan, the coils that generate these magnetic field gradients are repeatedly pulsed on and off with electric current during the scan, typically achieving a "rise time" from zero to peak gradient strength in 200 μs, and similar duration for the "fall time" from peak strength to zero. The magnetic field gradients have units of mT m^{-1} and the magnetic field strength increases linearly with the distances from isocenter. For example, if the gradient strength is 40 mT m^{-1}, the magnetic field due to the gradient at 0.1 m from isocenter is 4 mT.

Time-varying magnetic fields produce a risk to the patient through stimulation of peripheral nerves and muscles by inducing electric fields within the patients. Current FDA guidelines classify time-varying magnetic fields as a significant risk when the "time rate of change of gradient fields ($dB\ dt^{-1}$) is sufficient to produce severe discomfort or painful nerve stimulation." The IEC has set more refined limitations on $dB\ dt^{-1}$ for the normal mode and first-level controlled mode for MRI safety. For normal-mode scanning, the $dB\ dt^{-1}$ limit is set at 20 T s^{-1} for rise times exceeding 120 μs, and [2,400/(rise time in microseconds)] T s^{-1} for rise times between 12 and 120 μs (*e.g.*, if the rise time is 100 μs, the limit is 24 T s^{-1}). For the first-level controlled mode, the limiting value is [60,000/(rise time in microseconds)] T s^{-1} [*e.g.*, if the rise time is 200 μs (the fastest rise time possible on modern clinical MRI systems), the limiting value is 300 T s^{-1}]. This limiting value is set to prevent a scan from stimulating electric activity in the heart, possibly leading to an arrhythmia.

Nerve stimulation in the fetus has not been evaluated. Nevertheless, current FDA guidelines for the fetus are no different from the limits established for the adult. The risk of nerve stimulation increases the further the fetus is from the MRI scanner's isocenter. For example, when imaging the mother's chest, the fetus may be ~20 cm from the isocenter of the magnet. Imaging under these conditions may lead to relatively-high values of $dB\ dt^{-1}$ (*e.g.*, 40 T s^{-1} rate of change for 200 μs rise time). However, this value is below the 300 T s^{-1} IEC limit based on the first-level controlled mode. It is interesting to note that patient positioning conditions that decrease the risk to the fetus for RF field exposures (*i.e.*, when the fetus is further from isocenter) actually increase the risk to

the fetus for the adverse effects of time-varying magnetic fields, and vice-versa.

8.1.4 *Effect of Static Magnetic Fields*

The biological effects of static magnetic fields have been widely studied. Several reviews of the recent literature, which include possible health effects of exposure to the high static magnetic field levels used in the new generation of MRI systems up to 8 T, have been published (AGNIR, 2008; Noble *et al*., 2005; WHO, 2006).

Exposure to environmental static magnetic fields is ubiquitous and dominated by the Earth's natural field, which ranges from 30 to 70 μT, depending on location. Static magnetic fields under direct current transmission lines are ~20 μT. Small artificial sources of static fields (permanent magnets) are components of many commonly used commercial devices (*e.g*., audio speakers, electric motors, refrigerator magnets). These small magnets can produce fields of 1 to 10 mT within a centimeter or so of their magnetic poles. However, patients undergoing MRI procedures experience intense static magnetic fields typically in a range of 0.5 and 3.5 T which are required to establish magnetic resonance in human tissues containing water. MRI systems have their static magnetic field on all of the time due to the need for maintaining very intense, uniform fields during an imaging procedure.

Almost all of the more than 300 million clinical MRI studies performed since the early 1980s were completed without any evidence of adverse effects to the patients from the static field. The few cases of injury have been attributed to external ferromagnetic objects, implanted ferromagnetic materials in the patients such as prosthetic devices or cardiac pacemakers, or ferromagnetic particles in tattoos. The cases have not been due to interaction of biological tissue with the static magnetic field. In fact, results on humans in static magnetic fields up to 8 T and on animals up to 16 T indicate that there is a substantial margin of safety remaining above the highest static fields now in clinical use in the range of 3 to 4 T (Schenck, 2000). These results are not surprising when one considers the relatively weak diamagnetic susceptibility of tissues within the human body. While there have been reports of potentially-harmful biological effects of magnetic fields on cells, tissues or organisms, these results have not been verified or firmly established as scientific fact.

One of the most extensively studied effects of static magnetic fields is the induction of voltages in the aorta and other major arteries of the central circulatory system that can be observed as superimposed electrical signals in the electrocardiogram. The largest

magnetically-induced voltage occurs during pulsatile blood flow into the aorta, and results in an increased signal at the location of the T-wave in the electrocardiogram, as demonstrated in studies with rats, monkeys, baboons and dogs (Gaffey and Tenforde, 1979; 1981; Gaffey *et al*., 1980; Tenforde, 1989; 1992; 2005; Tenforde *et al*., 1983; 1985). Laboratory studies involving the measurement of electrocardiogram, blood pressure, blood flow rate, heart sounds, and cardiac valve displacements have been performed with monkeys and dogs exposed to static magnetic fields up to 1.5 T under conditions producing maximum induced voltages in the aorta. Results of these studies provided no indication of alterations in cardiac functions or hemodynamic parameters (Tenforde, 1989; 1992; 2005; Tenforde *et al*., 1983; 1985). Cardiac activity monitored by biotelemetry during continuous exposure of rats to a 1.5 T field for 10 d gave no evidence for any significant changes relative to 10 d prior to and following field exposure (Tenforde, 2005).

Theoretical modeling has been performed to calculate magnetically-induced voltages and current densities as a function of magnetic field strength for the aorta and surrounding tissue structures, including the sinoatrial node that regulates cardiac pacing (Kinouchi *et al*., 1996). Induced current densities in the region of the sinoatrial node are predicted to be >100 mA m^{-2} at field levels >5 T in an adult human under conditions of maximum electrodynamic coupling with aortic blood flow. Magnetohydrodynamic interactions are predicted to reduce the volume flow rate of blood in the human aorta by a maximum of 1.3, 4.9, and 10.4 % at field levels of 5, 10, and 15 T, respectively (Kinouchi *et al*., 1996).

The magnitudes of magnetically-induced voltages and current densities, and the associated magnetohydrodynamic effects on blood flow rate, are a function of the diameter of the aorta and other major blood vessels exposed to an externally applied magnetic field. They are therefore substantially greater (by about an order of magnitude) for an adult human than for an embryo, fetus or neonate. It is not expected that any cardiovascular or hemodynamic abnormalities would result from the magnetic induction of electrical signals at the level of microvolts in the central circulatory system of a fetus exposed to the highest MRI field levels now approved for use (up to 8 T).

At very high field strengths there are ample data showing mild sensory effects such as vertigo, metallic taste, and magnetophosphenes (flashes of light that are seen when one is subjected to a changing magnetic field) occurring in adults and children, but there is no evidence that these effects are at all harmful. These effects, vertigo in particular, can be reduced by moving patients

slowly while they are in regions of very strong fields (Schenck, 2000). While these effects cannot be monitored in the fetus, it is highly probable that they occur in some form in the developing fetus. However, there are no restrictions on MRI systems imposed by FDA or IEC to prevent the occurrence of these effects.

Based primarily on several experimental and theoretical studies of the safety of very strong static magnetic fields, FDA has deemed that the static field of the MRI system be >8 T for MRI to be considered a significant risk for adults, children, and infants more than one month old (FDA, 2003). However, FDA has deemed that the static field be only 4 T or greater for MRI to represent a significant risk for neonates. This lower tesla limit for neonates is a result of a general sense of caution; there is no direct evidence of greater risk to neonates at the higher field strength. No additional restrictions on the static magnetic field have been imposed when imaging a pregnant patient, nor when imaging the fetus directly.

In light of these recent literature reviews, the International Commission for Non-Ionizing Radiation Protection (ICNIRP) has updated their occupational and general public exposure guidelines to static magnetic fields (ICNIRP, 2009a), as well as their statement concerning patient exposure to static magnetic fields during MRI procedures (ICNIRP, 2009b). ICNIRP (2009a) concluded that in view of uncertainties regarding the effects of higher fields, including effects on embryos, fetuses and infants, the current upper limit for whole-body static magnetic field strength during normal clinical MRI examinations should be 4 T. The advice concerning patient exposure to the switched gradient fields and RF fields recommended previously by ICNIRP (2004) remains current.

8.1.5 *Clinical Guidelines for Magnetic-Resonance Imaging in Pregnant Patients*

FDA guidance for MRI devices recommends that user instructions include a statement that the safety of MRI with respect to the embryo or fetus "has not been completely established" (FDA, 1998a). However, all of the human clinical studies and most (but not all) of the laboratory animal studies evaluating MRI safety during pregnancy have failed to demonstrate significant adverse effects (Clements *et al*., 2000; Gu *et al*., 2001; Kok *et al*., 2004; Mevissen *et al*., 1994; Narra *et al*., 1996; Prasad *et al*., 1990; Shellock and Kanal, 1991; Yip *et al*., 1994; 1995). In addition, the American College of Radiology Blue Ribbon Panel on MR Safety stated that MRI examinations are thought to be appropriate during pregnancy regardless of the trimester when the outcome of the examination

has the potential to affect the care of the patient (ACR, 2010; Kanal *et al*., 2007).

The panel also summarized the rationale for proceeding with MRI examinations in pregnant patients and recommends that the following considerations be documented in the radiology report or the patient's medical record:

- information requested from the MRI study cannot be acquired *via* other nonionizing modalities (*e.g*., ultrasonography);
- data are needed to potentially affect the care of the patient, or embryo or fetus, during the pregnancy; and
- the referring physician does not feel it is prudent to wait until the patient is no longer pregnant to obtain these data.

A previous expert report of the National Radiological Protection Board (NRPB, 2004) in the United Kingdom stated that, while the preponderance of evidence in animal studies suggests that MRI examinations do not adversely affect *in utero* development at any stage of the pregnancy, rigorous scientific studies involving human subjects are not available, and there are general concerns that risk assessments based on data from animal studies may not fully reflect the risks carried by human subjects. Accordingly, NRPB (2004) guidelines advise that "it is prudent, until further information becomes available, to exclude pregnant women during the first three months of pregnancy" (NRPB, 2004). The American College of Radiology panel does not believe the current data have conclusively documented any deleterious effects of exposure to MRI on the embryo or fetus. They conclude therefore that, "no special consideration is recommended for the first, versus any other, trimester in pregnancy" (Kanal *et al*., 2007). As a practical matter, first trimester MRI examinations will usually be performed for maternal rather than embryonic or fetal indications. In this context, and considering the American College of Radiology rationale described above for proceeding with MRI examinations in pregnant patients, an MRI examination is appropriate for a pregnant patient when MRI is the best diagnostic tool for the clinical purpose.

The U.K. Health Protection Agency (which now incorporates the activities of the previous National Radiological Protection Board) published a review of the scientific literature relevant to MRI bioeffects and specific safety recommendations for limiting the exposure of patients and volunteers to the static magnetic fields, time-varying electromagnetic fields, and acoustic noise (HPA, 2008). The document also sets out recommendations on best practice and further research needs.

Regarding MRI during pregnancy, HPA (2008) advises that MRI examinations in the "controlled operating mode" (8 T static field and RF exposure that may result in an increase in core-body temperature up to 1 °C) should be restricted as far as possible during pregnancy.

Several reviews of the general health and safety aspects of MRI procedures have been published (*e.g.*, AGNIR, 2008; Bassen *et al.*, 2005; JC, 2008; Ordidge *et al.*, 2000; Shellock, 2001; 2009) as well as a website devoted to MRI safety related issues (IMRSER, 2009). More detailed health and safety information relating specifically to MRI procedures during pregnancy as well as the more general issue of maternal hyperthermia are available from numerous sources (Colletti, 2001; Dimbylow, 2007; Edwards, 2006; Edwards *et al.*, 1995; 2003; Hand *et al.*, 2006; ICNIRP, 2004; Kanal, 1994).

8.1.6 *Use of Contrast Agents*

Contrast agents should not be routinely administered for MRI examinations in pregnant patients. The risk to the fetus with administration of gadolinium-based MRI contrast agents remains unknown and may be harmful. There are no documented fetal indications for the use of MRI contrast, but there may be rare instances where contrast is needed for assessing maternal anatomy or pathology. The decision to administer a gadolinium-based MRI contrast agent to a pregnant patient should be accompanied by a well documented and thoughtful risk-benefit analysis that defends the decision to administer the contrast agent based on overwhelming potential benefit to the patient or fetus outweighing the theoretic but potentially-real risk of long-term exposure of the developing fetus to free gadolinium ions (ACR, 2010; IMRSER, 2012; Kanal *et al.*, 2007).

8.2 Risks to the Embryo or Fetus from Other Radiofrequency Sources

8.2.1 *Introduction*

Human exposure to electromagnetic radiation in the radiofrequency (RF) range, traditionally defined as 300 kHz to 300 GHz, has increased dramatically in the last few decades. Common *far field* sources of exposure in the United States (where the electromagnetic wave is more uniform and predictable) include AM radio (540 kHz to 1.6 MHz), FM radio (88 to 108 MHz), television (mainly ~470 to 700 MHz with the new digital conversion), mobile telephone base stations (~0.8 to 2 GHz), and public safety and future broadband communication (~700 to 800 MHz). Radar systems can

operate across a wide range of frequencies (a few megahertz to hundreds of gigahertz) but are usually isolated from access and focused away from public areas with the possible exception of antennas on military ships. The most common *near-field* source of RF exposure (where the electromagnetic wave is more unpredictable; similar to the complex wave pattern very near an irregularly shaped stone thrown in the water) is undoubtedly the mobile telephone handsets (cell phones) (~0.8 to 2 GHz) associated with the four billion service subscriptions worldwide that are expected to top six billion by 2013 (GSMA, 2010). Other common near-field sources include various types of cordless phones (0.9, 2, 2.5, 6 GHz), conventional and trunked radio handsets (mainly ~0.4 to 6 GHz), Wi-Fi and Bluetooth transmitters (2.45 GHz), garage door and other remote control devices (300 to 400, 900 MHz, 2.45 GHz), a handful of implantable medical device RF links (0.6, 1.4, 2.45 GHz), and perhaps some minimal leakage from microwave ovens (2.5 GHz). Collision avoidance systems for automobiles (often tens of gigahertz) and RF identification readers (0.4 to 6 GHz) can be intermittent sources of low-level RF exposure as well. Although terahertz imaging (thousands of gigahertz) is currently being considered for security scanning, it is not yet common in U.S. airports. Medical sources of exposure include scanning ultrasound (up to ~50 MHz), diathermy and RF ablation (27,915 MHz, 2.45 GHz), and the RF component of MRI (often 42 MHz for hydrogen protons). Although patients receiving treatment from such medical devices are addressed in other sections, the technologists operating these devices may be exposed as workers.

An electromagnetic wave at a frequency of ~1 GHz has energy of only $\sim 4 \times 10^{-6}$ eV and at ~1 THz has energy of $\sim 4 \times 10^{-3}$ eV. Because the threshold energy required to displace electrons from DNA, protein, and other molecules is ~12.5 eV, and the energy required to break covalent bonds is ~3 eV, frequencies in the RF (300 kHz to 300 GHz) and terahertz (300 GHz to 3 THz) ranges are considered nonionizing. While not able to directly damage DNA and other molecules, safety issues can still exist for the developing embryo and fetus as well as adult gonads if the rate of RF or terahertz energy deposition is high enough to raise temperature significantly.

8.2.2 *Limits for Human Exposure to Radiofrequency Sources (300 kHz to 300 GHz)*

National and international scientifically-derived radiofrequency (RF) safety standards are developed by reviewing the literature to establish the lowest exposure level that would be expected to result

in adverse human health effects. A review of the scientific literature on the biological effects of RF energy by a standards setting committee requires a broad range of scientific expertise and a considerable amount of time. The committee will typically use a "weight of the evidence approach" to reach decisions that represent the consensus of experts in the field. During the review process all effects and their mechanisms of action are considered. However, only established (*i.e.*, independently reproducible) effects that are considered harmful to human health (*i.e.*, not just normal adaptive responses) are considered for the purpose of establishing the safety standard. The ultimate goal of the committee is to identify what RF exposure conditions give rise to demonstrable harmful effects, and from this information, reduction (safety) factors are applied in the standard to keep human exposures far below these levels. Current safety standards incorporate a 10- and 50-fold margin of safety for occupational and public exposures respectively (ICNIRP, 1998; IEEE, 2005; NCRP, 1986).

The only accepted mechanism for adverse health effects due to an interaction of electromagnetic radiation in the RF and terahertz range with biological tissue (with the exception of neurostimulation below ~5 MHz) is the generation of heat. The occurrence of an auditory response to microwaves due to thermoelastic expansion of brain tissue (*i.e.*, the ability to hear microwaves) can be precipitated with lower levels of exposure from very high peak-pulsed RF sources (Elder and Chou, 2003), but this phenomenon is not known to be a significant health hazard and is associated with radar and military applications that are not normally encountered by the general public. Internationally recognized limits (ICNIRP, 1998; IEEE, 2005; NCRP, 1986) for human safety from RF exposure at frequencies above several megahertz are therefore derived entirely from thermal considerations.

8.2.3 *Electromagnetic Field Interactions*

When the oscillating electromagnetic wave is incident on lossy biological tissue (*i.e.*, tissue that causes attenuation or dissipation of electrical energy), a portion of the energy is reflected, a portion is transmitted, and the remaining energy is absorbed. The interactions of electromagnetic radiation with biological tissue in the near field is a bit more complex than when it emanates from a distant source (*i.e.*, the far field), but the transfer into heat is essentially the same and results from the rotation and vibration of dipole molecules (*e.g.*, water) as they continually attempt to align themselves with the oscillating charge of the passing electromagnetic wave. The frequency in hertz (number of oscillations per second) as well

as the dielectric properties of the tissue will determine the efficiency of the electromagnetic wave to cause molecular rotation/vibration and thus transfer heat into the tissue, which is characterized in terms of the time rate of energy absorbed (watt) per kilogram of tissue mass (W kg^{-1}).

Due to the high conductivity of muscle, skin, and other high water-content tissues, energy absorption at the higher frequencies (a few to hundreds of terahertz) is efficient and penetration is therefore quite limited. In fat, bone, and to a lesser extent brain tissue the energy absorption is not as efficient and penetration distance increases. At 1 GHz the penetration depth in the human body can range from ~3 to 15 cm depending upon the water content of the tissue (Johnson and Guy, 1972), but is generally closer to 3 to 4 cm in most water rich tissues. At 100 MHz the penetration depth can range from ~6 to 60 cm and heat transfer is dispersed over a larger volume. At 1 MHz the penetration depth ranges from ~0.9 to several meters and the human body becomes essentially transparent. Although the pattern of energy deposition across complex tissues can be nonuniform, thermal diffusion kinetics suggest rapid equilibrium (Foster and Glaser, 2007) and recent modeling studies suggest the best correlation between SAR and temperature occurs over a tissue mass of ~10 g (Hirata and Fujiwara, 2009; Razmadze *et al*., 2009). With these considerations in mind, limits for safe human exposure to RF sources have been defined (ICNIRP, 1998; IEEE, 2005; NCRP, 1986).

8.2.4 *Current Safety Standards*

In the range of wireless communication and information technologies, the most recent revision of the Institute of Electrical and Electronics Engineers C95.1 standard (IEEE, 2005) allows for a rate of absorbed RF energy for members of the general public (including those that are pregnant) equal to 0.08 W kg^{-1} averaged over the entire body, or a rate of 2 W kg^{-1} averaged over a local tissue mass of 10 g. Like other standards, the IEEE C95.1 standard incorporates a 10- and 50-fold margin of safety for occupational and public exposures respectively (ICNIRP, 1998; IEEE, 2005; NCRP, 1986). Comprehensive reviews of the literature regarding low-level RF exposure on teratogenesis, reproduction and development have been performed by IEEE (2005), ICNIRP (2009c), Yecchia *et al*. (2009), EMF-Net (2007), the European Commission Scientific Committee on Emerging and Newly Identified Health Risks (EC, 2009), NRPB (2004), and a number of international expert groups (IEEE/ICES, 2009). A comprehensive review of the most recent literature from 2006 to 2009 has also been compiled by the IEEE

Technical Committee 95 (Ziskin and Morrissey, 2011) in preparation for the next revision of the IEEE C95.1 standard. The collective conclusion of these reviews is that exposure at or below internationally accepted guidelines (ICNIRR, 1998; IEEE, 2005; NCRP, 1986) does not represent a hazard. It should be noted that the limits recommended by these organizations do not apply to medical use such as diathermy.

8.2.5 *Nonthermal Effects*

As with any new technology, rapid penetration into society often results in a variety of concerns. While current compliance requirements (Cleveland *et al*., 1997) for wireless devices sold in the United States ensure that they offer a high degree of protection against thermal effects (IEEE, 1991; NCRP, 1986), questions have been raised regarding long-term exposure at nonthermal levels.

While many experimental and epidemiological studies have failed to demonstrate any evidence of adverse health effects from low-level (nonthermal) RF exposure (IEEE/ICES, 2009) and the evidence for a mechanism by which such effects could occur is lacking (Sheppard *et al*., 2008), some evidence of potential adverse effects has been reported in the scientific literature and by scientific working groups. In particular, based primarily on limited epidemiological evidence, the IARC Working Group classified RF energy as a "possible human carcinogen" (Group 2B) (IARC, 2013). This classification came with the *proviso* that chance, bias or confounding could not be ruled out as likely explanations for the statistical association reported (IARC, 2013).

It might be worth commenting on the study by the INTEPHONE Study Group (ISG, 2010) that IARC (2013) relied upon for this classification. It was an international case-control study of 2,708 glioma and 2,409 meningioma cases and healthy controls who were interviewed (or their proxy) on the frequency, hours per month, and cumulative duration of use of cell phones. Data from 13 countries were pooled for analysis. Overall, the findings were reassuring in that cell phone users had no increased risk of brain tumor, glioma, or meningioma; in fact, users had lower risks than non-users: the odds ratio was 0.8 (95 % CI = 0.7 to 0.9) for glioma and 0.8 (95 % CI = 0.7 to 0.9) for meningioma. In the 10th decile of self-reported cumulative call time, >1,640 h, however, the odds ratio was 1.4 (95 % CI = 1.03 to 1.9) for glioma and 1.2 (95 % CI = 0.8 to 1.6) for meningioma. Remarkably, 10 glioma cases and no controls reported using their cell phone more than 12 h d^{-1} which cast reasonable doubt about the credibility of such reports. When these implausibly high values of reported cell phone use were removed from the

analysis, the findings were no longer statistically significant (ISG, 2010). Further, there was no evidence for a dose-response relationship; in fact, in the ninth decile of self-reported cumulative call time, the odds ratio was negative and statistically significant [odds ratio = 0.7 (95 % CI = 0.5 to 0.96)]. The authors concluded, "There were suggestions of an increased risk of glioma at the highest exposure levels, but biases and error prevent a causal interpretation."

Subsequent to the ISG (2010) study and IARC (2013) classification, additional studies and evaluations provided no support for a causal association between the RF waves from cell phones and risk of brain tumor. The first study specifically designed to address cell phone use among children and adolescents diagnosed with brain tumors (primarily glioma) found no convincing evidence that children who use cell phones are at higher risk of developing a brain tumor than children who do not regularly use cell phones (Aydin *et al*., 2011). Recent studies presenting brain tumor incidence trends among adults and children over the last 20 y in the United States; the United Kingdom; New Zealand; and Denmark, Norway, Sweden, and Finland (Boice and Tarone, 2011; Little *et al*., 2012). These nationwide time-trend studies are uniformly and remarkably consistent in showing no evidence of increases in brain tumors over recent years, up to and including 2009 in Sweden (Swerdlow *et al*., 2011).

ICNIRP (Swerdlow *et al*., 2011) concluded: "Although there remains some uncertainty, the trend in the accumulating evidence is increasingly against the hypothesis that mobile phone use can cause brain tumours in adults."

A small or a long-term effect from RF exposures from cell phone use, even in children, cannot be completely ruled out by epidemiologic study. Nonetheless, studies of cranial radiotherapy in childhood find relatively short latency intervals for radiation-induced brain cancer with statistically significant increases 5 to 9 y after exposure (Ron *et al*., 1988). Further, since there is little to no evidence that RF waves can damage DNA, a promotional effect of an underlying defect is a proposed mechanism which would argue for a "short latency." While children may be more sensitive than adults to brain insults, they may also text more and thus have less relevant RF exposure to brain tissue. It is unlikely that case-control studies based on interviews and low participation rates will provide much information on possible risk in the future (they are too susceptible to bias and incomplete exposure assessment). Thus, continued monitoring of trends of brain cancer over time should be encouraged (Aydin *et al*., 2011; Swerdlow *et al*., 2011).

For perspective it might be noted that the Group 2B classification is below the level of evidence needed for RF to be classified as

Group 2A "probably human carcinogen" or Group 1 "carcinogenic to humans" agent. Also, it should be noted that the ISG (2010) study was not for *in utero* exposure and the only study designed for children was negative (Aydin *et al*., 2011). The current consensus regarding long-term exposure at nonthermal levels is that there are no established adverse health effects of RF energy that are not associated with excessive heating (Swerdlow *et al*., 2011).

8.2.6 *Thermal Effects*

The human embryo and fetus can be deleteriously affected by exogenously or endogenously induced increases in temperature during development. With limited ability to regulate temperature on its own, the developing embryo and fetus is dependent upon the mother's ability to maintain core temperature, which generally runs ~0.5 °C cooler. Maternal core-body temperature increases of ~1.5 °C for extended periods of time (Miller *et al*., 2002), 2 to 2.5 °C for 0.5 to 1 h (Edwards *et al*., 1995; 2003), or 4 °C for periods of a few minutes (Miller *et al*., 2002) have been associated with developmental abnormalities in animal models. The influence of thermal dose and time course of exposure (Dewhirst *et al*., 2003; Miller *et al*., 2002) as well as thermo-protection due to prior hyperthermic exposure (Edwards *et al*., 1997; Walsh *et al*., 1993) is also a factor that has been characterized in some animal species. Because significant differences in thermoregulation and thermoneutrality make direct extrapolation of animal data to humans challenging, the above increases would be hypothetical threshold predictions for adverse developmental effects in humans.

Corresponding SAR values from RF exposures necessary to cause temperature elevations of 1 °C in the adult female would be in the range of 4 W kg^{-1} for extended periods of time or 15 W kg^{-1} for just a few minutes (Vecchia *et al*., 2009b; Ziskin and Morrissey, 2011). Extended exposures of 15 W kg^{-1} would lead to temperature elevations of about 4 °C. However, smaller levels of thermal stress in the mother that are asymptomatic might theoretically result in shunting of blood volume away from the placenta and umbilical flow to the periphery as a thermoregulatory heat dissipation mechanism. This could conceivably result in reduced heat exchange with the embryo or fetus. It is difficult to predict the magnitude and threshold for such an effect, as many factors are involved in the thermoregulatory response. However, a very conservative estimate for whole-body average of 1.5 W kg^{-1} (one-tenth the threshold to protect against predicted adverse core temperature increases in the mother) would seem sufficient to guard against such a scenario. This estimate for whole-body average of 1.5 W kg^{-1} is also greater than three

times above the current whole-body average limit (0.4 W kg^{-1}) for occupational exposure as outlined in both the IEEE standard (IEEE, 2005) and ICNIRP guidance (ICNIRP, 1998), suggesting that even as a worker a pregnant woman should never encounter RF exposures that would place her or the embryo or fetus at risk.

The predicted depth of penetration associated with wireless communication sources in the range of 1 to 6 GHz and higher would suggest most of the RF energy would be absorbed by the mother prior to reaching the embryo or fetus. Although penetration will increase as the frequency decreases, significant conductive and convective heat dissipation capacity near the mother's surface would offer additional protection. Even if significant energy did reach the embryo or fetus, a theoretical 1 W kg^{-1} exposure that was averaged over an entire 28 d old embryo, or averaged over a 1 g volume in the fetus, would not be expected to elevate temperature more than 0.2 °C (Vecchia *et al*., 2009).

Sensitivity of the male gonad to elevated temperature is also a well characterized phenomenon and can result in germ-cell death (Sinha Hikim *et al*., 2003) *via* a classic caspase-dependent apoptotic pathway (Johnson *et al*., 2008b; Vera *et al*., 2004). The reduced fertility associated with cryptorchidism (Hughes and Acerini, 2008) can be replicated in mammalian models when testes, which are normally held at a temperature of 33 to 35 °C, are heated by a variety of methods (*e.g*., hot water, infrared radiation, ultrasound) to temperatures close to that of normal abdominal temperature (37 to 39 °C) (Lue *et al*., 2002; Paul *et al*., 2009; Reed *et al*., 1977). Exposure of the testes to RF fields can also result in elevated temperature and affect fertility and sperm morphology (Goud *et al*., 1982; IEEE, 2005; Kowalczuk *et al*., 1983). Temporary sterility can be induced in rodent models with testicular temperatures ≥37.5 °C (Berman *et al*., 1980; Lebovitz and Johnson, 1983; 1987; Lebovitz *et al*., 1987), and permanent changes in reproductive efficiency have been demonstrated in rats with testicular temperature >45 °C (Fahim *et al*., 1975). At modest levels of exposure that are still higher than ICNIRP, IEEE, and NCRP limits, no effect on spermatogenesis in animal models has been observed (Johnson *et al*., 1984).

8.3 Risks to the Embryo or Fetus from Ultrasound Imaging

8.3.1 *Introduction*

Diagnostic ultrasound has been in use for over 50 y in obstetrics and gynecology. Its ability to depict fetal anatomy is extraordinary, and diagnostic ultrasound has become an essential component of

prenatal care. Its record of safety is excellent, and based on the epidemiological evidence to date there is little or no convincing evidence to support a causal relationship with any adverse effect. However, it is important to note that nearly all epidemiological studies published to date are based on information obtained with ultrasound machines manufactured prior to 1992. In 1992 the acoustic output of ultrasound systems was allowed to be increased for fetal use, from 94 to 720 mW cm^{-2}, an increment of nearly eight-fold (Abramowicz *et al*., 2008a). Furthermore, while B-mode gray-scale imaging continues to be the main examination mode, newer higher power technologies and their applications have been introduced over the years. Consequently, the concern for an increase in adverse developmental effects in the fetus requires continuing vigilance.

8.3.2 *Nature of Ultrasound*

Ultrasound is a form of energy that is transmitted through tissue by a propagation of a vibration from each excited molecule to its neighbor in the direction of the sound path. The frequency of vibration is >20 kHz, the nominal upper limit for human hearing. Typical ultrasound frequencies used in obstetrical examinations range from 2 to 10 MHz. When ultrasound propagates through human tissue, there is a potential for tissue damage. There has been much research aimed at understanding and evaluating the potential for ultrasound to cause tissue injury. Many studies are dose-effect studies. These laboratory studies provide two important capabilities. First, they provide an opportunity to use much higher exposure levels than those currently used in diagnostic ultrasound examinations to evaluate the adverse effects of ultrasound, and second, they permit a detailed study of mechanisms thought to be responsible for ultrasound-induced bioeffects. Virtually all ultrasonically-induced adverse biological effects have occurred at intensity levels and exposure times that are higher than those used for diagnostic ultrasound examinations.

The mechanisms that are responsible for ultrasound induced bioeffects are classified as thermal or nonthermal. The thermal mechanism is the most common and will be discussed first. It refers to the heating of soft tissue and bone as the ultrasound beam propagates through tissue. The heating results from the frictional forces resisting the molecular vibrations. A large percentage of ultrasound energy is absorbed as it passes through the body. Approximately 20 % of the sound is absorbed in traveling each 1 cm through soft tissue. If the rate of energy deposition exceeds the ability of the body to dissipate the heat, the local temperature will rise.

Ultrasonic intensities >10 W cm^{-2} cause significant temperature increases (*i.e.*, sufficient to literally "cook" tissue). Therapeutic ultrasound intensities, 0.5 to 2.5 W cm^{-2} are capable of raising temperature several degrees and thereby able to increase blood perfusion and accelerate soft-tissue healing. Ultrasound B-mode scanners, the common instrumentation used in fetal imaging, typically produce acoustic outputs <50 mW cm^{-2} (derated spatial-peak temporal-average intensity) and cause no perceptible increase in temperature and little to no measurable increases in temperature. Higher power Doppler devices, on the other hand, are capable of causing temperature rises of several degrees.

8.3.2.1 *Mechanisms of Tissue Heating*. Two widely accepted facts are that:

- ultrasound has the potential to elevate the temperature of the tissues being scanned (NCRP, 1992; Nyborg, 2002); and
- elevated maternal temperature, whether from illness or exposure to heat can produce teratogenic effects (Chance *et al*., 1978; Edwards, 1967; Layde *et al*., 1980; Miller and Ziskin, 1989; Milunsky *et al*., 1992).

Some believe that this is in fact the major mechanism for ultrasound bioeffects (Miller and Ziskin, 1989; Miller *et al*., 2002; NCRP, 1992). The temperature elevation in the insonated tissue can be calculated and estimated relatively accurately (Nyborg and O'Brien, 1989; Nyborg and Steele, 1983). Temperature change in insonated tissues depends on the balance between heat production and heat loss. Heating is proportional to the temporal average intensity. Physical characteristics of the ultrasound beam modify the temperature rise. These include: ultrasound frequency, focusing (which determines the beam width), whether the beam is scanned or not, and duration of exposure. The properties of the exposed tissues such as impedance, absorption coefficient, conduction, and convection also influence how much ultrasound energy is reflected and how much is transformed into heat (Nyborg and Steele, 1983). Other tissue properties that define the amount of heat absorbed include local perfusion, which very clearly diminishes the risk. Similar experimental conditions caused a 30 to 40 % lower maximal temperature increase in live versus dead sheep fetuses exposed in the near field (Duggan *et al*., 1995), compared with ~10 % difference in guinea pig fetuses exposed in the focal region of the ultrasound beam (Horder *et al*., 1998), secondary to vascular perfusion in live animals. A significant cooling effect of vascular perfusion was observed only when the guinea-pig fetuses

reached the stage of late-gestation, near term, when the cerebral vessels were well developed. In mid-term there was no significant difference, postmortem, when exposed in the focal region of the ultrasound beam (Horder *et al*., 1998). The loss of heat due to perfusion is more important in those parts of the beam close to the transducer and beyond the focus, where the beam has a large cross-sectional area. In the focal region, where the beam is narrow, the effect of perfusion is much lower (Vella *et al*., 2003). It is worth noting here that in early pregnancy (less than six weeks) there appears to be minimal maternal-fetal circulation (*i.e*., minimal fetal perfusion), which may potentially-reduce heat dispersion. There is no perfusion in very early gestation. Only at about week 10 to 11 does the embryonic circulation actually link up with the maternal circulation (Makikallio *et al*., 1999).

Motions (even very small) of the examiner's hand as well as patient's breathing and body movements (and in the case of obstetrical ultrasound, "both" patients) tend to spread the region being heated. However, for Doppler studies, it is necessary to have the transducer as steady as possible (Abramowicz *et al*., 2008b). This is because, in general, blood vessels are small, in comparison to the general organ or body size being scanned with B-mode and hand movements while performing B-mode scan will have less negative effects on the resulting image. The spatial peak-temporal average intensity (I_{SPTA}) and acoustic power associated with Doppler ultrasound are the highest of all the general use categories and hence the associated thermal index (TI) values and potential for heating are also the highest. Ziskin (1972) reported that among 15,973 Doppler ultrasound examinations, the average duration was 27 min at that time. Currently the average dwell time for Doppler examinations in the second half of pregnancy was measured to be 0.9 ± 0.8 min (Sheiner *et al*., 2007). Although no permanent developmental effects attributable to heat generation by diagnostic ultrasound has been described in the human medical literature, there is concern for potential harm to the embryo or fetus especially because of the increased use of Doppler in the first trimester and because of the body of evidence of hyperthermia-induced teratology in animals.

8.3.2.1.1 *Hyperthermia and teratology.* Temperature elevation *in utero* is a known teratogen in laboratory animals, in farm animals, and in nonhuman primates.

The strongest evidence that maternal pyrexia (fever) can damage the fetus comes from animal studies. The most comprehensive studies have been undertaken by M.J. Edwards of the University of Sydney. These studies were initially prompted by the observation

of Edwards that there was an unusually high rate of congenital malformations in farm animals following hot summer months in Western Australia. In his laboratory, Edwards has conducted an impressive series of experiments in which pregnant guinea pigs and other mammalian species are placed in a carefully controlled heated environment for various periods of time. Both the environmental temperature and the gestational age are important factors for determining the type and severity of developmental abnormalities observed (Edwards, 1967).

The core temperature of pregnant guinea pigs is normally 39 °C. Temperature elevations of 2.5 °C for prolonged exposures (*e.g.*, 1 to 3 h) resulted in progeny with microencephaly and other congenital malformations (Edwards *et al*., 1995). The peak for induction of microencephaly in newborn guinea pigs occurs between 18th and 25th days postconception, a period of rapid neuronal growth. Other effects seen are micro-ophthalmia, cleft palate, hypoplasia of long bones, and talipes, as well as defects of the face, vertebrae and heart. The developing brain and eye are most vulnerable (Edwards *et al*., 1995). Exposures of 2 °C above the normal pregnant rat's temperature for 4 or 8 h had no effect on embryonic development, and 3 °C above the rat's normal temperature for a 10 min exposure had no effect, but a 60 min exposure was clearly teratogenic (Germain *et al*., 1985).

It has been demonstrated that significant hyperthermia that has persisted in a pregnant woman early in gestation (before the neural tube closes) has an increased risk for neural-tube defects (Graham *et al*., 1998; Moretti *et al*., 2005; Pleet *et al*., 1981). There are many publications reporting that hyperthermia has teratogenic potential (Shepard, 1995). Smith *et al*. (1978) reported on the fetal outcome of patients who had either a fever or a very hot sauna bath during pregnancy. There were 21 patients, with temperatures ranging from 38.9 °C to higher than 40.5 °C. The study did not implicate a consistent effect of the higher temperatures on morphogenesis during the second half of gestation, but suggested that when high fever occurred at the four to six week gestational period there was an increased risk of fetal mental deficiency, seizures, microphthalmia, mid-face hypoplasia, and mild impairment of distal limb development. At the time, it was not clear whether these effects were due to the hyperthermia or due to the cause of the fever (Warkany, 1986). There are many clusters of newborns with malformations that were attributed to hyperthermia, but editorials in BMJ (1978) and Lancet (1978) have questioned these associations as being causal. Warkany (1986) in an extensive review stated, "One can state that many reports on hyperthermia of women

with malformed children have been published. Yet proof of a causal connection has not been possible." No pregnant woman has been subjected to the levels of hyperthermia reached in the many animal experiments. The one finding of the animal experiments that is important in this evaluation is to recognize the teratogenic environment necessitates at least 2.5 °C above the normal temperature and an exposure of at least 1 h.

Later studies have more clearly shown that hyperthermia is a human teratogen. For example, Edwards (2006) noted that children whose mothers experienced kidney-urinary tract infections with fever during pregnancy were nearly twice as likely to have neurological problems requiring institutional care as children whose mothers had the infection without fever.

Additional studies implicating hyperthermia as the culprit in causing congenital abnormalities in humans included Czeizel *et al*. (2007), Edwards (2007), and Moretti *et al*. (2005).

An extensive list of fetal abnormalities resulting from hyperthermia is provided in the review by Miller and Ziskin (1989). In this review the authors extracted from the literature those studies in which both the exposure duration and temperature were reported. No effects were observed at temperatures <39 °C no matter how long the exposure duration. The fetal temperatures requisite for damage appear to be several degrees above the norm. Furthermore, the higher the temperature, the shorter the exposure time required to achieve a deleterious effect. The relationship between temperature and exposure duration can be gleaned from those experiments in which the investigators found the same bioeffect with differing combinations of these variables.

For temperatures not exceeding 43 °C, the relationship between the required exposure duration and temperature to produce the same deleterious effect is given in the equation (Miller and Ziskin, 1989; Sapareto and Dewey, 1984):

$$t_{43} = t\, 4^{(43 - T)}, \tag{8.1}$$

where:

t = exposure time required to produce a thermal bioeffect at a temperature T

t_{43} = exposure time required to produce the same bioeffect if the temperature had been 43 °C

In general, t_{43} is a convenient measure of the risk of a thermally-induced adverse effect. The greater the value of t_{43} the greater the risk.

Within the past 10 y, progress has been made in clarifying the biophysical basis of the relationship between temperature elevation, exposure duration, and thermal dose (Church and Miller, 2007; Miller and Dewey, 2003; Miller *et al*., 2002; 2004; 2005; 2007). It was postulated that the temperature elevation above normal core-body temperature is more important than the absolute temperature in assessing thermal dose (Miller *et al*., 2004). By assuming that thermal damage can be modeled by a first-order rate equation, the relationship between temperature elevation and exposure duration is consistent with the Arrhenius equation (Miller *et al*., 2002). Furthermore, knowledge of the activation energy required to produce a specific thermally-induced birth defect permits the prediction of the increase in the prevalence of that birth defect from any combination of temperature elevation and exposure duration (Miller *et al*., 2005). This approach presumes that there is no threshold for hyperthermic events and that any temperature elevation during pregnancy has some potential for inducing a deleterious effect (Miller *et al*., 2005). It is very unlikely that hyperthermia is a stochastic effect, since it is clearly a multicellular effect (Table 5.11).

The utilization of the free energy of activation based on the Arrhenius development of chemical rate kinetics is a meaningful and scientifically useful approach. However, the assertion that there is no threshold for hyperthermic deleterious effects is critically important and deserves much scrutiny. It is true that within wide temperature ranges, simple chemical and enzymatic reaction rates show no temperature threshold. However, more complex processes may exhibit a temperature threshold (Edwards, 2006). For example, the thermal dose necessary to produce a developmental abnormality may need to exceed compensatory and repair processes. It is well known that temperature elevation may initiate the production of heat shock proteins which imbue cells with an increased resistance to thermal damage (Edwards, 2006). These processes would presumably become increasingly active with increasing temperature, up to a limit. When this limit is reached, these protective processes are overwhelmed and thermal damage ensues. The Arrhenius theory, as applied in the above approach, does not take into account the possibility of repair and compensatory processes, but does provide a scientifically sound measure of thermal dose.

In the species studied, Edwards *et al*. (2003) found the threshold for thermally-induced abnormalities to be an elevation of 2 to 2.5 °C above the normal body temperature. However, values in the literature have ranged from 2.5 °C to a low of 0 °C. In general, thresholds and dose-response relationships vary between species and even between different strains of the same species, depending

on genotype. Because of this biological variability, very large numbers of animals would be required to establish precise thresholds, but the number of animals and the number of abnormalities studied have been very limited. Changes in the incidence of subtle defects would probably not have been detected (Edwards *et al*., 2003).

The widespread use of ultrasound during pregnancy is due to its ability to provide valuable diagnostic information that has significant medical benefit. However, its usage always has to be balanced against the risk of an adverse effect (Abramowicz *et al*., 2008b). With regard to biological effects due to thermal mechanisms, consideration of the previous findings leads to the following recommendations concerning the use of ultrasound in an a febrile patient (NCRP, 1992):

- If the maximum expected temperature elevation is <1 °C, an ultrasound examination should need not be withheld because of any concern of an adverse thermal effect.
- If the maximum expected temperature elevation will exceed 2 °C, the duration of the exposure will need to be considered.

Situations for which t_{43} is >1 min pose a risk of a thermally-induced adverse effect, and will require balancing this risk against the benefits expected for any ultrasound examination under consideration.

8.3.2.1.2 *The thermal index*. The requirement to keep the temperature elevation below the threshold of any adverse bioeffect is an important goal. However, the estimation of the maximum expected temperature elevation for any given patient examination, although an important matter, is certainly not a trivial one. It requires knowledge of the dimensions and acoustic properties of the tissues being insonated, as well as knowledge of the physical characteristics of the sound beam emitted by the ultrasound scanner. Acoustic intensity, pressure, frequency, beam width, and pulse repetition rate are among the physical parameters that will affect the ultimate temperature elevation. Modern ultrasound instrumentation has become very sophisticated and changing one operator control will frequently change several output parameters simultaneously, with opposite effects on acoustic output. Thus, applying the ALARA principle is difficult.

In an attempt to help guide a sonographer to minimize temperature elevation during an examination, the thermal index (TI) was introduced by NCRP (1992). Based on acoustic output parameters and conservative estimates of average tissue properties, the TI was designed to provide the sonographer with a continuously updated on-screen display of the maximum reasonable worse-case *in vivo*

temperature elevation occurring anywhere in the ultrasound beam during an examination. Because of the uncertainty associated with this estimate, it was decided to make it a nondimensional index defined as the ratio of the output acoustic power to the power required to raise the *in vivo* temperature by 1 °C. The TI was later modified somewhat and then adopted by the American Institute of Ultrasound in Medicine (AIUM) and the National Electrical Manufacturers Association and ultimately by FDA. It is currently a required display on nearly all modern diagnostic ultrasound scanners. Although TI values may vary from zero to six, most diagnostic examinations can be performed with TI values between 0.5 and 3.

In time, the TI was shown to have a number of limitations. Under most conditions it was too conservative, with values as high as six in situations in which the actual temperature rise was <3 °C. However, in some situations, the actual *in vivo* temperature elevation was greater than the TI value. Consequently, the TI is recognized as an inaccurate estimate of temperature elevation, but one that tracks with temperature elevation and thus the risk of a thermally-induced adverse effect. The TI is the best guide available to a sonographer for applying the ALARA principle and for minimizing the risk of thermal harm (AIUM, 2008).

8.3.2.1.3 *Measured temperature rise in human fetal tissue*. Those faced with the problem of measuring temperature rise in the gravid human uterus *in vivo* during ultrasound scanning contend with almost insurmountable problems, both from the difficulty in managing a controlled experiment, and from ethical considerations. *In vitro* studies therefore are necessary. In one study, Doody *et al*. (1999) reported the temperature increase generated *in vitro* at the surface of samples of human fetal vertebrae ranging from 14 to 39 weeks of gestation. The exposure conditions (3.5 MHz weakly focused beam, acoustic power 50 mW cm^{-2}) compared well with estimated *in situ* exposure conditions towards the upper end of pulsed Doppler use. For a fully ossified vertebra from a 39 week fetus, a temperature rise of 1.8 °C after 5 min exposure was reported. For vertebrae from less mature fetuses, lower temperature rises were observed, which were related to the lower degree of ossification. For the 14 week vertebra studied, a temperature rise of no more than 0.6 °C was reported.

The potential that nonlinear propagation effects may enhance heating has been explored both experimentally and theoretically by, amongst others, Cahill *et al*. (2002). A condition was used which approximated an obstetric examination, using assumptions of a fixed attenuation near the source, transmission through a low-

attenuation fluid and a tissue-equivalent target. Both model and experiments found that temperature rise may be enhanced by up to 50 %, but that for higher pulse amplitudes the temperature rise may be reduced, due to increased dissipation of energy by the fluid. If one uses the TI as an indication for the potential for temperature increase, it is a fact that current clinical scanners can, under some conditions, operate with a displayed TI of six or more. This predicts a worst-case temperature rise of 6 °C, or up from an average 37 to 43 °C *in vivo*. Temperature increases similar to this have been demonstrated *in vitro* with commercial systems (Shaw *et al*., 1998).

8.3.2.2 *Nonthermal Mechanisms*. Nonthermal effects of ultrasound are not as well understood as heating. Nonthermal effects include acoustic radiation force, acoustic streaming, and most importantly, acoustic cavitation (Stratmeyer *et al*., 2008). Cavitation is the interaction of ultrasound with gas bubbles resulting in greatly enhanced mechanical activity of particles in the immediate vicinity of the bubbles. Sufficiently intense ultrasound can cause rapid expansion and the violent collapse of a bubble leading to the generation of a shock wave.

The threshold for producing cavitation varies widely depending upon exposure conditions and upon the presence of suitably sized bubbles (~1 μm in diameter). The important physical quantities are peak derated (estimated *in vivo*) rarefactional pressure (the peak reduction in pressure, accounting for attenuation, in the ultrasound beam) and center frequency (the median frequency of the transmitted ultrasound pulse). These have been combined to produce a mechanical index (*MI*) (AIUM/NEMA, 2010) which is defined as:

$$MI = \frac{p_r}{\sqrt{f_c}}, \tag{8.2}$$

where:

p_r = peak derated rarefactional pressure (megapascal)
f_c = center frequency (megahertz)

If the value of *MI* is less than one, the likelihood of cavitation is very low. The higher the value of *MI*, the greater is the risk of a nonthermal or mechanically-induced adverse effect. The maximum value for *MI* is limited by FDA to be 1.9, the corresponding maximum value of diagnostic ultrasound instruments prior to 1976.

Mechanical bioeffects are caused by local forces created as the ultrasound beam traverses tissue. In contrast to thermal mechanisms where effects are proportional to the temporal average intensity, nonthermal effects are proportional to acoustic pressure or

instantaneous intensity. Shear forces and eddy currents are generated by acoustic streaming. Mechanical bioeffects are greatly enhanced in the presence of liquid air interfaces, such as occur in pulmonary alveoli and especially when ultrasonic contrast agents are injected intravenously. In experimental animals pulmonary capillary bleeding and petechial hemorrhages in intestinal mucosa have been observed at ultrasound intensities used in diagnostic examinations. In humans, cardiac arrhythmias have been observed when ultrasonic contrast agents have been used to enhance visualization of blood flow. However, prior to the first breath of the newborn infant there is a complete absence of air bubbles and these mechanical bioeffects do not occur. Thus mechanical adverse effects are not known to occur in the embryo or fetus. The one exception, which is obviously not recommended, would be if an ultrasonic contrast agent was purposely injected into the fetal blood circulation or surrounding amniotic fluid. It should also be noted that the nursing infant has aerated lungs and may be vulnerable to pulmonary capillary bleeding at diagnostic levels of ultrasound exposure. Although this has not been reported to have occurred in humans, the effect may be small and not readily detected. The clinical significance of this effect is not known.

8.3.3 *Epidemiology*

A number of epidemiological studies on the use of ultrasound in pregnancy have been performed over the past 30 y. These include surveys, case-control, and randomized-control studies. There have been several major reviews published of epidemiological studies conducted over more than 25 y (Brent *et al*. 1991; Lyons *et al*., 1988; Moore *et al*., 1988; Salvesen and Eik-Ness, 1999; Ziskin, 1999; Ziskin and Petitti, 1988). In some studies an association with one or another bioeffect was identified, such as low birth weight, delayed speech, dyslexia, and nonright-handedness. However, the vast majority of studies have been negative for the association with any bioeffect (NCRP, 2002). The following is a more detailed review of those studies showing the possibility of an adverse effect.

8.3.3.1 *Low Birth Weight*. Several animal studies have described, albeit not always convincingly, that ultrasound may cause birthweight reduction. This raised the question of possible similar effects in humans. There have been reports of decreased birth weight after prenatal exposure to ultrasound in the monkey and the mouse but not the rat (Tarantal and Hendrickx, 1989). *In situ* intensities were higher than what is considered routine in clinical obstetrical imaging in the human. High-level exposures were

associated with decreased body weight at birth in exposed animals compared with controls but all showed catch-up growth when examined at three months of age (Jensh *et al*., 1994). Among retrospective studies in humans, only one (Moore *et al*., 1988) showed birth-weight reduction (116 g at term). These results were not reproduced in other retrospective studies (Lyons *et al*., 1988; Smith, 1984). Several randomized studies did not show any ill effect of one or two prenatal scans on growth. In fact, in one study, birth weight was slightly higher in the scanned group, but not statistically significant. The only randomized study that reports a difference with a higher proportion of newborns that were small for their gestational age suggests that multiple scans (five, including Doppler flow studies) may produce some decrease in birth weight (Newnham *et al*., 1993). Given the above, there is not enough evidence to determine that prenatal scanning for routine, clinical diagnosis has any effect on birth weight.

8.3.3.2 *Delayed Speech*. In an attempt to determine if there is an association between prenatal ultrasound exposure and delayed speech in children, Campbell *et al*. (1993) studied the clinical records of 72 children who had undergone a formal speech-language evaluation and were found to have a delayed speech of unknown cause. For each subject, two control subjects were matched for sex, date of birth, sibling birth order, and associated health problems. The children with delayed speech were found to have a higher rate of ultrasound exposure *in utero* than the 144 control subjects (odds ratio = 2.8; 95 % CI = 1.5 to 5.3; $p = 0.001$). There was neither a dose-response effect nor any relationship to time of exposure. Many of the records were more than 5 y old. Confounding is a serious problem in such a study; the conditions prompting the performance of an ultrasound examination during pregnancy may affect the likelihood of delayed speech. In a later study, Salvesen and Eik-Ness (1999) compared the incidence of delayed speech in 1,107 children who had been exposed *in utero* with 1,033 controls. They found no statistically-significant differences in delayed speech, limited vocabulary, or stuttering. In fact, children who were exposed to ultrasound *in utero* were less likely to be referred to a speech therapist.

Because of the many weaknesses in the study by Campbell *et al*. (1993), the absence of any credible mechanism for an association of *in utero* ultrasound exposures, and the finding of no association by Salvesen and Eik-Ness (1999) in a much larger sample of children, there is insufficient evidence showing an association of *in utero* ultrasound exposure and delayed speech.

8.3.3.3 *Dyslexia*. In one study (Stark *et al*., 1984), 425 children, 7 to 12 y of age, exposed to ultrasound *in utero* were used as a study group and compared to 381 matched control children for the incidence of adverse effects. A total of 17 outcome measures were examined. Several of these were determined at birth including Apgar scores, gestational age, head circumference, birth weight, length, congenital abnormalities, neonatal infection, and congenital infection. The tests performed subsequently in the children included hearing, visual acuity and color vision, cognitive function, and behavior. The authors concluded, "No biologically significant differences between exposed and unexposed children were found." However, of the 17 measures, the authors did note a statistically-significant greater proportion ($p < 0.01$) of those children exposed to ultrasound to be dyslexic based on a *Gray Oral Reading Test*. Statistical analysis by the authors indicated that given the design of the study and the numerous endpoints evaluated, it is possible that this was an incidental finding. However, the finding of potential dyslexia was considered sufficient to prompt further study. Subsequently, a long-term follow-up study was performed on 2,161 children who were part of two Norwegian randomized trials (Bakketeig *et al*., 1984; Eik-Nes *et al*., 1984). The endpoints included evaluation for dyslexia along with five additional hypotheses including an examination of nonright-handedness (see separate discussions below) said to be associated with dyslexia. These studies (Salvesen *et al*., 1992a; 1992b; 1993) included the specific examination of 603 children with tests for dyslexia including spelling, reading and intelligence (Salvesen *et al*., 1992a). There were no statistically-significant differences between children screened with ultrasound and controls in the teacher-reported school performance in the third year for reading, spelling, arithmetic, or overall performance. Specific dyslexia tests showed no differences between screened children and controls in reading, spelling, and intelligence scores and no discrepancy between intelligence and reading or spelling. The rates of occurrence for dyslexia were 21 of the 309 screened children (7 % with 95 % CI of 3 to 10 %) and 26 of the 294 controls (9 % with CI of 4 to 12 %). Given that the original finding of dyslexia was not confirmed in subsequent randomized controlled trials, it is considered unlikely that dyslexia results from routine ultrasound screening examinations. However, these studies did raise the issue of hand laterality which is also discussed here.

8.3.3.4 *Nonright-Handedness*. The first report of a possible link between prenatal exposure to ultrasound and subsequent nonright-handedness in children exposed to ultrasound *in utero* was

published by Salvesen *et al*. (1993). The acoustic outputs of the ultrasound instrumentation used are thought to have been around 1 mW cm^{-2}. The authors stressed in their analysis that the association was "only barely significant at the 5 % level, and the possibility of a chance finding should be kept in mind." Unknown confounding factors may have been present. The authors recommended that no clinical conclusions be made. When looking further at their data, as a response to a letter to the editor, they described that the association was restricted to males (Salvesen *et al*., 1993). A second group of researchers published similar findings of a statistically-significant association between ultrasound exposure *in utero* and nonright-handedness in males (Kieler *et al*., 1998). The fact that similar findings appeared to be present in two different populations added weight to the proposed finding. Salvesen and Eik-Ness (1999) published a meta-analysis of these two studies and of previously unreported results. No difference was found in general but a mild difference was present when analyzing boys separately. A word of caution is needed since the use of the term meta-analysis is somewhat of a misnomer as only two studies were included. Four comparisons were reported:

1. intention to treat analysis, comparing those randomly assigned to receive ultrasound versus those in the nonultrasound group;
2. further analysis of the above, limited to male infants;
3. comparison of those who were actually scanned versus those who were not, thus breaking the original randomization of each trial; and
4. analysis in Comparison 3 limited to male infants.

A small increase in nonright-handedness appeared to be present in males, but not in females. Other important points to consider are that the studies by Kieler *et al*. (2001) are population-based and observational rather than randomized and controlled as was that of Salvesen *et al*. (1993). No valid mechanistic explanation can explain the findings. Although there may be a small increase in the incidence of nonright-handedness in male infants, there is not enough evidence to infer a direct effect on brain structure or function.

8.3.3.5 *Intellectual Performance*. A recent large scale Swedish study (Kieler *et al*., 2005) explored the possible association between ultrasound exposure during pregnancy and intellectual performance among 18 y old males. In this study, the authors consulted the Swedish Birth Registry and collected 306,995 singletons, live-born males born from 1973 to 1978. They then consulted the National Service

Registry which includes information on all Swedish men enrolling for military service (which is mandatory at 18 y of age).

At enrollment, several intelligence tests are administered to measure general or overall intelligence, educational and verbal skills and general visualization. For the exposed group, the authors chose men born at University Hospital in Malmo, where since 1972, 90 % of pregnant women had an ultrasound examination. After various exclusions, they were left with 6,026 subjects and 161,033 unexposed controls. When comparing these two groups, their conclusion was: "This study failed to demonstrate a clear association between ultrasound scanning and intellectual performance."

Two additional comparisons were performed using cohorts of brothers: the first compared the results of the index cohort to the results of the period before introduction of routine ultrasound in Malmo. The older brothers were born before and the younger brothers after the introduction of ultrasound examinations. The second compared the results on 15,540 pairs of brothers, in which younger brothers were born in Malmo. There were no differences within brother pairs, when comparing the younger brothers, assumed to have been exposed to ultrasound, and the unexposed older brothers. Thus, the authors concluded that there was no association between ultrasound examination during pregnancy and intellectual performance in young adults.

8.3.3.6 *Childhood Malignances*. Naumburg *et al*. (2000) and Shu *et al*. (2002) found no association between ultrasound exposure *in utero* and the later development of leukemia. Studies of the possible association of solid tumors with ultrasound exposure *in utero* have been conducted by Bunin *et al*. (1994), Cartwright *et al*. (1984), Kinnier Wilson and Warterhouse (1984), Salvesen and Eik-Ness (1999), Sorahan *et al*. (1995), and Stalberg *et al*. (2008). All of these studies failed to show any increased incidence of malignancy resulting from prenatal exposure to ultrasound. In a recent prospective study, including first trimester scanning, Stalberg *et al*. (2008) found no association of a particular brain tumor (primitive neuroectodermal tumor), although these same investigators had found an increase in this type of tumor in a similar population following prenatal x-ray exposure (Stalberg *et al*., 2007). In summary, no association has been found between ultrasound exposure *in utero* and the later development of any form of childhood malignancy.

8.3.3.7 *Conclusions from Epidemiological Studies*. Whereas several earlier studies demonstrated some intrauterine growth retardation in fetuses of mothers who were exposed to ultrasound

during their pregnancies (Moore *et al*., 1988; Newnham *et al*., 1993; Stark *et al*., 1984), this may have been because of the inclusion of pregnancies at risk for intrauterine growth retardation, which was, in fact, the indication for the scan. Delayed speech was another described finding (Campbell *et al*., 1993), but never reproduced. Some studies have also been performed in human embryos (before elective termination of pregnancy), which failed to demonstrate morphological or structural changes when these were scanned at 9 to 12 weeks, prior to the termination of pregnancy (Cardinale *et al*., 1991). The only finding that may withstand careful review is a possible increase in nonright-handedness, but only in male fetuses (Kieler *et al*., 2001). But on further analysis this is barely significant statistically with the risk difference between exposed and nonexposed subjects being 0.02 for all children and 0.05 for boys. Even if this is a statistically-significant difference, it does not necessarily indicate brain pathology (Salvesen and Eik-Nes, 1999) or have obvious clinical implications.

Some of the studies have serious limitations such as small sample size, poorly matched controls, and absence of information on acoustic output and quantification of exposure (number of episodes, duration, or dose delivered to a particular target). This is particularly relevant in today's clinical situations because of the addition of new modalities, with potentially-very high energy levels (such as spectral Doppler) and the expansion of diagnostic studies to the early first trimester, which is known to be a period of high vulnerability of the embryo or fetus to teratogenic insults.

The results from the epidemiology studies over the past 40 y have yielded no firm evidence of any adverse effects of diagnostic ultrasound in spite of large clinical usage. The apparent safety is reassuring. However, it should be remembered that most ultrasound exposures were poorly quantified, and that nearly all the epidemiologic evidence is based on exposures that occurred before 1992 after which the exposure limits were raised nearly eightfold. Furthermore, the inability to find convincing proof of an effect, either from epidemiology or from the physician's experience, does not preclude the possibility of it happening. It is difficult to identify a small increase in the rate of a commonly occurring event, and subtle effects (such as minor chemical effects and minor behavior effects) and long-term delayed effects could escape detection (NCRP, 1983). Consequently, it is necessary to utilize laboratory experiments to gain an understanding of the basic interactions of ultrasound with the body and to better understand the mechanisms by which adverse effects might arise (such as described for ionizing radiation in Sections 5.1.7 and 5.1.7.3).

8.3.4 *Areas of Special Concern*

Presently there are several areas of special concern pertaining to diagnostic ultrasound examinations performed during pregnancy. They are transducer self-heating, the use of Doppler in the first trimester, the use of contrast agents, and keepsake fetal imaging.

8.3.4.1 *Transducer Self Heating*. The production of ultrasound by a transducer is not very efficient, and the energy loss in the process ultimately causes the temperature of the transducer to rise (Duck *et al*., 1989). Heating at the transducer surface can cause a significant temperature rise at the surface of the skin or epithelium in contact with the transducer, even if the internal tissue temperature rise within the ultrasound beam is small. This self heating is not included in the calculation of the TI and tends to be ignored. Clinicians have the experience of some patients reporting a warm feeling at the point of contact with their skin. This is not considered a problem because the skin is such a good thermal barrier (NCRP, 1992). However, transducer self heating is relevant in intracavitary scanning, such as transvaginal ultrasound where the temperature rise is not limited by the skin to just the contact surface. Fortunately to date, in wide clinical usage, there have been no reports of any injury from transvaginal ultrasound examinations.

8.3.4.2 *Use of Doppler in the First Trimester*. Doppler techniques measure blood velocity by analyzing the frequency content of returning echoes. Because they require longer pulse lengths, their acoustic outputs are typically greater than B-mode scanners. Although 720 mW cm^{-2} is the FDA upper limit for I_{SPTA} for all obstetrical applications, intensities used in B-mode scanning are typically less (*e.g*., 34 mW cm^{-2}). However, present day Doppler mode studies typically use much higher intensities, some near 720 mW cm^{-2}. This is reflected in high TI values, some as high as six (Abramowicz *et al*., 2008b).

The organ most commonly affected by major congenital disorders is the heart. As a result, extensive research has been published on the value of ultrasound examination of the fetal heart. The vast majority of published reports was, until recently, on B-mode examinations around 18 to 20 weeks of gestation.

Doppler techniques, pulsed spectral and color, are the ideal techniques to examine the heart structure and functionality. Doppler analysis of flow across the cardiac valves, and Doppler velocimetry of various fetal vessels has been valuable. Several authors have demonstrated the feasibility of examining the heart much earlier in pregnancy, beginning at 10 or 11 weeks of gestation

(Achiron *et al*., 1994; Carvalho, 2001; DeVore, 2002; Gembruch *et al*., 1990; Marques Carvalho *et al*., 2008). Studies have also been published on the Doppler study of flow through cardiac valves, beginning at six weeks of gestation (Leiva *et al*., 1999; Makikallio *et al*., 2005, Teixeira *et al*., 2008), and on performing a measurement of the heart diameter, heart rate, and inflow and outflow waveforms after five weeks of gestation (Wloch *et al*., 2007).

Ultrasonic imaging during the first trimester has become very valuable with the observation of what is referred to as the nuchal translucency sign (relates to the size of the translucent space behind the neck of the fetus). It is due to edematous changes behind the neck of the embryo or fetus that occurs in association with Down syndrome and in other chromosomal abnormalities. The scan is performed at 11 to 13 weeks of gestation. However, there is a false positive rate of ~24 %. It was later found that the presence of normal ductus venosus flow and normal flow across the tricuspid valve significantly decreased the number of false positives, resulting in raising the accuracy of the nuchal scan from 76 % to over 85 % (Borrell *et al*., 2005; Maiz *et al*., 2008; Matias *et al*., 1998; Mavrides *et al*., 2002).

However, in reviewing these studies, it should be noted that it is extremely difficult to obtain these tracings and very prolonged dwell times are necessary (dwell time is the total time that any part of the anatomy is exposed to the ultrasound beam). At these early stages of pregnancy, embryos and fetuses measure 1 to 2 cm in length and therefore total body scanning in B-mode is necessary to position the Doppler gate. Whereas dwell times for Doppler studies of the fetus in the second half of pregnancy are approximately a few minutes at most, dwell times in the first trimester may last between 20 to 30 min and even more. Such prolonged exposures of a small embryo or fetus should engender great caution because of the potential for adverse effects at this vulnerable stage. Consequently, AIUM (2011) has proposed the following statement:

> "The use of Doppler ultrasound during the first trimester is currently being promoted as a valuable diagnostic aid for some congenital abnormalities. The procedure requires considerable skill, and subjects the embryo and fetus to extended periods of relatively-high ultrasound exposure levels. Because of the increased risk of adverse effects, the use of Doppler ultrasound in the first trimester should be viewed with great caution, and should only be employed when there is a clear benefit-risk advantage."

8.3.4.3 *Use of Contrast Agents*. Ultrasonic contrast agents, usually injected intravenously, can greatly enhance the visualization of

blood flow. Their usage is continually increasing for many diagnostic applications. Essentially, contrast agents are suspensions of micron sized gas bubbles that present an air-liquid interface from which ultrasonic backscatter is enhanced many hundred-fold. This enhanced echogenicity results in a significantly enhanced visualization of blood flow. However, along with this diagnostic benefit is the greatly increased risk of a nonthermal adverse effect. Because of this increased risk, the use of contrast agents in fetal imaging has been limited, and usually advised against (WFUMB, 2011).

8.3.4.4 *Keepsake Fetal Imaging*. Because of the remarkable images of the fetus obtained by modern ultrasound scanners, there is an increasing desire of pregnant women to obtain and keep these images of their future infant. Copies of fetal sonograms are commonly provided to pregnant patients by their obstetrician. However, there have been a number of nonmedical ultrasound scanning stores opening in various shopping malls that offer fetal imaging to anyone willing to pay for it. Even though there is no known harm that has ever been detected from this practice, there is always a hypothetical risk. Because an ultrasound examination introduces energy into a patient and its safety cannot be guaranteed, several major professional ultrasound organizations and FDA, have advised against exposing the fetus to ultrasound except for direct medical benefit to the patient or fetus, and when performed by trained health professionals knowledgeable about ultrasound bioeffects (AIUM, 2005; WFUMB, 2011).

8.3.4.5 *Ultrasound Examination of Febrile Patients*. Patients occasionally develop fevers during the course of their pregnancy. The temperature elevation caused by the fever is experienced by the embryo or fetus as well as the mother. If an ultrasound examination is performed when the mother is febrile, any temperature elevation due to the ultrasound is additive to the temperature elevation caused by the fever, and further increases the risk of birth defect. Therefore, one should be careful about using ultrasound in a febrile patient, and should use the lowest possible TI value consistent with obtaining the needed diagnostic information.

8.3.4.6 *Possible Alterations in Neuronal Migration*. Neurons of the cerebral neocortex in mammals, including humans, are generated during fetal life in the brain proliferative zones and then migrate to their final destinations. This neuronal migration occurs in the human fetal brain mainly from ~6 to 11 weeks of gestation but continues until 32 weeks of gestation. Recently, Ang *et al*. (2006) evaluated the effect of ultrasound waves on neuronal position within

the cerebral cortex of mice at the 16th embryonic day postconception. The mice were exposed at diagnostic ultrasound intensities for periods lasting from 30 min up to 7 h. A small but statistically-significant number of neurons remained scattered within inappropriate cortical layers and in the subjacent white matter, and failed to acquire their proper position. Ang *et al*. (2006) suggest the possibility that these changes, if they occurred in humans, could lead to neuropsychiatric disorders such as epilepsy, autism and schizophrenia. However, the applicability of these findings to clinical ultrasound in humans is questionable because of a number of reasons. For example, the exposures were much longer than those normally used in clinical examinations, there was no real dose effect (*i.e.*, the greatest effect did not occur at the longest exposure), and the results have not been duplicated in other laboratories.

8.3.5 *Safety Guidelines*

Acoustic output indices, the thermal index (TI) and the mechanical index (MI), have been developed to provide ultrasound users with a continuously updated on-screen guide to the relative level of risk of an ultrasound examination while it is being performed. Values equal to or lower than one indicate minimal risk and that an ultrasound examination need not be withheld because of a safety concern. A value greater than one indicates some risk and that the benefit-risk ratio should be evaluated in deciding whether to do or continue the examination. The higher acoustic outputs of Doppler mode examinations are also reflected in higher TI values, where values as high as six may be seen and greater caution is needed. In general the TI and MI indices should be maintained as low as feasible while obtaining the required diagnostic information.

9. Communicating Benefits and Risks

9.1 State of Knowledge and Practice of Medical Professionals

The core curricular elements of a residency in medical school, family medicine, and obstetrics and gynecology residencies, and even maternal fetal medicine fellowships do not define cognitive objectives related to the biological effects of radiation before or during pregnancy. Good training on this topic may occur in such settings due to excellent faculty mentorship, but systematic training in counseling after such exposures is not generally a structural component of these programs.

The topic of radiation exposure during the course of gestation due to medical diagnosis or therapy is rarely addressed in formal continuing education venues. Information related to preconception exposure of either male or female reproductive systems also is rarely covered. A review of topics directed to obstetrical care providers either in courses, online education, or maintenance of certification activities reveals little if any discussion of ionizing radiation exposure and risks.

Unplanned exposure to ionizing radiation of the developing embryo or fetus in the first trimester of pregnancy due to diagnostic imaging is a fairly common clinical event. This most often occurs in an urgent setting where, although the presence of a pregnancy was known, the appropriate action was to proceed with the imaging. This is still considered an unplanned exposure and is a source of anxiety to patients and professionals alike. But, despite its high frequency of occurrence, diagnostic radiation exposure of the embryo or fetus during the first trimester of pregnancy is very unlikely to result in reproductive or developmental effects (*i.e.*, harmful tissue reactions).

Discussion of heat energy and cavitation impacts in medical ultrasound are commonly addressed in formal curricula of obstetrical care providers, almost certainly due to its expanding clinical applications in obstetrics care. The data available to practitioners on biological effects of ultrasound are in keeping with the available scientific knowledge, but the interpretation of that data as it

relates to increasing use of ultrasound energy at the very earliest weeks of gestation is a source of debate. Although the potential for harm through the application of ultrasound energy has been widely recognized, the absence thus far of any observable deleterious impact of the use of these technologies in the clinical setting has been interpreted as reassuring.

9.2 Professional Counseling

In the 1950s and 1960s, the concept of the 10 d rule was suggested to protect the embryo from the deleterious effects of ionizing radiation. The 10 d rule was discussed by ICRP (1991; 2000) for woman of reproductive age. It states: "whenever possible, one should confine the radiological examination of the lower abdomen and pelvis to the 10 d interval following the onset of menstruation." The original proposal was for 14 d, but this was reduced to 10 d to account for the variability of the human menstrual cycle. In most situations, there is growing evidence that a strict adherence to the 10 d rule may be unnecessarily restrictive. In reality, since the vast majority of diagnostic radiological procedures expose the embryo or fetus to a dose <0.1 Gy, there is literally no increased reproductive or developmental risks during the first four weeks of gestation. In the first 14 d the woman is not pregnant and in the second 14 d the exposure occurs during the all-or-none period. So there is no need to have either a 10, 14, or 28 d rule.

Although not codified in any way, common practice in medical counseling is loosely derived from the publications of Carl Rogers. The fundamental precepts of Rogerian counseling include congruence (being genuine in one's concern), empathy, and unconditional positive regard (Rogers, 1951). A widely-accepted component of genuine concern in medical counseling is the responsibility of the counselor to provide core knowledge of the evidence addressing the issue in question. In the case of radiation exposure, the counselor should attempt to establish a good understanding of the exposure in question and its timing. A list of information required to provide high-quality counseling to those exposed is listed in Table 9.1. To be genuinely concerned is to seek and provide reliable information. A further adaptation of these principles involves providing an unbiased discussion of the facts surrounding the problem addressed. Empathy requires some knowledge of and sensitivity to the social and cultural position of the persons being counseled in order to address their needs. Unconditional positive regard can be interpreted in this setting to mean the person providing the counseling should approach the interaction with the attitude that the person seeking counsel is sincere in his or her desire to determine the

TABLE 9.1—*Minimum information required to provide adequate counseling to women and couples with concerns regarding ionizing radiation exposure before or during pregnancy (adapted from Brent, 2009).*

• Is the woman pregnant, possibly pregnant, or planning to become pregnant?
• If the women is pregnant, does she know the date she became pregnant? Does she know the date of the first day of her last menstrual period?
• 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?
• Are there historical pregnancy risks for the mother or the family? For example, is there a history of miscarriages, birth defects, infertility, or serious illnesses in the woman, her parents, or her siblings?
• What was the type of radiation exposure? Lay individuals confuse ionizing radiation with nonionizing radiation and microwave antennas with microwave receivers (dishes)?
• If the woman or couple is concerned about ionizing radiation, has the dose to the embryo or fetus been estimated by a qualified expert? Was the exposure an acute, protracted or fractionated exposure?
• Has the woman or couple sought advice from another counselor about the developmental risks of this exposure?
• Was this a planned or wanted pregnancy? What are their concerns and thoughts about the pregnancy?
• If an exposure to one or both of the parents occurred before conception, is an estimate of the dose to the ovaries or testes of the exposed parent available? If pregnancy has not occurred, when does the family plan to initiate the pregnancy?

course of action that best suits his or her circumstances and is not based on motives intended to define fault or damages. A reasonable crystallization of the behavior defined by this standard for professional counseling might be that the needs of the person seeking counseling are the only operative issues to be considered.

The circumstances surrounding an inadvertent exposure of a patient to radiation in diagnostic or therapeutic procedures carry a burden of a pervasive concern regarding medical-legal implications of the incident (Brent, 1967; 1977b). Even in situations where

the radiation exposure occurs in circumstances outside the realm of professional medical services, the question of responsibility and in turn, liability, related to the exposure often burdens the counseling interaction. Approximately 8 % of women or families who are concerned about the developmental or reproductive effects of radiation exposure have been provided inaccurate risk estimates by their physician or other health professional who provided the preliminary counseling (Brent, 2009). These initial consultations may have provided inaccurate risk estimates that can stimulate negligence litigation (Brent, 1967; 1977b; 1977c; 1982; 1995c; 1995d; 1999a).

The circumstances of exposure are often complex and allocation of risk for congenital anomalies or miscarriage, and subsequent malignancy after radiation exposure are, by necessity, estimates. In most cases, however, the uncertainty of estimates derived from scientific studies is quite well understood. In circumstances where there is a need for more accurate dose estimates to decrease the risk uncertainty, seeking the services of a qualified expert may be appropriate.

9.3 Information Resources for Professionals

The risk to the embryo or fetus for tissue reactions (deterministic effects) (*i.e.*, birth defects, growth retardation, pregnancy loss, mental retardation) from prenatal exposure to the common sources of ionizing radiation in the United States (*i.e.*, environmental, occupational and medical) is generally very low. At doses to the embryo or fetus <0.1 Gy there may be no increased risk based on extensive mammalian animal studies (Section 5), since there are so few epidemiological studies at these low doses. The risk is often overestimated by practicing professionals.

Continuing medical education, including that required for maintenance of board certification should be provided to obstetrical care providers, primary care providers, radiologists, and radiotherapists. The observations in this Report indicate that a gap in providing such continuing education exists, and contributes to the needs assessment criterion of the Accreditation Council for Continuing Medical Education. Initial certification and maintenance of certification through specialty organizations are generally overseen by the American Board of Medical Specialties.

Online education resources that can inform professionals at the point of need are becoming increasingly utilized within clinical medicine. For example, this Report will be available on the NCRP website (NCRP, 2013). A fairly new source for dissemination of radiation risk information is *via* the internet. However, on the internet, excellent scientific presentations are in competition with less scholarly

material. Therefore, counseling is markedly improved if quality websites or published documents provide access to radiation consultants who are readily available to respond and complete the consultation to the satisfaction of the contacts.

9.4 State of Public Knowledge

Due to public perception of the risks from medical procedures that utilize ionizing radiation, magnetic fields, and ultrasound (and the complexity of the procedures), discussion of the risks associated with such procedures during pregnancy often is difficult. Therefore it is important that reliable scientific information be made available in an easily understood and comfortable manner to pregnant women and their families as soon as it is needed. Usually the families seek information concerning the risks of radiation before or during pregnancy from the obstetrician, the family physician, the radiology department where the procedure will or has been performed, or the internet. While these professionals may provide counseling, the information provided may or may not be accurate or complete.

Although decision making requires a consultation with a healthcare professional, the consultation should include not only verbal communication, but a written report with supporting information and clarifications.

The frequency of inadvertent or medically-necessary prenatal exposure to diagnostic radiological procedures justifies that appropriate patient education materials be made available to the patient. Commonly used professional health information websites may also provide good background information on general facts related to prenatal radiation exposure. It should be pointed out that not all professional websites claiming to provide radiation risk information provide accurate risk analyses. If the counselor refers the patient to a website it is important that the website has been evaluated for accuracy and current information by the counselor.

The family that is concerned about possible radiation exposure from diagnostic radiological studies during pregnancy is best served by writing down the circumstances of the exposure, the date(s) involved as well as the most accurate gestational age assessment possible for the exposure (Table 9.1). Ideally, with this information, a discussion with the obstetrical care provider will enable empathetic counseling regarding the risks of the exposure to the unborn child. If the obstetrician is uncertain about the risks the patient should be referred to a consultant experienced in the area of reproductive and developmental radiation risks. In the vast majority of cases the additional radiation risk will be inconsequential in

comparison to the background risks of 3 % for birth defects and 15 % for miscarriage. The embryo may not even have been exposed.

It is important for the consultant to answer all the questions of the contact and to make certain that the patient understands the information that has been provided. A written note can be placed in the chart with a copy to the patient with regard to the results of the consultation. If the consultation occurs over the internet, then the patient has a written record of the interaction, which is best for the patient and the consultant. The consultant has to indicate that he or she is willing to be contacted again if further questions arise. It is important for the counselor to indicate that he or she is a teacher about reproductive risks and that the final decision with regard to this pregnancy is decided by the family.

9.5 Information Resources for Members of the Public

Information related to radiation exposure can be obtained from qualified experts commonly based at academic health centers and other medical institutions which provide radiation therapy and diagnostic radiological studies.

Many professional and government organizations have websites that provide reproductive risk information. Some of these websites provide the information in written form but do not provide the availability of personal contact with a counselor who is an expert in radiation reproductive risks. Since the content of websites can change, it is important to determine if the information is current.

Resources for members of the public on the internet include:

- American Academy of Family Physicians (no counselor available), http://www.aafp.org/afp/990401ap/1813.html
- American College of Radiology (no counselor available), http://www.radiologyinfo.org/en/safety/index.cfm?pg=ImageWiselyMenu
- Centers for Disease Control and Prevention (no counselor available), http://www.cdc.gov/ncbddd/pregnancy_gateway/during.html
- Health Physics Society
  - *Ask the Expert* (counselors available), http://hps.org/publicinformation/asktheexperts.cfm; click on “go to the list of questions and answers” and select the category *Pregnancy and Radiation*
  - *Pregnancy and Radiation Exposure,* http://www.hps.org/hpspublications/articles/pregnancyandradiationexposureinfosheet.html

  - *Radiation Answers* (a service of the Health Physics Society for members of the public), http://www.radiationanswers.org/radiation-questions-answers/radiation-and-pregnancy.html; the *Radiation Answers* website is dedicated to public education. This website contains scientific, objective information about radiation risks in a friendly, easy-to-read format.
- International Atomic Energy Agency, https://rpop.iaea.org/RPOP/RPoP/Content/SpecialGroups/1_PregnantWomen/index.htm
- Organization of Teratogen Information Specialists (counselors available), http://www.mothertobaby.org/fact-sheets-s13037; the Organization of Teratogen Information Specialists website has counselors who can be reached by telephone. If these counselors do not have expertise in reproductive radiation risks, they know how to obtain the information or refer the contact.
- U.S. Department of Labor (no counselor available), http://www.osha.gov/SLTC/radiationionizing/index.html#healtheffects

10. Conclusions and Recommendations

The conclusions and recommendations are listed in the general order that the corresponding topics are addressed in this Report, and the section(s) of this Report where each is addressed is noted.

For ionizing radiation, the doses to the embryo or fetus presented in gray refer generally to the quantity absorbed dose from low-LET radiation. The one exception is for the study of atomic-bomb survivors exposed *in utero* at the time of the bombings, where the doses presented in gray are identified as the weighted uterine dose (*i.e.*, the absorbed dose from gamma rays plus 10 times the absorbed dose from neutrons); however, the weighted uterine dose is primarily from low-LET gamma rays.

10.1 Conclusions

1. While there are limited epidemiologic studies of ionizing radiation exposures in human pregnancies from which to determine directly the no-adverse-effect level for developmental and reproductive effects, there are extensive mammalian animal studies that support a conclusion that the no-adverse-effect level from acute exposure for birth defects, growth retardation, pregnancy loss, and other tissue reactions (deterministic effects) is ~0.2 Gy (dose to the embryo or fetus) at the most vulnerable stage of pregnancy (Sections 3.2.2 and 5.2). The experimental animal data also indicate that tissue reactions for protracted and fractionated irradiation are diminished compared to the effects of acute irradiation (Section 5.1.4). Ionizing radiation from ubiquitous background sources, occupational exposure within regulatory limits, dental radiography, or medical diagnostic radiography (including procedures of the abdomen and pelvis) typically result in doses to the embryo and fetus <0.1 Gy.
2. There is no convincing direct evidence of germline mutation manifest as heritable disease in the offspring of humans that is attributable to preconception exposure to ionizing radiation, yet preconception exposure clearly induces mutations in microbes and somatic cells of rodents and humans,

and in offspring of irradiated male mice (Sections 4.1, 4.2, and 4.6).

3. The normal background rate of adverse pregnancy outcomes is considerable. For example, birth defects are observed for 3 % of all live births and miscarriage occurs after the first missed menstrual period for 15 % of all pregnancies (Section 5.1.1).
4. Based on animal studies, absorbed doses to the embryo >0.2 Gy increase the incidence of embryonic loss during the preimplantation and presomite developmental stage, but in general the surviving embryos do not have an increased incidence of malformations (reflecting an all-or-none phenomenon) (Section 5.1.5).
5. Increased risks to the embryo or fetus have not been observed for mental retardation, birth defects, growth retardation, neurobehavioral effects, impaired school performance, convulsive disorders, or embryonic or fetal death below a dose of 0.1 Gy (weighted uterine dose) (Section 5.2).
6. Mental retardation (IQ < 70) can be produced by ionizing radiation exposure during the 8th to 15th week postconception (10th to 17th week of gestation) with an incidence of 40 % Gy^{-1} (weighted uterine dose), and during the 16th to 25th week postconception (18th to 27th week of gestation) with an incidence of 15 % Gy^{-1} (weighted uterine dose). No increase in mental retardation has been observed at fetal doses in the diagnostic imaging range (<0.1 Gy) (Section 5.2.1).
7. Concerning the association between *in utero* exposure and cancer in the offspring (Section 5.2.6):
   a. Data from case-control studies (including two large studies that relied on medical records for exposure determination) support a statistical association between childhood leukemia in offspring and the mother's exposure to diagnostic x rays during pregnancy. The excess relative risk (ERR) of childhood leukemia based on a meta-analysis of 32 case-control studies is estimated as 1.3 (95 % CI = 1.2 to 1.5). Investigators have debated whether the statistical associations are causal as well as the magnitude of the leukemogenic risk per unit fetal dose.
   b. Meta-analyses of cohort studies (concerning exposure of mothers to diagnostic x rays during pregnancy) have found small, but not statistically-significant increases

of total cancer, but confidence intervals (CI) were compatible with a composite increase similar to that of the case-control studies of 30 % or a composite estimate compatible with no increase in risk. Overall, the cohort studies are characterized by limited numbers of total childhood cancer and the subset of childhood leukemia cases, and with insufficient statistical power and substantial uncertainties, thus limiting the ability to draw firm conclusions.

c. Among atomic-bomb survivors *in utero* at the time of the bombings, there was no statistically-significant evidence of a dose-related increase in cancer mortality among persons younger than 15 y of age at follow-up. This study did not provide detailed radiation-related childhood cancer incidence data between 1945 and 1957.

d. The Japanese Atomic-Bomb Survivor Study is the only study to evaluate and compare adult leukemia and cancer risks following *in utero* exposure to those following early childhood exposure. There have been too few leukemia deaths (and data lacking on leukemia incidence during 1945 to 1957) to estimate radiation-related dose response. To date, the study reveals statistically-significant radiation-dose related increases in solid cancer risks [ERRs per gray (weighted uterine dose)] at the same attained age of 50 y in both groups. ERRs for cancer per gray (weighted uterine dose) following *in utero* exposure are lower than those exposed in early childhood. Excess absolute rates (EAR) per 10,000 person years per gray in the study revealed a substantially lower increase with attained age among those exposed *in utero* than the marked increase with attained age among those exposed in early childhood (Section 5.2.6).

e. The possible role of background radiation in the occurrence of leukemia or other childhood cancers in offspring of mothers exposed during pregnancy has not been specifically evaluated, although it would be almost impossible to ascertain prenatal exposures separately from postnatal exposures since the exposures are ubiquitous. For man-made sources from nuclear accidents, nonstatistically-significant increases in childhood leukemia were reported from Belarus following the Chernobyl nuclear reactor accident, but no excess or dose response was observed in 35 countries in Europe. Investigations of nuclear weapons testing has not provided

information specific to clarifying risks in childhood leukemia in offspring of women who were pregnant at the time of the testing.

8. Diagnostic nuclear medicine protocols can usually be modified to result in a low dose and risk to the embryo or fetus; however, the use of ^{131}I radiation therapy may result in ablation of the fetal thyroid (Section 6.1). Dose reduction in an appropriate nuclear medicine imaging examination is only warranted if it will not compromise the medical care of the patient or unborn child (Section 7.2.1).
9. Applying the available guidance concerning when it is necessary to interrupt breast-feeding following nuclear medicine procedures will reduce the dose to the nursing infant (Section 6.1).
10. Diagnostic radiological procedures necessary for the care of the mother, or the embryo or fetus, can be performed at any time during pregnancy (Section 7.2.1). Diagnostic imaging can be extremely important in the care of pregnant or potentially-pregnant women when indicated (Section 3.2.1). However, every effort should be made to ensure that such procedures are justified and the dose is commensurate with the medical purpose (*i.e.*, consistent with the ALARA principle) (Section 3.3).
11. Radiation therapy when the abdomen or pelvis is in or near the treatment field carries a high risk of embryonic or fetal death and therefore requires serious consideration of all available options (Section 7.2.2).
12. Radiation therapy when the treatment field is distant from the abdomen and pelvis (*e.g.*, treatment of the brain, head and neck, upper chest, and breast) often can be performed with a relatively low dose to the embryo or fetus (Section 7.2.2.2). Each case requires careful consideration of the benefits and risks of the treatment, including the medical benefit to the patient and the potential risk to the embryo or fetus.
13. Most studies evaluating MRI safety during pregnancy have failed to demonstrate any significant adverse reproductive or developmental effects (Section 8.1.5).
14. There have been no established increases in risks to the embryo or fetus from commonly encountered levels of RF radiation from sources such as cell phones and television and radio broadcast towers (Sections 8.2.5 and 8.2.6).
15. The display of thermal and mechanical indices (TI and MI) on ultrasound scanners has been developed to assist

sonographers in employing the ALARA principle developed for ionizing radiation protection to ultrasound (Sections 8.3.1 and 8.3.5).

16. Although some epidemiology studies have reported effects from intrauterine exposure to diagnostic ultrasound, such as low birth weight, delayed speech, dyslexia, and non-right-handedness, most studies have not. Most of these studies were based on exposure conditions before 1992, the year in which acoustic limits of ultrasound machines were substantially increased for obstetric applications (Section 8.3.1). Based on these epidemiologic data and on current knowledge of interactive mechanisms, there is little or no convincing evidence to warrant conclusion of a causal relationship between diagnostic ultrasound and adverse effects during pregnancy, but continued vigilance is recommended (Section 8.3.2).
17. There is a general misconception by members of the public and many health practitioners that ionizing radiation at any level is much more detrimental to the embryo or fetus than is actually the case (Section 9).
18. When medical practitioners are poorly informed about the differences in the potential for adverse effects from various doses to the embryo or fetus, tragic consequences may occur as a result of inappropriate counseling and providing erroneous information. Medical practitioners with questions on proper counseling should seek expert opinion prior to counseling or direct the patient or family to a qualified expert (Section 9).

10.2 Recommendations

1. Medical procedures using ionizing radiation should be performed only when there is a recognized or established medical need (*i.e.*, application of the principle of justification of practices). Strategies for managing dose (*i.e.*, application of the principle of optimization of radiation protection) should be employed for medical diagnostic imaging, as well as for fluoroscopically-guided interventional procedures and radiation therapy. However, any adjustments should not be made at the expense of obtaining the necessary diagnostic information, compromising treatment, or affecting maternal health. Consideration should be given, when applicable, to the utilization of nonionizing imaging modalities (Sections 3.2.1 and 7.2.1).

2. If the embryo or fetus is involved in a direct radiation exposure (*i.e.*, the embryo or fetus is in or very close to the radiation field), a retrospective dose estimate for the embryo or fetus should be performed for higher dose procedures such as abdominopelvic CT, and the dose estimate from any direct or proximal exposure should be made available to the patient if requested (Sections 3.2.1, 7.2, and 7.2.4.1).
3. Occupationally-exposed pregnant radiation workers who have declared their pregnancy should be monitored monthly and provided with their monthly dose record (Section 3.2.2).
4. Interruption of breast-feeding should be evaluated for each type of diagnostic nuclear medicine procedure and the appropriate guidance is dependent on the radiopharmaceutical administered to the mother (Table 6.1). If the mother has received a therapeutic dose of ^{131}I, breast-feeding should be discontinued (Section 6.1). When a mother is exposed to environmental radioiodine from an accident or other incident, decisions regarding breast-feeding should be dependent on the potential exposure to the child from ^{131}I in the breast milk (Section 6.3).
5. Prior to the receipt of any medical exposure using ionizing radiation, pregnancy status should be assessed. Each medical practice and institution should have a policy for assessment and documentation of pregnancy status (Section 7.1).
6. Each medical practice and institution should have a policy for imaging or otherwise irradiating pregnant or potentially-pregnant patients. This should include guidelines for use of informed consent that is understandable based on established standards for informed consent (Sections 7.1.3, 7.1.4, and 7.2.1).
7. The use of radiation therapy that may present an increased risk to the embryo or fetus should be the subject of an interdisciplinary consultation (Section 7.2.2.).
8. MRI scans involving the embryo or fetus should be performed only when useful clinical information will potentially be obtained, the examination cannot wait until the completion of pregnancy, information cannot be reliably obtained by ultrasonography, and the examination is performed within specified exposure parameters called the "normal mode" (Section 8.1.2).
9. Pulsed Doppler (spectral, power, and color-flow imaging) ultrasound examinations during the first trimester should

only be employed when there is a clear benefit to risk advantage (Section 8.3.4.2).

10. The obtaining of fetal ultrasound images solely for entertainment or souvenir (keepsake) purposes should not be performed (Section 8.3.4.4).
11. Diagnostic ultrasound equipment should only be used when medically indicated and by individuals who are appropriately trained and certified in the safe and proper operation of the equipment (Section 8.3.5).
12. Education for health professionals who care for pregnant patients should include information on the risks of radiation, and obstetric care providers should be educated on the impact of radiation exposures to pregnant or potentially-pregnant patients and the embryo or fetus (Section 9.3).
13. A pregnant patient should be counseled as an educational interaction with care and compassion about radiation exposure from medical procedures during pregnancy to assist in the family's decision making (Sections 9.2, 9.3, and 9.4).

Appendix A

Radiation Exposure Consultations

A.1 Introduction

The following information is intended to assist those who counsel contacts concerned about:

- reproductive risks of radiation exposures to women who are pregnant;
- risk of birth defects, miscarriage, mental retardation, growth retardation, and cancer in the exposed embryo or fetus; and
- impact of preconception radiation exposures on the development of sperm or ova (eggs) and any resulting increased risk of infertility or genetic diseases due to such exposure.

This following final statement should be included in every consultation:

> It is important for each pregnant woman to realize that pregnancy has inherent risks and that each healthy woman without a personal or family history of reproductive or developmental problems begins her pregnancy with a 3 % risk for birth defects and a 15 % risk for miscarriage. At the present time we cannot change these risks, but women who anticipate pregnancy or who are of reproductive age can minimize their risks by receiving prenatal care at a qualified facility, and taking multivitamins, folic acid (400 μg), vitamin B-12 (6 μg), and calcium supplements (1,500 mg) with vitamin D (400 units) each day.

Sections A.2 and A.3 provide an introduction to help readers understand the specific examples provided in Section A.4.

A.2 Ionizing Radiation

Ionizing radiation includes x rays generated by x-ray machines and x and gamma rays emitted by radionuclides. They are used

widely for diagnostic imaging and the treatment of cancer. If the patient is pregnant during these procedures, her embryo or fetus will receive some radiation exposure, usually small amounts. Occasionally, particularly during radiation therapy, the dose to the embryo or fetus may be high enough to produce deleterious biological or pathological effects. In such instances it may become important to estimate the increased risk of adverse effects to the embryo or fetus. That requires determining first the magnitude and timing of the dose to the embryo or fetus. A qualified expert (trained specialist) may be needed to carry out such a determination. In many instances for diagnostic procedures, an evaluation of the dose would not be necessary because the developing embryo or fetus would not be directly in the radiation field (*e.g.*, a diagnostic x-ray procedure of the skull).

Most diagnostic procedures expose the embryo or fetus to a dose <0.1 Gy. This level of dose will not increase the risk of reproductive effects (either birth defects or miscarriage). According to published information derived from mammalian animal studies, the estimated minimum acute dose of radiation that results in an increased incidence of birth defects is 0.2 Gy. The risk of miscarriage (spontaneous abortion) is greatest during the preimplantation stages when a pregnant woman will not know that she is pregnant and may not even be aware that she miscarried.

Another important consideration is the stage of pregnancy in which the radiation exposure occurred:

- In the 3rd and 4th weeks of gestation (1st and 2nd weeks postconception), the embryo is very resistant to the malforming effects of x rays. The embryo is, however, vulnerable to the lethal effects of x rays although an acute dose in the range of 1.5 to 0.2 Gy is necessary to cause a pregnancy loss (resorptions in mammals). At this stage the pregnant woman may not even be aware that she is pregnant or that the embryo has miscarried.
- From the 5th to 10th weeks of gestation (3rd to 8th weeks postconception), the embryo is in the period of early embryonic development but is not at an increased risk for birth defects, pregnancy loss, or growth retardation unless the dose is above the estimated no-adverse-effect level of 0.2 Gy. Malformations, growth retardation, and pregnancy loss are at increased risk as the dose increases.
- From the 10th to 27th weeks of gestation (8th to the 25th weeks postconception), the embryo or fetus is vulnerable to the effects of radiation on the CNS (*i.e.*, mental retardation). The no-adverse-effect level has been estimated to be >0.5 Gy

(with a lower 95 % CI value of ~0.3 Gy) before an increase in the incidence of severe mental retardation will be manifested in surviving embryos or fetuses. Diagnostic radiological studies do not reach these levels and, therefore, these effects should rarely be of concern for pregnant patients.

- Beyond the 22nd week of gestation (20th week postconception), when the fetus is well developed, the fetus is more resistant to radiation developmental effects. However, the brain, overall growth, and the genitourinary system can be affected by doses that are higher than the doses that occur in almost all diagnostic radiological procedures. The most important point to remember is that practically no diagnostic radiological procedure will affect a fetus at this late stage of pregnancy and there is not an increased risk for birth defects or miscarriage from the range of doses that occur from diagnostic studies.

A.3 Nonionizing Modalities and Sources

The reproductive risk of nonionizing modalities and sources which include electromagnetic fields emitted from computers, microwave communication systems (antennae), microwave ovens, power lines, cell phones, household appliances, heating pads and warming blankets, airport screening devices for metal objects, laser therapy for hair removal or other cosmetic procedures, tanning salons, and diagnostic and therapeutic exposures to ultrasound has been studied extensively. Two national committees of scientists evaluated the risk from these nonionizing modalities and sources. Both of the committees published books on the subject. The first was from the Oak Ridge Associated Universities panel created by the White House (Davis *et al*., 1992) while the second was the product of a committee of the National Academies (NA/NRC, 1997). Both of these groups concluded that the reproductive risk of nonionizing radiation is minimal if even existent. MRI which also utilizes nonionizing electromagnetic and permanent magnetic fields has been less well studied with regard to the risk of developmental effects; however, the exposures are not mutagenic or cytotoxic.

A.4 Examples of Consultations

A.4.1 *Diagnostic X-Ray Studies When the Abdomen and Pelvis are Not Exposed*

When a diagnostic x-ray study or CT scan is of the head, teeth, sinuses, chest, arms, neck or legs is performed, the primary radiation beam is not directed to the pregnant patient's embryo, fetus or

ovaries. The amount of scattered radiation that might reach the embryo, fetus or ovaries would be extremely small and would not increase the risk for birth defects, miscarriage, or genetic diseases from preconception exposures.

For the diagnostic x-ray imaging studies cited above, a developing embryo or fetus would not be at an increased risk for radiation-induced tissue reactions (deterministic effects). Only studies that involve exposure of the embryo or fetus to the primary beam, such as imaging of the pelvis or abdomen, need be of possible concern.

A.4.2 *Diagnostic X-Ray Studies that Directly Expose the Abdomen and Pelvis*

The following x-ray imaging studies frequently involve exposing the embryo or fetus and ovaries to the primary x-ray beam because the abdomen is in the primary beam at least during part of the procedure:

- studies of the back (lumbar spine) for evaluating a lower back pain or a nerve root pain;
- intravenous pyelogram to examine kidney function;
- upper GI series for evaluation of GI symptoms;
- lower GI series (barium enema) to examine the structure and function of the large intestine;
- studies of bladder function;
- studies of the gallbladder and gallbladder function;
- studies of the structure and function of the uterus and tubes with the procedure known as a hysterosalpingogram;
- studies of the pelvis and hips due to hip pain; and
- standard abdominal x-ray procedures (flat film of the abdomen).

When the uncertainty in the dose to the embryo or fetus is of concern to the patient or referring physician, the imaging department and its attending medical physicist (qualified expert) usually can provide the relevant dose data that will assist in the counseling.

There are two important facts to consider when an evaluation is performed. First, the dose in the vast majority of instances will be lower than 0.1 Gy and will not represent a reproductive risk to the embryo or fetus for birth defects, miscarriages, or other tissue reactions (deterministic effects). Second, the risk of cancer is far below the spontaneous risk of cancer and has not been accurately determined at the low doses received from these procedures.

A.4.3 *Diagnostic Nuclear Medicine Studies*

Pregnant women may be administered radiopharmaceuticals to diagnose various medical conditions while they are pregnant. Sometimes these radiopharmaceuticals may be administered before the patient knows that she is pregnant. The administered activities for most of the radiopharmaceuticals utilized for diagnostic studies do not expose the embryo or fetus to absorbed doses >0.1 Gy. The dose for many of the procedures is much less than one-tenth of this (*i.e.*, 0.01 Gy). Table 3.2 (Section 3.2.1) gives some examples of the doses to the embryo or fetus for specific radiopharmaceuticals and the administered activities (megabecquerel). The risk of cancer is far below the spontaneous risk of cancer and has not been accurately determined at the low doses received from these diagnostic nuclear-medicine studies.

A.4.4 *Ionizing Radiation Therapy with Radionuclides that Exposes the Abdomen and Pelvis*

Many radionuclides are administered orally or intravenously for cancer treatment. Radioactive seeds are used for implantation into malignant tumors. Iodine-131 is used to treat hyperthyroidism and thyroid cancer. In such cases an embryo or fetus, if present, could receive several gray of fractionated doses over the treatment time. However, it is highly unlikely that the physicians involved in such treatment will not know or not seek to determine the pregnancy status of a female patient. When it is known or suspected that the patient may be pregnant and the responsible physician concludes that postponing treatment until after birth is not advisable, the patient should be advised of the risks involved and should share in the decision to treat or not or possibly to terminate the pregnancy. In the case of ^{131}I therapy, if ^{131}I is administered during the first two or three weeks of pregnancy, the probability is that most of the iodine will have been excreted or decayed before the fetal thyroid develops the ability to concentrate the iodine, which does not happen until after ~10 weeks of gestation. Determining fetal dose from radionuclide therapy requires the services of a qualified expert.

A.4.5 *External High-Dose Radiation Therapy During Pregnancy*

Since radiation treatment for cancer involves quite high doses of radiation, in the tens of gray, it is very likely that the embryo or fetus will be affected if radiation therapy is initiated during pregnancy and the embryo or fetus is directly exposed. In the early stages of pregnancy, embryonic vulnerability is such that doses of

several gray per day of fractionated radiation therapy would prevent the embryo from surviving. When exposures occur later in gestation, fetal sensitivity decreases but it is still vulnerable to cell killing effects and this concern remains a source of anxiety to all involved. Determining the radiation risk and counseling the patient and her family about these concerns requires the close cooperation of all health professionals involved including the nuclear medicine physician or the radiation oncologist and the medical physicist (qualified expert).

Many pregnant women have been treated with a six to eight week course of radiation in which the embryo or fetus is not directly exposed. This can occur in the treatment of a brain tumor, breast cancer, lymphoma, or skeletal bone cancer without apparent harm to the embryo or fetus even when the target volume for cancer treatment received 40 Gy or more. Each case is different requiring careful consideration of all of the treatment parameters as well as the radiation biology aspects and emotional status of the patient. What might be good advice for one breast cancer patient, for example, might be inappropriate for another breast cancer patient receiving the same dose but whose concerns and willingness for risk-taking might be different. The family can be informed that in many cases the surviving embryo or fetus may be normal due to the fact that the relatively low doses of protracted radiation received by the embryo or fetus over a period of weeks will not increase the risk of tissue reactions (deterministic effects).

A.4.6 *Family Members or Friends Receiving External-Beam Radiation Therapy*

Some members of the public perceive that after radiation therapy with a high energy x-ray machine, an electron-beam linear accelerator or teletherapy equipment (a machine with a high-energy gamma-ray source) the person who received the treatment may become radioactive. The x-ray, gamma-ray and electron-beam energies typically used in radiation therapy do not induce radionuclides in the patient and therefore the patient does not become a source of radiation exposure to relatives and friends. Therefore patient contact need not be restricted for this concern.

A.4.7 *Family Members or Friends Administered Radioactive Material for Diagnosis or Therapy*

If a family member or friend has been administered radioactive material for diagnosis or therapy, the patient will have residual radionuclides when they leave the facility. After a diagnostic

procedure, the patient will be allowed to leave the hospital immediately, unless there are other reasons for which they need to be hospitalized. In these cases, the patient will have received a relatively low administered activity of a short half-life radionuclide. If one of the family members is pregnant she should refrain from being in the same room with the patient for 24 h. In most cases there should be no special concerns about interacting with the patient within 3 d. However, each radionuclide has a different half-life and the length of time that a pregnant woman should refrain from being close to the patient varies. A special case may be a pregnant woman with a small child who is being breast-feed and the child has been administered radioactive material for diagnosis or therapy. The nuclear medicine facility will have directions that pertain to each nuclear medicine study and any special circumstances and will provide recommendations for the pregnant woman. Any individual that does not enter the room where the patient is located will not be exposed to radiation. Distance is a great exposure reducer.

If the patient has received radioactive material for therapy, the patient, depending on the radionuclide used, may have to remain in the hospital for a few days because of the high dose that was administered. Even when the patient is allowed to go home, the amount of radionuclide in the patient's body will still necessitate precautions with regard to handling the urine and stools. Depending on when the patient is allowed to leave, which radionuclide was used and how much radionuclide was administered, there may or may not be any special precautions that are recommended. In cases where additional guidelines are needed, the patient is given instructions from their healthcare provider regarding extra precautions to be taken. Some of these precautions might include limiting time around children or someone who is pregnant. If a pregnant woman seeks counseling about the radiation risks to her embryo or fetus from contact with a patient who has been treated with a high dose of a radionuclide, it is possible to calculate the dose rate to the embryo or fetus at various distances from the patient on different dates following the radionuclide administration. Information is available that permits the calculation of the dose rate [total effective-dose equivalent per hour ($mSv\ h^{-1}$)] at one meter for the administered activity (gigabecquerel or curie) of the radionuclide (Howe *et al*., 2005; Siegel *et al*., 2007). By utilizing the biological half-life (the combined metabolic and physical half-life of the radionuclide) and the administered activity, the dose rate to those in the proximity of the patient can be estimated at any particular post-therapy time.

A.4.8 *Exposure to the Sperm from Diagnostic X-Ray Studies*

There are no observed increased risks for genetic changes in the sperm if the testes have not been directly exposed to ionizing radiation. Direct testicular exposure and, therefore, sperm exposure may occur from diagnostic x-ray studies [*e.g.*, abdomen, hips or pelvis, lower spine, and bladder studies (conventional or CT); intravenous pyelogram; fluoroscopy for urinary tract function; and barium enema (lower GI series)]. Exposures to the sperm from these procedures are generally below a dose of 0.1 Gy.

The risk from radiation exposure of sperm prior to conception has been studied in two large populations. The concern of most patients is whether the radiation exposure to the sperm will result in birth defects or genetic disease. In one study, thousands of individuals who were exposed to radiation in Hiroshima and Nagasaki and parented families were studied for the incidence of genetic disease and other reproductive effects. After 50 y of studying this population, there has been no demonstrable increase in genetic disease. The observed incidence of mutations in the offspring of the atomic-bomb survivors was too small to demonstrate statistically the presence of radiation-induced mutations in the atomic-bomb exposed population due to the high incidence of spontaneous mutations.

Men exposed to mutagenic drugs and radiation therapy have been studied by the National Cancer Institute. There are now several thousands of patients who have survived cancer, which occurred in childhood, adolescence or early adulthood. Families of these individuals also have not demonstrated an increase in birth defects or miscarriage, although increased infertility has occurred.

It is possible that infertility or sterility may result if the testes receive high enough doses of radiation. Because of the theoretical risks it is advisable that men whose testes have been exposed to the primary beam, even in diagnostic imaging, avoid conceiving for at least two spermatogenesis cycles, which is about four months. This recommendation is made even in the absence of an observable increased risk of radiation-induced mutations as a simple precaution that is easy to carry out. Most likely the risk is very small and not detectable at the present time. The patient or family members will discover on the internet or from other literature that irradiation of sperm can cause chromosome abnormalities or point mutations. In most instances these abnormal sperm fail to fertilize the female ovum, or if fertilization occurs the early embryo does not survive, thus resulting in our inability to demonstrate genetic effects in the offspring of radiated populations.

A.4.9 *Exposure to the Sperm from Radiation Therapy*

External-beam radiation therapy of the pelvis, hip, femur (upper long bone of the leg), bladder, and prostate could involve irradiation of the testes. While it is possible to shield the testes for some of these radiation procedures, the scattered radiation could still be quite high. The principle effect of high doses to the testes is infertility. For those patients who remain fertile after therapy, their reproductive risks are not increased significantly. In other words, the risk of birth defects in the next generation for those men who remain fertile and conceive is quite low. Studies of the atomic-bomb survivors indicate that even in the high-dose group there is not an increased incidence of chromosome abnormalities or genetic disease in the next generation. Similar results were seen in studies from the National Cancer Institute, which indicate that patients who had cancer and received chemotherapy and radiation did not have an increased incidence in genetic disease or birth defects in the next generation although they did have problems with infertility.

A.4.10 *Exposure from Communication Microwave Sources*

Microwave sources include the ubiquitous communication towers and cell phones in use everywhere. The energy of microwaves is much too low to ionize matter and the microwave power in areas accessible to members of the public is much too low to induce thermal heating. Hence microwaves used in communication do not have the potential to increase the risk of birth defects or miscarriage in pregnant women. Microwave dishes mounted to homes are seen everywhere. These dishes are microwave receivers only and do not emit any radiation and thus cannot cause biological harm.

Appendix B

Radiation Exposure Questions and Answers

This appendix presents questions concerning preconception exposure or exposure during pregnancy that have been asked of various counseling services along with suggested answers. It is intended to be helpful both to those who are personally concerned about these issues and to health providers who would benefit from a better understanding of the range of concerns people have expressed. The first part provides single questions and answers. The second part gives an example of a more complex consultation.

B.1 Single Questions and Answers

Q: I am pregnant. What are the risks to my baby from x-ray procedures (dental, mammogram, chest, extremity, head, CT) that don't directly expose my abdomen?

A: In all of the above mentioned types of medical and dental procedures there is very little exposure to the embryo or fetus because x-ray images are taken of areas other than the abdomen. This is because the x-ray beam is focused only on the area of interest to minimize doses to other areas of the body. When you receive a diagnostic x-ray study of your head, teeth, chest, arms or legs, the embryo or fetus is not directly in the x-ray field. The amount of scattered radiation reaching the embryo or fetus would be extremely low and there is essentially no increased risk of a harmful effect in the embryo or fetus from that radiation.

Q: How long should I wait to conceive after x-ray examinations that have exposed my ovaries or my husband's testes? Can I become sterile after having x-ray examinations?

A: Preconception exposure of the ovaries or testes is a very low risk situation, especially for exposures from diagnostic radiological

procedures. There is no risk for sterility. Since the vulnerable irradiated ova will have been ovulated in two menstrual cycles (two months) and the irradiated sperm replaced in two spermatogenesis cycles (four months), it is best that the family wait that period of time before attempting conception. If pregnancy occurs during these windows of time, the radiation risks are minuscule compared to spontaneous risks. The spontaneous risks without radiation exposure for the conceptus are 15 % for miscarriage and 3 % for birth defects.

Q: How long should I wait to conceive after I or my spouse or partner has been treated with radioiodine?

A: The recommended waiting period prior to trying to conceive after radioiodine therapy is four to six months. After the first course of therapy the clinician cannot be certain whether the disease has been cured so it is necessary to perform diagnostic studies with small amounts of radioactive iodine to determine whether any tumor remains. If any tumor is found it is not desirable for the patient to be pregnant because a high dose of radioactive iodine may be needed in order to treat the residual tumor.

Q: What are the chances I am sterile after radioiodine therapy?

A: It is very unlikely that the ovaries or testes of a person who undergoes radioiodine therapy received enough radiation to render the person sterile. In addition, while the likelihood of biological effects in the next generation may be theoretically possible, such effects have not been demonstrated clinically.

Q: Is a lead apron over the abdomen necessary for x-ray examinations on a pregnant individual?

A: Many state regulations regarding this issue require lead shielding to be used during x-ray procedures when the ovaries or testes are in the direct beam as long as the shield does not interfere with the procedure. This implies that lead shielding is not required when the ovaries or testes won't be in the useful beam. Many facilities choose to use aprons for most of their procedures anyway simply as prudent practice.

Q: I am pregnant — is it okay to stand next to one of those airport baggage-screening machines? Is it okay to be screened by the full-body scanners now used at airports?

A: The x-ray machines used for baggage-screening at the airport are appropriately shielded. There is essentially no increased risk of a harmful effect to the operators or pregnant passengers from that radiation. There are two kinds of full-body scanners. The type called a millimeter wave unit uses nonionizing radiation that does not present a risk to you or the unborn child. The backscatter x-ray scanner uses a very low-energy and low-intensity of ionizing radiation. The exposure standard for this device is at a level that ensures that you or your unborn child can be safely scanned with these devices.

Q: I was standing next to or holding the patient when the x-ray image was taken and I'm pregnant. What are the risks to my baby?

A: In radiological imaging procedures where you might be next to or holding the patient the dose to the patient is usually very low. Since you and your baby were not in the direct x-ray field, you both would receive only a very much lower dose from x rays scattered from the patient. Therefore you and your baby have essentially no increased risk of a harmful effect from that radiation.

Q: I am pregnant and want to have a procedure performed that involves the use of a laser on my skin. Can I do this without harming my baby?

A: There is no risk to the baby from the laser exposure. Laser beams barely penetrate the outer layers of skin when external to the body and never expose the embryo or fetus. The beam emitted from a laser is simply a special form of light.

Q: I am pregnant and want to use a tanning bed. Any risks?

A: There is no evidence that radiation from a tanning bed would cause harm to the embryo or fetus. Lights in a tanning bed emit ultraviolet A (UVA) radiation, similar to the tanning rays emitted by the sun although they are more concentrated in a tanning bed. UVA radiation is not very penetrating; clothes can stop UVA radiation as seen by tan marks when one wears a T-shirt on a sunny afternoon. UVA radiation is not able to penetrate through the skin and abdominal tissue to expose the embryo or fetus. There is no reason for concern for the embryo or fetus but the increased risk of skin cancer should be of concern to the mother.

Q: I'm pregnant and plan on flying in the near future but am worried about possible risks of radiation to my baby.

A: Ubiquitous background radiation comes from cosmic rays, Earth, and our own bodies. You receive ~0.8 mSv (effective dose) (the estimate for 2006) from these radiation sources in a year. The embryo and fetus receive a total of three-quarters of that amount [equates to 0.6 mSv (equivalent dose)] during the nine months of your pregnancy. Flying at 30,000 feet increases your exposure a little bit from cosmic radiation but reduces it from exposure to radiation in Earth. Thus, the overall dose to the embryo or fetus is not much different due to commercial flying. The dose while flying would be higher during the occurrence of solar flares; however, the radiation risk would still be similar to that from the usual background radiation because the exposure is of short duration. For more information on pregnancy and flying refer to the following website: http://hps.org/publicinformation/ate/faqs/pregnancyandflying.html.

Q: I might be exposed to radiation from a satellite dish at work. I am pregnant. Is it okay to continue working?

A: Satellite dishes for reception of cable television or microwave transmissions (for communication) do not emit any radiofrequency (RF) or electric and magnetic field signals that would pose a health hazard to nearby persons. You can also refer to the information sheet at: http://hps.org/hpspublications/articles/rfradiation.html.

Q: Occasionally I read that power lines cause biological effects and kids are especially at risk. I am pregnant and wonder what effect power lines might have on my baby.

A: There is no convincing scientific evidence that low frequency electromagnetic radiation from power lines cause birth defects or miscarriages. For details see the following quotations and the noted references.

- "The epidemiologic evidence does not, taken as a whole, suggest strong associations between exposure to [power-frequency fields] magnetic fields and adverse reproductive outcome ... Animal studies do not suggest strong effects on embryonic development or reproduction" (Huuskonen *et al*., 1998).
- "There is no convincing data that [electromagnetic field exposure] of the sort pregnant women or potential fathers

meet in occupational or daily life exposures does any harm to the human reproductive process ..." (Robert, 1999).

- "Studies involving nonhuman mammalian organisms dealing with fetal growth, congenital malformations, embryonic loss and neurobehavioral development were predominantly negative and are therefore not supportive of the hypothesis that [power-frequency field] exposures result in reproductive toxicity" (Brent, 1999b).

For more information, see Brent (1992), Brent *et al*. (1993), and visit the following websites: http://hps.org/publicinformation/ate/faqs/radiofrequencyqa.html and http://hps.org/hpspublications/articles/rfradiation.html.

Q: I know that microwave ovens should not be left unattended while operating but I am pregnant and concerned whether my baby might be affected if I stand near it.

A: Microwave ovens are shielded against leakage of microwaves. So as long as the oven cannot operate with the door open, there is very little microwave leakage. There have been no reports of microwave-induced adverse effects or miscarriages of the embryo or fetus from the use of consumer microwave ovens. More information is available at the following websites: http://hps.org/hpspublications/articles/microwaveovens.html or http://hps.org/publicinformation/ate/faqs/microwaveovenq&a.html.

Q: I use my cell phone quite a bit for both personal and work reasons. Last week I found out I was pregnant and want to know if it is safe for me to continue using it.

A: A cell phone emits very small amounts of microwave electromagnetic radiation of moderate frequency, which is much different than the type of radiation used for x-ray procedures. There is no convincing evidence that the use of cell phones can increase the risk of birth defects or miscarriage of the embryo or fetus or cause any other biological harm. More information is available at the following website: http://hps.org/publicinformation/ate/cat60.html.

Q: I am pregnant and my doctor has ordered an MRI examination to rule out some issues for back pain. Am I putting my baby at risk?

A: There is no scientific evidence that a standard diagnostic MRI study performed on a pregnant woman can cause biological effects

in the embryo or fetus. The scientific literature suggests that the strength of the magnetic-resonance field at diagnostic levels does not affect DNA synthesis, cell cycle, or proliferation kinetics in an embryo or fetus (Kanal *et al*., 2007). The U.S. Food and Drug Administration (FDA, 1998b) and other expert bodies [*e.g*., International Electrotechnical Commission (IEC, 2010); International Commission on Non-Ionizing Radiation Protection (ICNIRP, 2009b)] have established guidelines for limits on MRI field strengths for diagnostic imaging.

Q: My coworkers and I work with computers all day. Some of my coworkers are pregnant and I wonder if there are any risks to their babies from nonionizing radiation emitted from the computers.

A: The monitor screens of some older computers (built in the 1980s or before) emitted measurable amounts of electric and magnetic fields. There was some concern at the time that these fields might be hazardous contrary to lack of such evidence. In any case the levels today from new computers are very low and do not increase the risk of birth defects or miscarriage in pregnant women. More information is available at the following website: http://hps.org/publicinformation/ate/faqs/computervdtscreen.html.

Q: I am a female security guard who uses a portable radio for communication. We use our radios a lot. I am three months pregnant and am beginning to worry whether my using these radios is bad for my baby or not.

A: You should not be concerned. The Federal Communications Commission (Cleveland *et al*., 1997) issues strict regulations on the radiation characteristics of such devices. They produce no increased risk of birth defects or miscarriage to the embryo or fetus.

B.2 A More Complex Consultation

Patients, relatives of patients, physicians, radiologists, obstetricians, genetic and teratology counselors, health physicists, and many other individuals are concerned about radiation exposure to the embryo, fetus and the reproductive organs. The majority of questions posed by these individuals can be answered from a statement that has been prepared in advance. Even prepared statements have to be modified because of the different circumstances of even similar radiation exposures. About 10 % of consultations are very complex and may consume several days to complete with multiple

interactions. An example of a more complex consultation is presented here.

The consultation concerns a patient (**AA**) that has undergone preconception chemotherapy and postconception radiation therapy and responses from the counselor (**Dr. B**):

On January 18, 2009, AA submitted the following question:

AA: I became pregnant while doing therapeutic radiation for non-Hodgkin's lymphoma. I have been in remission for six months, but was doing the radiation as a precautionary measure. I am concerned about the possible effects the radiation could have had on the fetus and how much scattered radiation the fetus received. Just hoping you might be able to help determine the scattered-radiation potential in order to determine if the pregnancy should be terminated.

Additional information:

- *Exposure*: From November 19, 2008 to December 19, 2008, I received 39.6 Gy of radiation over 22 treatments. The radiation was TomoTherapy® [Accuray, Inc., Sunnyvale, California] directed at the abdomen ~15 cm from the fetal area.
- *History*: This is my first pregnancy. I have no history of miscarriage or abortion. We have no family history of birth defects. Other than the non-Hodgkin's lymphoma I have no history of medical problems.
- *Pregnancy stage*: I had my last menstrual period on November 30, 2008. I do not know the exact date of conception, but based on my past history of a 25 d cycle, I estimate around December 12, 2008 for conception. Therefore following the conception the fetus got somewhere between one to one and a half weeks or five to seven treatments. I have had a vaginal ultrasound which determined I was seven weeks, give or take a day on January 13, 2009. At the ultrasound the heartbeat was detectable.
- *Occupation*: I currently have a desk job doing paperwork.
- *Counseling*: We have sought counseling from many sources. My radiation oncologist is concerned about the doses received; however, the other research I have done online does not support her concern.

Dr. B: I need some more information in order to provide you with a definitive answer with regard to the risk to your embryo from the radiation therapy. I understand that the actual treatment with radiation occurred six months before you became pregnant.

Correct? You said that you were in remission. Why did they treat you with radiation if you were in remission or were these diagnostic x-ray procedures? Please provide me with the dates of the radiation therapy and the amount of radiation that was given to the tumor site after you were pregnant. Did the radiation oncologist (therapist) know that you were pregnant and/or did he/she attempt to shield your uterus? Where was the lymphoma located in your abdomen? Has the dose to the embryo been calculated per therapeutic session and the total dose to the embryo from the beginning to the end of the radiation therapy? Were you treated with chemotherapy as part of the treatment? Was the gestational age measured using ultrasound? What was the date of the ultrasound and the result?

AA: I was diagnosed in November 2007 with non-Hodgkin's lymphoma. I did eight rounds of CHOP-R chemotherapy from November 2007 to April 2008. In April 2008 I went into full remission. I moved from Hawaii to [city, state] in September 2008. When I arrived in [city], my new medical oncologist suggested I see a radiation oncologist since I did not do any radiation in my initial treatment. I started therapeutic radiation in November 2008 because they predicted that it would reduce my chances of relapse 50 to 75 %. I did not have a relapse, it was simply precautionary. I started TomoTherapy® radiation on November 19, 2008. I had a negative pregnancy test on that same day. Then I had a menstrual period on November 30, 2008. I finished 22 treatments of therapeutic radiation on December 19, 2008. I did not know that I was pregnant until after the radiation treatments were finished so the uterus was not shielded. I had a total dose of 39.6 Gy throughout the 22 treatments, but it is hard to predict when conception happened, so the amount of radiation I received after I was pregnant is not known exactly. My original tumor was located just above my right kidney ~15 cm from the uterus. The possible radiation to the fetus was not calculated per session, but it was calculated for all 22 treatments. The maximum was 0.4 Gy and minimum 0.14 Gy. However based on my last menstrual period we figure conception happened around December 12, 2008, therefore the fetus would have only received ~6 d worth of radiation or a fraction of the number calculated. I had an ultrasound on January 13, 2009 which predicted the gestational age to be seven weeks and 1 d. There was a heartbeat and the fetus seems normal for that stage.

Thank you for your help and please let me know if there is anything else I can answer to make this easier. If it is easier to call me, my cell-phone number is [XXX-YYY-ZZZZ]. Again, thank you.

Dr. B: You now have provided me with a complete picture from your recollection and the records. While the total dose to your abdominal tumor area was 39.6 Gy, the total dose to the embryo was 0.4 Gy. Actually, for my evaluation, it is more important to know the embryonic dose for each day of radiation therapy. If we use the maximum embryonic dose estimate of 0.4 Gy and divide that figure by 22, the average dose for each day of radiation is 0.018 Gy. If that is accurate, then the embryo is not at an increased risk for birth defects or miscarriage for a number of reasons.

If we assume that the embryo was exposed for 7 d in the earliest days of your pregnancy, this stage is referred to as the all-or-none period, which means that the embryo is unlikely to have an increased risk of birth defects.

Furthermore, the total dose to the embryo after the embryo was conceived would be 0.14 Gy for the protracted radiation during the latter part of your radiation therapy. So the risks for birth defects and miscarriage would not be increased.

Since an accurate estimate is crucial, I have a few questions. Who performed the calculation? Was he/she a qualified expert (trained specialist) experienced in making estimates of dose to the embryo? I would like to speak with the individual who calculated the dose to the embryo. I have your telephone number and will call you tomorrow.

AA: The estimate was done by the medical physicist that works at the radiation oncologist office. However, I do not know if he is experienced in fetal estimates. The only estimate he gave was for the entire radiation period. This is how the report reads:

> "Upon reviewing the treatment plan and the isodose line of one percent, it (the isodose line of 1 %) covers about <10 % of the uterus area. One percent (of the tumor dose) is estimated as the max fetus dose. The isodose line of 0.35 % covers 100 % of the possible fetus area. We use 0.35 % as minimum dose. Possible dose to fetus:
>
> - maximum: 39.6 Gy × 1 % = 0.396 Gy
> - minimum: 39.6 Gy × 0.35 % = 0.138 Gy."

Hopefully this helps and I am available all afternoon if you would like to call me. Thank you so much for your help.

Dr. B: Thank you for the new information and for speaking with me on the telephone this afternoon. Please keep in touch with me with regard to your pregnancy. As we discussed on the telephone, I never tell a family what to decide. Since this was a wanted pregnancy,

your decision to continue the pregnancy is medically and scientifically correct. We are here to educate you and therefore our job is completed after the counseling is completed. However, we are interested in the welfare of you and your unborn child, so keep in touch. My role is to educate you regarding the risk of an environmental exposure and whether it will increase or not increase the risk to the developing embryo or fetus. I look forward to hearing from you. Have a very good pregnancy.[9]

[9]We were informed that a normal appearing newborn, weighing 7 pounds and 4 ounces was born after 39 weeks of gestation.

Appendix C

Example Forms

C.1 Pre-examination Pregnancy Determination[10]

Patient: _____ **MRN:** _____

Date: _____ **Time:** _____

Technologist: _____

Pregnancy check: For female patients of reproductive age [post menarche to menopause (*e.g.*, 12 to 50 y of age)], indicate the patient's response to the following two questions:

1. What was the first day of your last complete menstrual period?
   Month _____ Day _____Year _____
2. To the best of your knowledge, are you pregnant (or do you think you could be)?
   Yes ____ No ____ Possibly/Not sure ____

Patient/guardian signature: _____ Date: _____

Urine pregnancy testing required (per department guideline)?
Yes ____ No ____

Pregnancy Test Performed in Diagnostic Imaging:
Verbal consent to test from: Patient ____Guardian ____
Results: Negative ____ Positive ____
Testing technician/nurse initials: _____

Pregnancy Test Performed Outside the Department:
Has it been performed by patient with a home pregnancy test or at an outside approved laboratory?
Test date: _____
Results: Negative ____ Positive ____
Source of results: _____

[10]From ACR (2008). This information is provided only as an example that is more fully discussed in ACR (2008). No attempt is made by NCRP to determine the precise content of the form or in which situations it may be appropriate to use such a form.

C.2 Informed Consent for X-Ray Examinations of Pregnant or Potentially-Pregnant Patient[11]

Patient: _____ **MRN:** _____

Date: _____ **Time:** _____

To the patient: This informed consent form applies only to single-examination diagnostic radiographic studies and single-phase size-adjusted abdominal-pelvic CT studies. You are scheduled for an x-ray examination of your body. You and your unborn child will be exposed to x rays. The risk to you is very small. The examination might slightly increase the possibility of cancer later in the child's life, but the actual potential for a healthy life is very nearly the same as that of other children in circumstances similar to yours. The examination does not add to risks for birth defects. Your physician has considered the risks associated with this examination and believes it is in your and your child's best interests to proceed. Any questions you have regarding this examination should be directed to the radiologist.

Radiologist or referring physician: _____ Date: _____
I, _____, have read and fully understand the above and hereby give my consent to have an x-ray procedure performed. I have been informed of the estimated risks to my embryo or fetus.

Patient/guardian signature: _____ Date: _____

This signed informed consent form shall be placed in the patient's medical record.

[11]From ACR (2008). This information is provided only as an example that is more fully discussed in ACR (2008). No attempt is made by NCRP to determine the precise content of the form or in which situations it may be appropriate to use such a form.

Abbreviations, Acronyms and Symbols

β-HCG	β-human chorionic gonadotropin
ALARA	as low as reasonably achievable (the ALARA principle)
AM	amplitude modulation
CI	confidence interval
CNS	central nervous system
CT	computed tomography
DNA	deoxyribonucleic acid
D_T	mean absorbed dose in an organ or tissue
DTPA	diethylenetriamine pentaacetic acid
E	effective dose
EAR	excess absolute rate
ERR	excess relative risk
ESTR	extended simple tandem repeat
FISH	fluorescence *in situ* hybridization
FM	frequency modulation
GI	gastrointestinal
HCG	human chorionic gonadotropin
H_T	equivalent dose
IQ	intelligence quotient
I_{SPTA}	spatial peak-temporal average intensity (ultrasound)
LD_{50}	lethal dose, 50 %; the dose required to kill 50 % of a test population
MI	mechanical index
MRI	magnetic-resonance imaging
PCR	polymerase chain reaction
RBE	relative biological effectiveness
RF	radiofrequency
RNA	ribonucleic acid
RR	relative risk
SAR	specific absorption rate
SI	Systeme Internationale (International System of Quantities and Units)
TI	thermal index
UVA	ultraviolet A (radiation)
w_R	radiation weighting factor
w_T	tissue weighting factor

Glossary

absorbed dose (D): The mean energy dε imparted to matter of mass dm by ionizing radiation at the point of interest. In the Systeme Internationale (SI), the unit for absorbed dose is J kg^{-1} with the special name gray (Gy).

absorption: To take in and make part of an existent whole; normally refers to the fractional passage of material through a membrane, such as the fraction of intake that passes through the gut wall into the blood.

accelerator: A device that accelerates charged particles (*e.g.*, protons, electrons) to high speed in order to produce ionization or nuclear reactions in a target; often used for the production of certain radionuclides or directly for radiation therapy. The cyclotron and the linear accelerator are types of accelerators.

accident: An unintentional or unexpected happening that is undesirable or unfortunate, especially one resulting in injury, damage, harm or loss.

accuracy: A measure of the extent of agreement between the measured value and the true value.

acoustic cavitation: The mechanical response of one or more cavities to a sound field; it may be inertial or noninertial.

inertial cavitation: A class of acoustic cavitation involving growth and collapse of one or more cavities (previously called *transient cavitation*).

noninertial cavitation: A class of acoustic cavitation in which collapse does not occur. It includes acoustically induced translational motion of bubbles, bubble growth by rectified diffusion or coalescence, continuous heat production, radiation forces on neighboring particles and microstreaming.

acoustic output: The sound field emitted by a device.

acoustic power: Acoustic energy transported per interval of time. The unit for acoustic power is watt (W).

acoustic pressure: The excess of the instantaneous pressure at a point in a sound field over the pressure in the absence of sound.

acoustic pressure amplitude: For a sound field where the acoustic pressure varies sinusoidally with the time, the maximal value of the acoustic pressure. Applies for a pulsed field of ultrasound or for nonlinearly distorted waves.

acoustic radiation force: Time-averaged force on an object produced by a sound field.

acoustic radiation torque: Time-averaged torque on an object produced by a sound field.

acoustic streaming: Time-averaged flow of a liquid or gas produced by a sound field.

activity: The average number of spontaneous nuclear transformations occurring in a radioactive material per interval of time. The unit for activity in the SI system is reciprocal second (s^{-1}) (*i.e.*, one nuclear transformation per second), with the special name becquerel (Bq). The special unit previously used was curie (Ci): 3.7×10^{10} Bq = 1 Ci; 37 MBq = 1 mCi.

acute radiation exposure: Radiation exposure received during a short time period (*e.g.*, hours).

additive (absolute risk) model: A model in which excess risk is expressed as a term to be added to the underlying natural or baseline risk (compare with the multiplicative model).

administered activity: The amount, in terms of activity, of a radionuclide given to a patient during a diagnostic or therapeutic procedure.

alpha particle: A positively charged particle ejected spontaneously from the nuclei of some radioactive elements. It is identical to a helium nucleus with a mass number of 4 and an electric charge of +2. Alpha particles from radioactive decay (<10 MeV) have low penetrating power and a short range (*e.g.*, a few centimeters in air).

amnion: The avascular membranous sac that immediately surrounds the amniotic fluid and embryo or fetus.

amniotic fluid: The fluid that is contained within the amnion.

ampere (A): Unit of electric current. One ampere is produced by 1 V acting through a resistance of 1 ohm.

angiography: The radiographic visualization of blood vessels following introduction of contrast material.

antenna: A structure that is designed to radiate or receive EM fields efficiently. Individual antennas, or antenna elements, are often used in combinations that are called *antenna arrays*.

apoptosis: Genetically-programmed or externally-induced self-destruction of a cell.

as low as reasonably achievable (the ALARA principle): A principle of radiation protection philosophy that requires that doses from ionizing radiation be kept as low as reasonably achievable, economic and societal factors being taken into account. The ALARA principle is satisfied when the expenditure of further resources would be unwarranted by the reduction in dose that would be achieved.

atomic number (Z): The number of protons contained in the nucleus of an atom. Low-Z refers to atomic nuclei with $Z \leq 26$. High-Z refers to atomic nuclei with $Z > 26$.

attenuation: The reduction of radiation intensity upon passage of radiation through matter.

background radiation: (see *ubiquitous background radiation*).

basal cell: Cells that form a single row along basement membrane and are responsible for the pseudostratified appearance of the epithelium.

baseline rate: The cancer experience observed in a population in the absence of the specific agent being studied. The baseline rate might, however, include cancers from a number of other causes, such as smoking and ubiquitous background radiation.

base pairs (of DNA): Normally, a base pair involves a pyrimidine (cytosine, thymine) hydrogen-bonded to a purine (adenine, guanine), with each component (the purine, the pyrimidine) part of two antiparallel strands winding "right handed" in a double-stranded helix of DNA.

beam: A flow of electromagnetic or particulate radiation that is either (1) collimated and generally unidirectional or (2) divergent from a small source but restricted to a small-solid angle (charged-particle beam, radiation beam).

becquerel (Bq**):** The special name for the unit of activity in the SI system [*i.e.*, one nuclear transformation per second (s^{-1})]. The special unit previously used was curie (Ci): 3.7×10^{10} Bq = 1 Ci; 37 MBq = 1 mCi.

benign: A noncancerous condition that does not spread to other parts of the body.

beta particle: An energetic electron emitted spontaneously from nuclei in the decay of many radionuclides.

bias: Tendency for an estimate to over- or underpredict an actual event.

bioassay: A technique used to identify, quantify or specify the location of radionuclides in the body by direct (*in vivo*) or indirect (*in vitro*) analysis of tissues or excretions from the body.

biological filtration: The proposition that some deleterious mutations (spontaneous or as a result of preconception radiation exposure) would not be expressed as effects in an offspring because they are lethal to the developing ova or sperm or to the developing embryo because of defective ova or sperm.

biopsy: Removal of an entire abnormality (excisional biopsy) or a sampling or portion of an abnormality (core biopsy and incisional biopsy) for microscopic examination in order to diagnose a problem.

blastocyst: Developmental stage of most mammalian embryos that follows the morula; typically consists of a hollow sphere of trophoblast cells with an "inner cell mass" of formative cells.

blastomere: A cell of a cleavage stage or morula; excludes persisting cells of the polar body.

brachytherapy: A method of radiation therapy in which an encapsulated source is utilized to deliver low-energy photons or beta particles to a treatment site at a distance up to a few centimeters from a surface, intracavitary or interstitial applicator.

bubble: A cavity that is nearly, or completely, surrounded by liquid.

cancer: A general term for more than 100 diseases characterized by abnormal cells and altered control of proliferation of malignant cells.

cancer detection rate: The overall number of cancers detected per 1,000 patients examined.

carcinogenesis: Induction of cancer (*e.g.*, by radiation or other agent).

cavitation nucleus: A small body, usually a cavity, which can serve as a site for acoustic cavitation.

cavity: A volume filled with gas or vapor, or both.

charged particle: An atomic or subatomic quantity of matter (*e.g.*, electron, proton, alpha particle, ionized atom) having a net positive or negative electrical charge of one or more elementary units of charge.

childhood cancer: A term used to describe cancers that occur between birth and 15 y of age. Childhood cancers are very rare and may differ from adult cancers in the way they grow and spread, how they are treated, and how they respond to treatment. Common types of childhood cancer include leukemia (begins in blood-forming tissue such as bone marrow), lymphoma (begins in cells of the immune system), neuroblastoma (begins in certain nerve cells), retinoblastoma (begins in the tissues of the retina), Wilms tumor (a type of kidney cancer), and cancers if the brain, bone, and soft tissue). Because investigators may define childhood cancers differently (*e.g.*, by ages of occurrence), care should be taken when making any comparisons among studies.

computed tomography (CT): An imaging procedure that uses multiple x-ray transmission measurements and a computer program to generate tomographic images of the patient. Tomography is a method of producing three-dimensional images of the internal structures of the human body by the observation and recording of the differences in the effects on the passage of the x-ray waves impinging on the structures.

conceptus: General term referring to all the products of conception, from the time the ovum is fertilized through the time of birth or parturition.

confidence interval (CI): A measure of the extent to which an estimate of risk, dose or other parameter is expected to lie within a specified interval (*e.g.*, a 95 % CI of a risk estimate means that, based on available information, the probability is 0.95 that the true but unknown risk lies within the specified interval).

contamination (radioactive): Radioactive material that is present in undesired locations such as on the surface of or inside structures, areas, objects or individuals.

convection: Movement of material within a fluid at a nonuniform temperature due to the variation in its density and the action of gravity.

conventional fluoroscopy: An imaging technique using x rays to visualize the dynamics of bodily functioning. For example, a material with high x-ray absorption is injected or ingested and fluoroscopy is used to monitor the progress of the material through the blood vessels or gastrointestinal tract. The image receptor can be either an image intensifier and video-camera tube, or a large-area solid state detector.

conventional radiography: An imaging technique where the image receptor consists of a combination of (usually two) intensifying(s) screens in intimate contact with a photographic film (usually a dual-emulsion film). After exposure to the x-ray image, the photographic film is then processed in chemical solutions. Photographic film is relatively insensitive to x rays; the light from the intensifying screens produces most of the film optical density. Also referred to as *screen-film radiography.*

correlation: A measure of the interdependence of two random variables. Positive correlation is the simultaneous increase or decrease in value of two numerically-valued random variables while negative correlation is the simultaneous increase in one and decrease in the second.

cosmic radiation: Penetrating ionizing radiation, both particulate and electromagnetic, that originates in outer space.

curie (Ci): The previous special unit for activity equal to 3.7×10^{10} becquerels (or disintegrations per second) (see *becquerel*).

deoxyribonucleic acid (DNA): Genetic material of cells; a complex molecule of high molecular weight consisting of deoxyribose, phosphoric acid, and four bases which are arranged as two long chains that twist around each other to form a double helix joined by bonds between the complementary components.

derated (ultrasound): Accounts for attenuation of the ultrasound field by the tissue between the transducer and a particular location in the body along the beam axis.

deterministic effect: (see *tissue reaction*).

diagnostic reference level: Used in medical imaging with ionizing radiation to indicate whether, in routine conditions, the patient dose or administered activity from a specified imaging procedure is unusually high or low for that procedure.

diplotene: The fourth stage of the prophase of meiosis, following pachytene, during which the paired chromosomes begin to separate into two pairs of chromatids.

Doppler (ultrasound): A diagnostic ultrasound procedure that measures blood velocity by analyzing the frequency content of returning echoes.

dose (ionizing radiation): A general term used when the context is not specific to a particular ionizing radiation dose quantity. When the context is specific, the name for the quantity is used (*e.g.*, mean absorbed dose, equivalent dose, effective dose).

dose limit: A limit on dose that is applied for exposure to individuals in order to prevent the occurrence of radiation-induced tissue reactions (deterministic effects) or to limit the probability of radiation-related stochastic effects.

dose rate (ionizing radiation): Dose delivered per interval of time. Dose rate can refer to any dose quantity (*e.g.*, absorbed dose, equivalent dose).

dose-response curve: A graphical characterization of the relationship between a defined biological endpoint and the dose received.

dosimeter: A radiation detection device worn or carried by an individual to monitor the dose from the individual's radiation exposure.

dosimetry: The science or technique of determining dose from ionizing radiation.

doubling dose (DD): The dose required to double the effect under consideration assuming a linear dose response.

dwell time (ultrasound): The total time that any part of the anatomy is exposed to an ultrasound beam.

effective dose (E): The sum over specified organs and tissues of the products of the equivalent dose in a tissue (H_T) and the tissue weighting factor for that tissue or organ (w_T):

$$E = \sum_{T} w_T H_T . \quad \text{(G.1)}$$

The tissue weighting factors have been developed from a reference population of equal numbers of both males and females and a wide range of ages (ICRP, 1991; 2007a). Effective dose applies only to stochastic effects. The quantities E, w_T, and H_T are used primarily in implementing the radiation protection system. The unit for E is joule per kilogram (J kg^{-1}) with the special name sievert (Sv) (see also *total effective-dose equivalent*).

equivalent dose (H_T): Mean absorbed dose in a tissue or organ ($D_{T,R}$) weighted by the radiation weighting factor (w_R):

$$H_T = \sum_{R} w_R D_{T,R} . \quad \text{(G.2)}$$

The SI unit of equivalent dose is joule per kilogram (J kg^{-1}) with the special name sievert (Sv). 1 Sv = 1 J kg^{-1}. For exposure from external sources, w_R applies to the radiation type and energy incident on the body.

radiation weighting factor (w_R): A factor used to allow for differences in the biological effectiveness between different radiations when calculating equivalent dose (H_T). The set of w_R values are general and are independent of the tissue or organ irradiated. They are selected by judgment after review of a broad range of experimental relative biological effectiveness data that are relevant to stochastic effects. The quantities H_T and w_R are used primarily in implementing the radiation protection system.

tissue weighting factor (w_T): The dimensionless factor by which H_T is weighted to represent the relative contribution of that tissue or organ to the total health detriment resulting from uniform irradiation of the body (radiation detriment).

electric field: A term that is often used to mean the same as electric field strength. A vector force field that is used to represent the forces between electric charges. Electric field strength is defined as the force per unit charge on an infinitesimally small charge at any given point in space, and it is usually represented by the symbol E. The unit of electric field strength is volt per meter (V m^{-1}).

electromagnetic radiation: A traveling wave motion consisting of changing electric or magnetic fields. Familiar types of electromagnetic radiation are: x and gamma rays of short wavelength and high energy; ultraviolet, visible and infrared; microwave; and radiofrequency radiation of relatively long wavelength and low energy.

electron: Subatomic charged particle. Negatively charged particles are parts of stable atoms. Both negatively and positively charged electrons may be expelled from the radioactive atom when it disintegrates (see *beta particle*).

electron volt (eV): A unit of energy = 1.6×10^{-12} ergs = 1.6×10^{-19} J; 1 eV is equivalent to the energy gained by an electron in passing through a potential difference of 1 V; 1 keV = 1,000 eV; 1 MeV = 1,000,000 eV.

embryo: In the human, the developing individual from one week after conception to the end of the second month.

epigenetic: The study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence.

equivalent dose (H_T): (see *effective dose*).

excess absolute rate (EAR**):** The excess rate of a specified disease in a specified population among exposed persons per unit dose. In radiation-exposed populations the EAR is designated as the number of excess cases of a specific disease in radiation-exposed persons per 10,000 person years per gray [$(10^4$ PY Gy$)^{-1}$] (see also *excess absolute risk coefficient*).

excess absolute risk coefficient: The excess absolute rate expressed as percent per gray (*e.g.*, 6.5 % Gy^{-1}).

excess relative risk (ERR**):** The ratio of the excess risk of a specified disease to the probability of the same effect in the unexposed population (*i.e.*, the relative risk minus one) (see *relative risk*).

exposure: In this Report, a general term used to express the act of being exposed to ionizing or nonionizing radiation, magnetic fields or ultrasound. Exposure is also a defined ionizing radiation quantity. It is a measure of the ionization produced in air by x or gamma rays. The SI unit of exposure is coulomb per kilogram (C kg^{-1}). The previous special unit for exposure was roentgen (R), where 1 R = 2.58 × 10^{-4} C kg^{-1} (see *irradiation*).

external dose: Dose to organs or tissues of an organism due to radiation sources outside the body.

far field: The electromagnetic field at a point far enough away from a radiofrequency source such that the fields are approximately plane-wave in nature.

fetus: In the human, the developing young in the uterus after the second month.

fluoroscopy: A medical x-ray procedure used for observation of the internal features of the body by means of the fluorescence produced on a screen by a continuous field of x rays transmitted through the body. Fluoroscopy is intended to observe moving objects for relatively long periods of time (seconds to minutes) without the intent of preserving the images.

fractionation (of dose): The delivery of dose intermittently over a period of time (*e.g.*, a series of radiation-therapy treatments given over a set schedule to achieve the desired total treatment dose; multiple diagnostic x-ray procedures over a period of hours or days).

frequency: (1) The time rate at which a quantity, such as an electric field, oscillates. The frequency is equal to the number of cycles through which the quantity changes per second. Frequency is expressed in hertz (Hz). The unit for hertz is the reciprocal second (s^{-1}). (2) The number of occurrences of an event in some defined interval of time.

gamete: A mature sexual reproductive cell, as a sperm or ovum, that unites with another cell to form a new organism.

gamma rays: Electromagnetic radiation emitted by the atomic nucleus. Gamma rays have high penetrating ability compared with alpha and beta particles (the approximate range of energy for gamma rays is 10 keV to 9 MeV).

genetic effects: (see *heritable effects*).

germ cell: Any biological cell that gives rise to the gametes of an organism that reproduces sexually.

gestation: Maintenance of a developing embryo or fetus within the body of the parent, in a uterus, ovary or oviduct.

gestational age (menstrual age): Typically defined in humans from the first day of the last menstrual period. This date precedes ovulation and fertilization by 10 to 14 d, and therefore precedes implantation by about three weeks.

gonad: An ovary or testis.

gray (Gy**):** The special name for the SI unit of the quantity absorbed dose. 1 Gy = 1 J kg^{-1}. 1 milligray (mGy) = 10^{-3} Gy.

hereditary (effects): (see *heritable effects*).

heritable effects: Changes in reproductive cells that may result in abnormal offspring of persons or animals.

homologous (chromosomes): Chromosome pairs of approximately the same length, centromere position, and staining pattern, with genes for the same characteristics at corresponding loci.

hormetic response (radiation): The hypothesis that low doses of ionizing radiation (within the region and just above natural background levels) are beneficial, stimulating the activation of repair mechanisms that protect against disease, that are not activated in absence of ionizing radiation.

hyperthyroidism: A condition in which an overactive thyroid gland produces excessive thyroid hormone, leading to a characteristic clinical picture. Since the thyroid uses iodine to make its hormone (thyroxine or T-4), radioactive iodine in small dosages can be used to image the thyroid and in large dosages to treat it (reduce its function).

image quality: The overall clarity of a radiographic image. Image sharpness, image contrast, and image noise are three common measures of image quality.

impedance, wave: The ratio of the electric field strength to the magnetic field strength of a wave. For a plane wave in free space, the wave impedance is equal to the square root of the ratio of the permeability to the permittivity of free space and is equal to 377 ohms. For a plane wave in a material, the wave impedance is equal to 377 times the square root of the ratio of the relative permeability to the relative permittivity of the material.

incidence: The rate of occurrence of a disease, usually expressed in number of cases per million.

incidence rate: The number of new cases per population in a given time period.

***in situ*:** Refers to being in the natural or original position or place.

intake: The amount of radioactive material taken into the body by inhalation, absorption through the skin, ingestion, or through wounds.

intensity (of radiation field): Radiation fluence rate, radiation energy fluence rate, or quantities derived from these, such as absorbed-dose rate and dose-equivalent rate.

internal dose: Dose to organs or tissues of an organism due to intakes of radionuclides (*e.g.*, by ingestion, inhalation, or dermal absorption).

***in utero*:** In the uterus; refers to a fetus or embryo.

***in vitro*:** From Latin "in glass," refers to a procedure done outside the body (*e.g.*, in a test tube), as opposed to *in vivo*.

***in vivo*:** From Latin "in life," refers to a procedure carried out in the living body, as opposed to *in vitro*.

ionizing radiation: Electromagnetic radiation (x rays or gamma rays) or particulate radiation (alpha particles, beta particles, electrons, positrons, protons, neutrons, and heavy charged particles) capable of producing ions by direct or secondary processes in passage through matter.

irradiation: The process of exposure to ionizing radiation.

isonated: Exposure to, or treatment with ultrasound.

justification (in radiation protection): The principle of radiation protection that any decision that alters the existing radiation exposure situation should do more good than harm.

laser: A device that utilizes the natural oscillations of atoms or molecules between energy levels for generating coherent electromagnetic radiation in ultraviolet, visible or infrared regions of the spectrum. Laser is an acronym for *light amplification by stimulated emission of radiation*.

lead apron: An apron made with lead, a radiation absorbing material used to reduce radiation exposure.

leakage (microwaves): A minimal amount of microwave radiation that is emitted from a properly designed and operated microwave oven.

leakage radiation (ionizing): All radiation, except the useful beam, coming from within a medical ionizing radiation source.

lifetime risk: The lifetime probability of dying of a specific disease.

limit: In radiation protection, the dose in a given time interval established by authoritative or consensus bodies above which the health consequences to an individual would be regarded as unacceptable.

linear accelerator (electron): A device that accelerates electrons along a linear path into an electron target or converter where the energy is converted into bremsstrahlung or x-ray photons.

linear energy transfer (LET): Quotient of the mean energy dE lost by charged particles due to all electronic interactions in traversing a distance dl through a material, commonly expressed in keV μm^{-1}.

high-LET: Greater than ~10 to 100 keV μm^{-1} such as for neutrons and alpha particles.

low-LET: Below ~10 keV μm^{-1} such as for electrons.

linear-quadratic model (linear-quadratic dose-response relationship): Expresses the incidence of a biological or health endpoint (*e.g.*, mutation or cancer) as partly directly proportional to the dose (linear term) and partly proportional to the square of the dose (quadratic term).

The linear term will predominate at lower doses, the quadratic term at higher doses.

lossy: The causing of attenuation or dissipation of electrical energy.

magnetic field: A term that is often used to mean magnetic flux density. However, in common usage, magnetic field is also used to mean magnetic field strength. In the absence of specific terminology the context and units given can be used to identify which term is being referred to (*e.g.*, magnetic flux density or $\boldsymbol{B}$ field measured in units of tesla (T) or gauss (G), or magnetic field strength or $\boldsymbol{H}$ field measured in units of A m^{-1}) (see *magnetic field strength* and *magnetic flux density*).

magnetic field strength: A vector field, usually designated $\boldsymbol{H}$, that is equal to the magnetic flux density $\boldsymbol{B}$ divided by the magnetic permeability of the medium (μ). Magnetic field strength is the component of the magnetic field that is measured. The SI unit of magnetic field strength is ampere per meter (A m^{-1}). $\boldsymbol{H}$ is a useful quantity because it is independent of the magnetization current in materials.

magnetic flux density: A vector force field that is used to describe the force perpendicular to the velocity of a moving charged particle. Magnetic flux density is defined as the force per unit charge on an infinitesimal moving charge at a given point in space according to the equation:

$$\frac{\boldsymbol{F}}{q} = \boldsymbol{v} \times \boldsymbol{B}, \tag{G.3}$$

where $\boldsymbol{v}$ is the velocity of the particle, q is its charge, $\boldsymbol{F}$ is the vector force acting on the particle, $\boldsymbol{B}$ is the magnetic flux density, and $\times$ denotes the vector product. The magnetic flux density is the product of the magnetic field strength and permeability. The SI unit for magnetic flux density is kg $s^{-2}A^{-1}$ (newton-meter per ampere) which is given the special name tesla (T). In the centimeter/gram/second system, the $\boldsymbol{B}$ field is measured in gauss (G), where 1 T = 10,000 G.

magnetic-resonance imaging (MRI): An imaging modality using a strong magnetic field and radiofrequency signals to produce multiplanar images of the body. A superimposed magnetic field gradient enables spatial localization of the image plane. Image contrast is based on the hydrogen concentration, molecular response to radiofrequency signals, and flow of structures within the part of the body being imaged.

malignant: Cancerous; a growth of cancer cells.

mammography: An x-ray examination of the breast.

mean: Sum of the measured values divided by the number of measurements. The mean value is also often called the (arithmetic) average value. The mean of a distribution is the weighted average of the possible values of the random variable.

mean absorbed dose (D_T): The mean absorbed dose in an organ or tissue (also referred to as organ dose), obtained by integrating or averaging the absorbed dose D over the entire volume of an organ or tissue (*i.e.*, the total energy deposited in the organ or tissue divided by the total mass of the organ or tissue).

meiosis: A special type of cell division necessary for sexual reproduction. In humans, the gametes produced are called sperm and egg cells.

meiotic prophase I: In meiotic prophase I, chromosomes become visible, crossing-over occurs, the nucleolus disappears, the meiotic spindle forms, and the nuclear envelope disappears.

member of the public: An individual who is not already considered occupationally exposed by a radiation source or practice under consideration. When being irradiated as a result of medical care, patients are a separate category.

Mendelian disease: A disorder that follows a classic inheritance pattern as described by Mendel, reflecting the action of a single gene that has mutated.

mental retardation: Congenital, but nonspecific reduction in cognitive capacities. *Severe mental retardation* is often used to signify an individual who is unable to perform simple calculations, to make simple conversation, to care for himself or herself, or was or is institutionalized. Such individuals are generally found to have an intelligence test score which is <70 on conventional tests.

meta-analysis: The process of using statistical methods to combine the results of different studies.

microcephaly: Condition of abnormal smallness of the head, sometimes associated with mental defects.

microsatellite (DNA sequence): A section of DNA that consists of a short series of bases (two to six base pairs).

milliampere (mA**):** 10^{-3} ampere. In radiography, the current flow from the cathode to the anode that, in turn, regulates the intensity of radiation emitted by the x-ray tube.

milligray (mGy**):** (see *gray*).

minisatellite (DNA sequence): A section of DNA that consists of a short series of bases (10 to 60 base pairs). These occur at more than 1,000 locations in the human genome.

mitosis: The process by which a cell separates the chromosomes in its cell nucleus into two identical sets, in two separate nuclei.

monitor unit (MU**):** The unit of measure of the quantity of ionizing radiation passing through a monitor chamber assembly located in the path of the useful beam from an accelerator. The value of the monitor unit is determined by calibrating the resulting absorbed dose in water usually at the isocenter under specified conditions.

morbidity: Illness of any type or the risk of such illness (*e.g.*, number of illnesses per 1,000 appendectomies).

mortality: Death or the risk of death (*e.g.*, number of deaths per 1,000 appendectomies).

morula: Globular solid mass of blastomeres formed by the initial cleavages of the zygote; period of embryonic development that precedes the blastula (an early embryonic form produced by cleavage of a fertilized ovum and consisting of a spherical layer of cells surrounding a fluid-filled cavity).

mutagen: (see *mutagenesis*).

mutagenesis: Induction of a change in genetic material by radiation or any other agent; this could be either a somatic or a genetic effect, depending on whether body cells or germ cells are affected (noun: mutagen; adverb: mutagenic).

mutagenic: (see *mutagenesis*).

mutation: In molecular biology and genetics, the changes in a genomic sequence (*i.e.*, the DNA sequence of a cell's genome or the DNA or RNA sequence of a virus) (see *mutagenesis*).

near field: The electromagnetic field close enough to the radiofrequency source such that the field is not plane-wave in nature. The spatial variation of the strength of the electromagnetic wave is usually more rapid in the near field than in the far field.

neuron: The nerve cell with its processes, collaterals and terminations; it is regarded as the structural unit of the nervous system.

neutron: An uncharged elementary particle having a mass slightly greater than a proton that is usually stable when within the nucleus but is unstable otherwise.

nonionizing radiation: Electromagnetic radiation that includes the ultraviolet, visible, infrared, microwave, radiofrequency, and extremely-low-frequency portions of the electromagnetic spectrum. Unlike ionizing radiation, nonionizing radiation is unable to ionize atoms in its interactions with matter.

nonthermal (radiofrequency radiation and ultrasound): Refers to low-level exposures that result in deposition of energy ultimately deposited as heat that is well within the body's thermoregulatory control thus avoiding a core temperature increase.

occupational exposure: Radiation exposures to individuals that are incurred in the workplace as a result of situations that can reasonably be regarded as being the responsibility of management (radiation exposures received by patients associated with their medical diagnosis or treatment are excluded).

odds ratio: A measure of the odds of an event happening in one group compared to the odds of the same event happening in another group. Odds ratios are most often used in case-control studies to determine if being exposed to a certain substance or other factor increases the risk of a disease outcome.

oncogene: Genes that under normal circumstances code for proteins associated with normal cell growth, but may foster malignant processes if mutated or activated abnormally.

optimization (of radiation protection): The principle of radiation protection that the likelihood of incurring exposures, the number of people exposed, and the magnitude of their individual doses should be kept as low as reasonably achievable, taking into account economic and societal factors [see *as low as reasonably achievable (the ALARA principle)*].

organ dose: (see *mean absorbed dose*).

ovum (ova): A female gamete or reproductive cell; an egg in the ovary of the female.

pathway (radiation): Route or mechanism of transport of contaminants in the environment, the means of release of contaminants from a facility, or the means of exposure of humans or other organisms.

peak tube potential: The crest value in kilovolts of the potential difference of a pulsating potential generator. When only one-half of the voltage wave cycle is used, the value refers to the useful half of the cycle. A kilovolt (kV) is a unit of electrical potential difference equal to one thousand volts.

percentile (of a distribution): The value of a variable below which a certain percent of observations fall. For example, the 20th percentile is the value below which 20 percent of the observations may be found.

person-year (PY): The number of persons exposed times the average number of years of follow-up after exposure.

photon: Quantum of electromagnetic radiation, having no charge or mass, that exhibits both particle and wave behavior, such as a gamma ray or x ray.

placenta: Vascular, membranous structure that forms within the uterus from maternal and embryonic tissues during pregnancy; it provides communication between the woman and her embryo or fetus *via* the umbilical cord.

positron-emission tomography: An imaging technique using radionuclides that emit positrons (positively charged electrons), whose annihilation photons are imaged in coincidence to form tomographic views of the body.

preimplantation period: Time between egg fertilization and the implantation of the embryo in the wall of the uterus.

presomite: Refers to embryos before the appearance of somites. In vertebrates, somites are masses of mesoderm distributed along the two sides of the neural tube that will eventually become dermis, skeletal muscle, and vertebrae.

prevalence: The number of cases of a disease in existence at a given time in a population, usually per 100,000 persons.

proton: An elementary nuclear particle with a positive charge equal to the charge of an electron and a mass equal to the nucleus of the hydrogen atom.

protraction (of dose): The delivery of dose over an extended period of time rather than over a brief period of time. Examples include the doses received during a transcontinental or transatlantic flight, from some occupational work environments, from continuous exposure to a radionuclide with a long half-life, and from ubiquitous background radiation.

pulmonary: Refers to the gas-exchange region of the lungs; consisting of alveoli and respiratory bronchioles.

***p* value:** A probability value summarizing the strength of the statistical evidence against a particular null hypothesis (*i.e.*, that no statistical significance exists in a set of given observations) in favor of a particular alternative hypothesis. For example, if the null hypothesis is true, observational data corresponding to a p value of 0.05 or less are likely

to occur ~5 % of the time (*i.e.*, about one time in 20). Thus, the smaller the p value, the greater the strength of the evidence is considered to be against the null hypothesis. Conventionally, $p \leq 0.01$ is considered highly significant, $p \leq 0.05$ significant, p somewhat >0.05 marginally significant, $p \leq 0.10$ not significant but suggestive, and $p > 0.10$ not significant.

qualified expert (radiation protection): For the purpose of this Report, a person having the knowledge and training to measure radiation, to evaluate radiation safety techniques, and to advise regarding radiation protection needs. For ionizing radiation, the qualified expert is a person who is certified by the American Board of Health Physics, the American Board of Radiology, the American Board of Medical Physics, the American Board of Science in Nuclear Medicine, or the Canadian College of Physicists in Medicine.

radiation: Energy propagated through space in the form of electromagnetic waves or particles (see *ionizing radiation* and *nonionizing radiation*).

radiation detriment: (1) Measure of stochastic effects from exposure to ionizing radiation that takes into account the probability of fatal cancers, probability of severe heritable effects in future generations, probability of nonfatal cancers weighted by the lethality fraction, and relative years of life lost per fatal health effect (ICRP, 1991; NCRP, 1993). (2) A concept used to quantify the harmful health effects of radiation exposure in different parts of the body. It is defined as a function of several factors, including incidence of radiation-related cancer or heritable effects, lethality of these conditions, quality of life, and years of life lost owing to these conditions (ICRP, 2007a).

radiation oncologist: Physician licensed to practice medicine who is qualified by training and experience to prescribe the administration of radiation therapy. Use of the term radiation oncologist does not require that this physician be part of a facility's radiation-oncology department or group. In certain jurisdictions, the qualifications required under the appropriate regulatory authority may also be met by osteopaths.

radiation weighting factor (w_R): (see *effective dose*).

radioactive contamination: Unintended and undesirable sources of radiation deposited on the environment, research laboratories, or other facilities.

radioactive decay: The spontaneous transformation of one nuclide into a different nuclide or into a different energy state of the same nuclide. The process results in a decrease, with time, of the number of the radioactive atoms in a sample.

radiography: The production of images produced on a film or other media by the action of x rays transmitted through an individual or an object.

radiology: That branch of healing arts and sciences that deals with the use of images in the diagnosis and treatment of disease.

radionuclide: An unstable (radioactive) nuclide. A nuclide is a species of atom characterized by the constitution of its nucleus (*i.e.*, the number of protons and neutrons, and the energy content).

radiopharmaceutical: A radioactive substance administered to a patient for diagnostic or therapeutic nuclear medicine procedures. A radiopharmaceutical contains two parts, the radionuclide and the pharmaceutical (*e.g.*, ^{99m}Tc DTPA). In some cases the two are one (*e.g.*, ^{133}Xe gas).

radon, thoron (and their progeny): Radon (^{222}Rn) and thoron (^{220}Rn) are colorless, odorless, naturally-occurring gases resulting from radioactive decay of isotopes of radium. Radon and thoron progeny are short-lived decay products of ^{222}Rn or ^{220}Rn.

rare earth: A member of the lanthanide series (atomic number 58 through 71) or, more rarely of the actinide series (atomic number 90 through 103).

relative biological effectiveness (RBE**):** A factor used to compare the biological effectiveness of absorbed doses from different types of ionizing radiation, determined experimentally. RBE is the ratio of the absorbed dose of a reference radiation to the absorbed dose of the radiation in question required to produce the same level of an identical biological effect in a particular experimental organism or tissue.

relative risk (RR**):** The ratio of the incidence rate of a given disease in those exposed to the incidence rate of that disease in those not exposed (see also *excess relative risk*).

risk: The probability of a specified effect or response occurring.

risk estimate: (see *confidence interval*, *excess absolute rate*, *excess absolute risk coefficient*, and *excess relative risk*).

roentgen (R**):** The previous special unit of exposure. Exposure is the amount of ionization produced by the absorption of x-ray or gamma-ray energy in a small mass of air, with the SI unit of coulomb per kilogram. 1 R = 2.58×10^{-4} coulomb per kilogram (C kg^{-1}).

sarcoma: A tumor, often highly malignant, composed of cells derived from connective tissue such as bone, cartilage, muscle, blood vessel, or lymphoid tissue.

scattered radiation: Radiation that, during passage through matter, is changed in direction and is usually accompanied by a decrease in energy.

shielding: Any material or obstruction that attenuates radiation (*i.e.*, reduces the radiation level by absorption and scattering) and thus tends to protect personnel or materials from the effects of ionizing radiation.

sievert (Sv**):** The special name (in the SI system) for the unit of equivalent dose and effective dose; 1 Sv = 1 J kg^{-1}.

single-photon emission computed tomography: An imaging technique in which one or more gamma cameras sample a region of the body from several angles, producing tomographic images ("slices") of the region.

somatic: Related to the body of an organism (see *somatic cell*).

somatic cell: Any biological cell forming the body of an organism (*i.e.*, any cell other than a gamete, germ cell, gametocyte, or undifferentiated stem cell).

source (or radiation source): Radiation-producing equipment or an aggregate of radioactive nuclei.

spatial peak-temporal average intensity (I_{SPTA}): The maximum intensity in an ultrasound beam averaged over the pulse repetition period. I_{SPTA} is the best measure of the amount of heat delivered to a tissue by ultrasound.

specific absorption rate (SAR**):** The time rate at which radiofrequency energy is absorbed in an incremental mass divided by that mass. Average SAR in a body is the time rate of the total energy absorbed divided by the total mass of the body. The units are watt per kilogram ($W\ kg^{-1}$).

sperm: A male gamete or reproductive cell; a spermatozoon.

standardized incidence ratio: The observed number of cancers in the study population divided by the expected number, based on rates in the general population.

stochastic effects: Effects, the probability of which, rather than their severity, is assumed to be a function of dose without a threshold. For example, cancer and hereditary effects are regarded as being stochastic.

symporter: An integral membrane protein involved in the movement of different molecules or ions in the same direction across a phospholipid membrane.

Systeme Internationale (SI**):** The International System of Quantities and Units as defined by the General Conference of Weights and Measures in 1960. The units are generally based on the meter, kilogram and second. The special names for the quantities used for ionizing radiation include the becquerel, gray and sievert.

systemic: Pertaining to or affecting the body as a whole.

teratogen: A substance or agent that tends to produce abnormal development and congenital malformations.

teratogenesis: The production of physical defects in offspring *in utero*.

thoron: [see *radon*, *thoron (and their progeny)*].

tissue reaction (deterministic effect): Injury in populations of cells, characterized by a threshold dose and an increase in the severity of the reaction as the dose is increased further. In some cases, tissue reactions are modifiable by post-irradiation procedures including biological response modifiers. Examples for irradiation of the embryo or fetus are radiation-induced malformations and mental retardation in the live-born child.

tissue weighting factor (w_T): (see *effective dose*).

total effective-dose equivalent: A quantity used by regulatory agencies in the United States. The sum of the effective-dose equivalent (for external exposure) and the committed effective-dose equivalent (from intake of radionuclides) as defined by NRC (2009) (see *effective dose*).

ubiquitous background radiation: As used in this Report, includes external exposure from space radiation (solar particles and cosmic

rays), external exposure from terrestrial radiation, internal exposure from radionuclides incorporated in the body, and internal exposure from inhalation of radon and thoron from elevated levels in homes.

ultrasonography: The use of sonic energy (sound) to produce a pictorial representation of an internal structure. The image is produced by pulse-echo techniques, with detection and display of tissue interfaces rather than densities.

ultrasound: Sound at a frequency above the upper limit of human hearing, usually taken to be 20 kHz.

umbilical cord: Vascular cord that connects a fetus to its placenta.

uncertainty: Lack of sureness or confidence in predictions of models or results of measurements. Uncertainties may be categorized as those due to stochastic variation, or as those due to lack of knowledge founded on an incomplete characterization, understanding or measurement of a system.

up-regulation: An increase in the number of receptors on the surface of target cells, making the cells more sensitive to a hormone or another agent.

variability: A heterogeneity, diversity or range that characterizes a measured value or parameter (*e.g.*, differences in body weight in a population) or response (*e.g.*, differences in sensitivity to a hazardous agent in a population). Further study cannot reduce variability but may provide greater confidence in quantitative characterizations of variability (see *uncertainty*).

watt (W): (see *acoustic power* and *specific absorption rate*).

weighted colon dose: (see *weighted organ dose*).

weighted organ dose (Radiation Effects Research Foundation studies): The estimated absorbed dose from gamma rays plus 10 times the estimated absorbed dose from neutrons. In this Report, the weighted organ dose (in this case the weighted uterine dose) is presented in gray; it has also been reported in the literature in sievert.

weighted uterine dose: (see *weighted organ dose*).

x rays: (1) Electromagnetic radiation emitted after ejection or excitation of an atomic orbital electron referred to as characteristic x rays, or (2) electromagnetic radiation produced in deceleration of energetic charged particles (*e.g.*, electrons) in passing through matter, referred to as continuous x rays or bremsstrahlung (see *gamma rays* and *photon*).

zygote: Fertilized ovum from the time of intermingling of the contents of the male and female pronuclei.

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Scientific Committee

ROBERT L. BRENT (*Chairman)* is the Distinguished Professor, Louis and Bess Stein Professor of Pediatrics, Radiology and Pathology at the Jefferson Medical College, Director of the Clinical and Environmental Teratology Laboratories at the Alfred I. duPont Hospital for Children in Wilmington, Delaware. Robert Brent was born in Rochester, New York in 1927, received his AB (1949); MD with honor (1953), a PhD (1955) in radiation biology and embryology and Honorary DSc degrees from the University of Rochester and the Jefferson Medical College. From 1944 to 1954 he worked in the cosmic ray research laboratories of the physics department and as a research associate in the genetics and embryology divisions of the Manhattan Project of the University of Rochester, where he began his studies on the teratogenic effects of ionizing radiation. As a graduate student he was appointed the Head of the embryology section of the medical school's atomic energy facility. He was the first research (1953) and clinical fellow (1954) of the March of Dimes involved in congenital malformations research. He spent his army tour at the Walter Reed Army Institute of Research as Chief of Radiation Biology (1955 to 1957).

He came to Jefferson in 1957 and has received every award that Jefferson can offer a faculty member, and for having received continuous federal research funding as a principal investigator for his entire research career. In 1989, he was named the third Distinguished Professor in Jefferson's 188 year history.

He was elected to NCRP in 1973. In 2006 he delivered the L.S. Taylor Lecture, having already received the highest honor of the Teratology Society and the Health Physics Society. He was elected to the Institute of Medicine of the National Academy of Sciences in 1996. He was the editor of "Teratology" for 17 y, and has been invited to China five times and to Japan seven times as a Visiting Lecturer and has had invited lectureships in 27 countries. In 1994 he was selected by the Chinese government as the President of the first International Congress on Birth Defects in China.

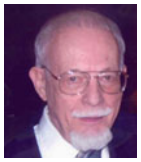
Dr. Brent's greatest recognition has come from his research, publications and lecturing. He is the most frequently consulted authority on the effects of radiation on the embryo and is frequently consulted about other possible teratogenic exposures. His research on the effects of radiation on the embryo demonstrated the no-effect dose for congenital malformations, established that radiation effects on the embryo were due to the direct effects of the radiation, and demonstrated some of the characteristics of the "all-or-none period" of embryonic development.

His writings in the field of litigation concerning the proper role of an expert witness were important. As one of the defense experts in the Bendectin litigation, his testimony contributed to the famous Daubert decision that allowed judges to reject the testimony of junk scientists. His publications include six books and monographs, five movies, 458 publications, and over 400 abstracts.

DONALD P. FRUSH is Professor of Radiology and Pediatrics, faculty member of the Medical Physics Graduate Program, and Chief of the Division of Pediatric Radiology at Duke University Medical Center in Durham, North Carolina. Dr. Frush earned his undergraduate degree fro the University of California, Davis, medical degree from Duke University Medical Center, was a pediatric resident at University of California, San Francisco, and completed a radiology residency at Duke Medical Center and a fellowship in pediatric radiology at Children's Hospital in Cincinnati. He is certified by the American Board of Radiology with additional certification in Pediatric Radiology.

Dr. Frush's research interests are predominantly involved with pediatric body computed tomography (CT), including technology assessment, techniques for pediatric multidetector computed-tomography (MDCT) examinations, assessment of image quality, and CT radiation dosimetry. Other areas of investigation include CT applications in children and patient safety in radiology.

Dr. Frush is or has been a member of various committees and scholarly societies. Committee memberships include past chair of the Commission on Pediatrics, American College of Radiology; Trustee (Pediatrics), American Board of Radiology; current chair of the board and recent past president (2011 to 2012) for the Society for Pediatric Radiology; councilor, National Council of Radiation Protection and Measurements; chair of the RSNA Refresher Course Committee; as well as steering committee for the Alliance for Radiation Safety in Pediatric Imaging (Image Gently® Campaign). Dr Frush has also worked internationally with both the World Health Organization and International Atomic Energy Agency with radiation protection projects in medical imaging. Dr. Frush is a member of numerous associations including the American Roentgen Ray Society, Society of Computed Body Tomography and Magnetic Resonance Imaging (Fellow), Radiological Society of North America, and is also a subspecialty Fellow and Section member for Radiology in the American Academy of Pediatrics.



ROBERT O. GORSON is Professor Emeritus of Radiology (Medical Physics), and Professor Emeritus of Radiation Oncology and Nuclear Medicine, Thomas Jefferson University in Philadelphia where he served as Chief of the Medical Physics Division in Radiology from 1959 to 1989 and served as Assistant Director of the Stein Research Center (1964 to 1989). From 1949 to 1951 he was the University Health Physicist at the University of Pennsylvania and then Instructor and Associate in Radiologic Physics in the Graduated School of Medicine until 1959. For 40 y he taught medical students, residents, graduate students, nurses, technologists and post doctoral fellows at University of Pennsylvania and at Thomas Jefferson University. He served in various positions on the American Board of Radiology, the American Board of Health Physics, and the American Board of Medical Physics and was certified by each of them. He became a fellow of the American College of Radiology (ACR) in 1965, of the American Association of Physicists in Medicine (AAPM) in 1989 and of the American College of Medical Physics (ACMP) in 1990. Gorson was elected President of the AAPM in 1969. During his career, he served on many committees of the AAPM, ACR, ACMP, Health Physics Society, International Commission on Radiation Protection, NCRP, National Research Council, U.S. Public Health Service, Radiological Society of North America, the National Cancer Institute, and the International

Atomic Energy Agency. He presented memorial tributes to Lauriston S. Taylor among others at national meetings. Among the honors Gorson received were the ACMP and AAPM Professional Achievement Awards. As chairman and videographer of the AAPM History Committee (1989 to 2005), Gorson conducted over 120 videotaped interviews of senior medical physicists and other scientists including Nobel Laureate Rosalyn Yalow. Among the NCRP committees he chaired was the Ad Hoc Committee on Exposure of Potentially Pregnant Women in Diagnostic Radiology (NCRP Report No. 54, 1977). During World War II, Gorson served in the U.S. Navy as an Aviation Electronics Technician (1944 to 1946), then as a Lieutenant in the Medical Corps Reserve (1946 to 1962).

ROGER W. HARMS has been a consultant in the Department of Obstetrics and Gynecology at the Mayo Clinic in Rochester, Minnesota, for the past 31 y. His clinical practice concentration is in Obstetrics and Obstetrical Ultrasound. He served as Vice-Chair and then Chair of the Practice and Quality Committee within the Department from 2006 to 2011. With a career goal of improving medical education and advancing health literacy, Dr. Harms has served sequentially as Associate Dean for Student Affairs and Academic Affairs at the Mayo Medical School, and then led the Rochester campus of the College of Medicine as Director for Education from 2000 to 2005. Dr. Harms was named Distinguished Educator, Mayo Clinic, in November 2008. In 2005, Dr. Harms was named Medical Editor-in-Chief, MayoClinic.com and recently has been named Senior Medical Director for the Operations Division of Mayo Clinic Global Business Solutions, roles in which he continues to serve.

LINDA A. KROGER is Assistant Clinical Professor of Radiology at the University of California (UC) Davis School of Medicine and has served as the Radiation Safety Officer for the UC Davis Health System for the past 10 y. Ms. Kroger received her undergraduate degree and her Masters Degree from Rutgers University. She has been with UC Davis for 25 y. Prior to her arrival at UC Davis, Ms. Kroger worked for private industry in biopharmacology research and drug development. She transitioned to cancer research when she joined UC Davis in 1988. From 1988 through 2000, her research focused on the development of new radiopharmaceuticals for both diagnostic imaging and treatment of non-Hodgkin's lymphoma and breast cancer. Since assuming her role as Radiation Safety Officer in 2003, she has focused on regulatory compliance, quality assurance issues as well as education of medical students, residents and fellows with the overall goal of improving workplace radiation safety. Ms. Kroger oversees the nonclinical aspects of nuclear medicine training for the radiology residency program at UC Davis. In addition, she has taken an interest in radiologic emergency preparedness. Ms. Kroger has authored or co-author more than 50 peer-reviewed journal articles and has presented at numerous scientific conferences. She has served in a number of roles in both the local chapter as well as the national Health Physics Society and been an active participant on NCRP committees since 2005.

MARTHA LINET has served as Chief of the Radiation Epidemiology Branch of the National Cancer Institute since 2002. Dr. Linet has studied risk of childhood leukemia in relation to residential magnetic fields from power lines, electrical appliances, and to radon; risk of brain tumors and cell-phone use; and strategies for improving questionnaire assessment of ultraviolet radiation exposures. She leads studies quantifying cancer risks in large cohorts of medical radiation workers in relation to work history, occupational radiation doses, ultraviolet radiation, and other risk factors. Dr. Linet is internationally recognized for etiologic studies of childhood and adult hematopoietic malignancies investigating the role of benzene, occupational, environmental, medical, and genetic factors. Her service includes President of the American College of Epidemiology (2004 to 2005), advisory and site visit review committees (International Agency for Research on Cancer and the United Kingdom Leukemia and Lymphoma Research Society), and membership on NCRP (2010 onward), the National Academy of Sciences Nuclear and Radiation Studies Board (2011 onward), and journal editorial (American Journal of Epidemiology) and advisory (Journal of the National Cancer Institute) boards. Dr. Linet's awards include NIH Merit and Director's Awards, and election to the American Epidemiological Society and the Johns Hopkins Society of Scholars.

ANDREW D. MAIDMENT is Associate Professor of Radiology and Chief of the Physics Section at the University of Pennsylvania in Philadelphia. Dr. Maidment received his Ph.D. in Medical Biophysics from the University of Toronto in 1993 for developing scanned-slot digital mammography. From 1993 to 2002, he was the Director of Radiological Physics and Assistant Professor of Radiology at Thomas Jefferson University. In 2005, Dr. Maidment received support from the Howard Hughes Medical Institute to establish a graduate program in Biomedical Imaging Sciences at the University of Pennsylvania. Dr. Maidment is now co-director of that graduate program. In 2010, he received the University of Pennsylvania Dean's Special Award in Education for that work. He has been active in the NCRP, the American College of Radiology, the American Association of Physicists in Medicine, and International Atomic Energy Association, including co-editing a textbook on diagnostic radiology physics for the International Atomic Energy Agency. Dr. Maidment is a Fellow of the American Association of Physicists in Medicine, and in 2012 was recognized as a Distinguished Investigator by the Academy of Academic Radiology. Dr. Maidment has more than 200 peer-reviewed journal articles, book chapters, proceedings papers and abstracts. His research interests include digital mammography, three-dimensional x ray imaging of the breast, contrast-enhanced breast imaging, and digital radiography detector physics.

JOHN J. MULVIHILL is a pediatrician and medical geneticist with 20 y experience at the National Cancer Institute, where he was chief of the Clinical Genetics Section of the Clinical Epidemiology Branch and Director of the Interinstitute Medical Genetics Program of the National Institutes of Health (NIH). In 1990, he became founder, chair and professor of Human Genetics at the

University of Pittsburgh and Co-Director of the Pittsburgh Genetics Institute. In 1998, he became the Children's Medical Research Institute-Kimberly V. Talley Chair of Genetics, Professor of Pediatrics, University of Oklahoma and adjunct professor of Epidemiology and Biostatistics. A graduate of the College of the Holy Cross, Dartmouth Medical School, and the University of Washington Medical School, he was on the house staff at University of Washington Hospital and at the Johns Hopkins Hospital. Dr. Mulvihill has been a member of 13 professional societies, and cofounder and past president of the International Genetic Epidemiology Society. In addition to belonging to the editorial boards of eight scientific journals, he was co-editor-in-chief of Genetic Epidemiology and editor of the Neurofibromatosis Research Newsletter. In 1989, the National Neurofibromatosis Foundation awarded him its first Friedrich von Recklinghausen award. Mentoring is his major commitment. Dr. Mulvihill's research has focused on the genetics of human cancer, with an emphasis on late effects, reproductive and genetic, in cancer survivors and on germ-cell mutagenesis. He maintains a unique Registry of Pregnancies Exposed to Cancer Chemotherapy. He organized the first International Conferences on the Genetics of Human Cancer in 1975 and on Neurofibromatosis in 1980 and, in Oklahoma City in 2003, an International Conference on Family Cancer. He has had NIH and other national research grants for neurofibromatosis, pancreatic cancer, and fetal alcohol syndrome and has written 322 scientific articles and edited 13 monographs and syllabi. He is a member of the Scientific Council of the Radiation Effects Research Foundation, Hiroshima and Nagasaki, and the Ethics Committee of the International Human Genome Organisation.

SHIAO Y. WOO is Professor and Chairman, Department of Radiation Oncology, Kosair Children's Hospital/Norton Healthcare Chair in Pediatric Oncology, School of Medicine, University of Louisville, Louisville, Kentucky. Shiao Woo was born in Ipoh Malaysia in 1948. After 2 y of matriculation (college equivalent under the British system), Shiao was admitted to medical school (University of Malaya) for a 5 y program and skipped a year of pre-med. At the tender age of 23, Shiao graduated from medical school after completing a year of rotatory internship and 2 y of internal medicine. Dr. Woo then traveled to the United Kingdom in 1975 to take the internal medicine board and passed. He continued training and rotations at several pediatric hospitals and gained an interest in Pediatric Oncology after meeting Dr. Lucius Sinks at Georgetown University Medical Center in Washington D.C. in 1978. Dr. Woo did a Fellowship under Dr. Sinks, his first mentor, at the Lombardi Cancer Center at Georgetown. Once he passed the American Board of Pediatrics and the sub-board of Pediatric Hematology/Oncology he became an Assistant Professor at Georgetown in 1980. In 1981 he went with Dr. Sinks to be an Assistant Professor of Pediatrics at the Tufts New England Medical Center in Boston.

By 1985, Dr. Woo had decided to be re-trained in radiation oncology and went to a residency program for the third time at Stanford University Medical Center. There he met his second mentor, Dr. Sarah Donaldson with whom he became lifelong friends. In 1988 he passed the American Board of Radiology (Radiation Oncology) and moved to Houston to become an Assistant Professor in Radiation Oncology at the MD Anderson Cancer Center. After only a year, Dr. Woo was elected by the residents to be the Residency Training Program Director and won a residency teaching award in 1990. In 1991, Dr. Woo lifted the Residency Program at Baylor College

of Medicine out of probation, became one of the earliest investigators in the country in the field of IMRT and became recognized as an expert in treating childhood cancers as well as brain tumors. In 1996, he was promoted to Professor with Tenure at the Baylor College of Medicine; in 2001 he was named an Associate Chairman in the Department of Radiology; in 2004, he was recruited by Dr. James Cox back to MD Anderson to be the Professor and Section Chief of Pediatric/CNS Radiation Oncology and the medical Director of the Proton Therapy Center. In 2010, he was recruited to be the Chairman and Professor of the Department of Radiation Oncology at the University of Louisville, School of Medicine in Louisville, Kentucky.

Dr. Woo is an internationally recognized authority on the treatment of brain, spinal cord, and pediatric cancers. He is superbly trained, has obtained extensive clinical and research experience at the world-class MD Anderson Cancer Center of Houston, is widely published and serves on the Board of Directors of the Pediatric Radiation Oncology Society.

He is board certified in pediatrics, pediatric hematology-oncology, and radiation oncology. Dr. Woo's areas of clinical and research interest are tumors of the blood, bone, nervous system, and soft tissue in children and adults. He has published more than 140 articles in peer-reviewed journals and authored more than 20 book chapters.

JERROLD T. BUSHBERG (*Consultant*) is the is the Senior Vice President of the National Council on Radiation Protection and Measurements, and Clinical Professor of Radiology and Radiation Oncology, University of California (UC) Davis School of Medicine. He is an expert on the biological effects, safety and interactions of ionizing and nonionizing radiation and holds multiple radiation detection technology patents. Dr. Bushberg is a fellow of the American Association of Physicist in Medicine and is certified by several national professional boards with specific subspecialty certification in radiation protection and medical physics. Prior to coming to the UC Davis Health System as technical director of nuclear medicine, Dr. Bushberg was on the faculty of Yale University School of Medicine where his research was focused on radiopharmaceutical development. Dr. Bushberg has served as an advisor to government agencies and institutions throughout the nation and around the world on the biological effects and safety of ionizing and nonionizing radiation exposure. He has worked for the U.S. Department of Homeland Security, the World Health Organization, and the International Atomic Energy Agency as a subject matter expert in radiation protection and radiological emergency medical management. Dr. Bushberg has responsibility for medical postgraduate education in medical physics, radiation (ionizing and nonionizing) protection, and radiation biology. The third edition of the textbook "The Essential Physics of Medical Imaging," authored by Bushberg, Seibert, Leidholdt, and Boone, is used extensively by radiology residency programs throughout the United States.

SUSAN D. WILTSHIRE (*Consultant*), now retired, previously held the position of Vice President of the consulting firm JK Research Associates, Inc. Ms. Wiltshire has been involved in the development of public policy and technical reviews for more than 22 y. She has consulted in risk communication; supported multi-faceted decision-making; planned and implemented citizen involvement, and assisted in peer review processes, especially in the development of nuclear waste management policy. Her expertise in these areas results from her extensive experience as an involved citizen, consultant, local official, and member of numerous state and national advisory groups. She has served on study committees and advisory groups for the U.S. Environmental Protection Agency; the National Academy of Sciences, including the Board on Radioactive Waste; the U.S. Department of Energy; and NCRP. In addition, she has served on the NCRP Board of Directors and was elected a Distinguished Emeritus member in 2009.

Ms. Wiltshire is author of the Conservation Foundation Report *Managing the Nation's High-Level Radioactive Waste* and the 1993 revision of the League of Women Voters publication *A Nuclear Waste Primer* as well as of numerous papers and presentations concerning radioactive waste management and cleanup of the weapons complex.

MARVIN C. ZISKIN (*Consultant)* is a Professor of Radiology and Medical Physics at Temple University Medical School, Philadelphia, Pennsylvania. He also is the Director of the Temple University Center for Biomedical Physics. Dr. Ziskin is a pioneer in the field of medical ultrasound. Starting in 1965, he has been involved with developing ultrasound as a useful diagnostic modality. All along, he has been particularly concerned with its safety, especially with respect to fetal imaging. He served for 20 y on NCRP SC-66, the committee, under Dr. Wesley Nyborg, that prepared the three authoritative NCRP volumes on the biological effects of ultrasound and exposure criteria for diagnostic ultrasound. Dr. Ziskin served as the President of the American Institute of Ultrasound in Medicine from 1982 to 1984 and as the President of the World Federation of Ultrasound in Medicine and Biology from 2003 to 2006. In the past 20 y, he has also been involved with the safety of nonionizing electromagnetic fields. He serves as the Co-Chairman of the Institute of Electrical and Electronics Engineers, Inc. (IEEE) International Committee on Electromagnetic Safety SC-4, the committee responsible for the IEEE standards on the safety of radiofrequency electromagnetic exposures. Dr. Ziskin has authored or co-authored seven books and over 250 scientific publications. He has received numerous awards, including the 2011 D'Arsonval Award, the highest award of the Bioelectromagnetics Society.

The NCRP

The National Council on Radiation Protection and Measurements is a nonprofit corporation chartered by Congress in 1964 to:

1. Collect, analyze, develop and disseminate in the public interest information and recommendations about (a) protection against radiation and (b) radiation measurements, quantities and units, particularly those concerned with radiation protection.
2. Provide a means by which organizations concerned with the scientific and related aspects of radiation protection and of radiation quantities, units and measurements may cooperate for effective utilization of their combined resources, and to stimulate the work of such organizations.
3. Develop basic concepts about radiation quantities, units and measurements, about the application of these concepts, and about radiation protection.
4. Cooperate with the International Commission on Radiological Protection, the International Commission on Radiation Units and Measurements, and other national and international organizations, governmental and private, concerned with radiation quantities, units and measurements and with radiation protection.

The Council is the successor to the unincorporated association of scientists known as the National Committee on Radiation Protection and Measurements and was formed to carry on the work begun by the Committee in 1929.

The participants in the Council's work are the Council members and members of scientific and administrative committees. Council members are selected solely on the basis of their scientific expertise and serve as individuals, not as representatives of any particular organization. The scientific committees, composed of experts having detailed knowledge and competence in the particular area of the committee's interest, draft proposed recommendations. These are then submitted to the full membership of the Council for careful review and approval before being published.

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Lauriston S. Taylor Lecturers

John E. Till (2013) *When Does Risk Assessment Get Fuzzy?*
Antone L. Brooks (2012) *From the Field to the Laboratory and Back: The "What Ifs," "Wows," and "Who Cares" of Radiation Biology*
Eleanor A. Blakely (2011) *What Makes Particle Radiation so Effective?*
Charles E. Land (2010) *Radiation Protection and Public Policy in an Uncertain World*
John D. Boice, Jr. (2009) *Radiation Epidemiology: The Golden Age and Remaining Challenges*
Dade W. Moeller (2008) *Radiation Standards, Dose/Risk Assessments, Public Interactions, and Yucca Mountain: Thinking Outside the Box*
Patricia W. Durbin (2007) *The Quest for Therapeutic Actinide Chelators*
Robert L. Brent (2006) *Fifty Years of Scientific Research: The Importance of Scholarship and the Influence of Politics and Controversy*
John B. Little (2005) *Nontargeted Effects of Radiation: Implications for Low-Dose Exposures*
Abel J. Gonzalez (2004) *Radiation Protection in the Aftermath of a Terrorist Attack Involving Exposure to Ionizing Radiation*
Charles B. Meinhold (2003) *The Evolution of Radiation Protection: From Erythema to Genetic Risks to Risks of Cancer to ?*
R. Julian Preston (2002) *Developing Mechanistic Data for Incorporation into Cancer Risk Assessment: Old Problems and New Approaches*

Wesley L. Nyborg (2001) *Assuring the Safety of Medical Diagnostic Ultrasound*
S. James Adelstein (2000) *Administered Radioactivity: Unde Venimus Quoque Imus*
Naomi H. Harley (1999) *Back to Background*
Eric J. Hall (1998) *From Chimney Sweeps to Astronauts: Cancer Risks in the Workplace*
William J. Bair (1997) *Radionuclides in the Body: Meeting the Challenge!*
Seymour Abrahamson (1996) *70 Years of Radiation Genetics: Fruit Flies, Mice and Humans*
Albrecht Kellerer (1995) *Certainty and Uncertainty in Radiation Protection*
R.J. Michael Fry (1994) *Mice, Myths and Men*
Warren K. Sinclair (1993) *Science, Radiation Protection and the NCRP*
Edward W. Webster (1992) *Dose and Risk in Diagnostic Radiology: How Big? How Little?*
Victor P. Bond (1991) *When is a Dose Not a Dose?*
J. Newell Stannard (1990) *Radiation Protection and the Internal Emitter Saga*
Arthur C. Upton (1989) *Radiobiology and Radiation Protection: The Past Century and Prospects for the Future*
Bo Lindell (1988) *How Safe is Safe Enough?*
Seymour Jablon (1987) *How to be Quantitative about Radiation Risk Estimates*
Herman P. Schwan (1986) *Biological Effects of Non-ionizing Radiations: Cellular Properties and Interactions*
John H. Harley (1985) *Truth (and Beauty) in Radiation Measurement*
Harald H. Rossi (1984) *Limitation and Assessment in Radiation Protection*
Merril Eisenbud (1983) *The Human Environment—Past, Present and Future*
Eugene L. Saenger (1982) *Ethics, Trade-Offs and Medical Radiation*
James F. Crow (1981) *How Well Can We Assess Genetic Risk? Not Very*
Harold O. Wyckoff (1980) *From "Quantity of Radiation" and "Dose" to "Exposure" and "Absorbed Dose"—An Historical Review*
Hymer L. Friedell (1979) *Radiation Protection—Concepts and Trade Offs*
Sir Edward Pochin (1978) *Why be Quantitative about Radiation Risk Estimates?*
Herbert M. Parker (1977) *The Squares of the Natural Numbers in Radiation Protection*

Currently, the following committees are actively engaged in formulating recommendations:

Program Area Committee 1: Basic Criteria, Epidemiology, Radiobiology, and Risk
SC 1-20 Biological Effectiveness of Photons as a Function of Energy
SC 1-21 Multiplatform National Approach for Providing Guidance on Integrating Basic Science and Epidemiological Studies on Low-Dose Radiation Biological and Health Effects
Program Area Committee 2: Operational Radiation Safety
SC 2-6 Radiation Safety Aspects of Nanotechnology
Program Area Committee 3: Nuclear and Radiological Security and Safety
Program Area Committee 4: Radiation Protection in Medicine

Program Area Committee 5: Environmental Radiation and Radioactive Waste Issues

SC 5-1 Approach to Optimizing Decision Making for Late-Phase Recovery from Nuclear or Radiological Terrorism Incidents

Program Area Committee 6: Radiation Measurements and Dosimetry

SC 6-8 Operation TOMODACHI Radiation Dose Assessment Peer Review
SC 6-9 U.S. Radiation Workers and Nuclear Weapons Test Participants Radiation Dose Assessment

Program Area Committee 7: Radiation Education, Risk Communication, Outreach, and Policy

In recognition of its responsibility to facilitate and stimulate cooperation among organizations concerned with the scientific and related aspects of radiation protection and measurement, the Council has created a category of NCRP Collaborating Organizations. Organizations or groups of organizations that are national or international in scope and are concerned with scientific problems involving radiation quantities, units, measurements and effects, or radiation protection may be admitted to collaborating status by the Council. Collaborating Organizations provide a means by which NCRP can gain input into its activities from a wider segment of society. At the same time, the relationships with the Collaborating Organizations facilitate wider dissemination of information about the Council's activities, interests and concerns. Collaborating Organizations have the opportunity to comment on draft reports (at the time that these are submitted to the members of the Council). This is intended to capitalize on the fact that Collaborating Organizations are in an excellent position to both contribute to the identification of what needs to be treated in NCRP reports and to identify problems that might result from proposed recommendations. The present Collaborating Organizations with which NCRP maintains liaison are as follows:

American Academy of Dermatology
American Academy of Environmental Engineers
American Academy of Health Physics
American Academy of Orthopaedic Surgeons
American Association of Physicists in Medicine
American Bracytherapy Society
American College of Cardiology
American College of Medical Physics
American College of Nuclear Physicians
American College of Occupational and Environmental Medicine
American College of Radiology
American Conference of Governmental Industrial Hygienists
American Dental Association
American Industrial Hygiene Association
American Institute of Ultrasound in Medicine
American Medical Association
American Nuclear Society
American Pharmaceutical Association
American Podiatric Medical Association
American Public Health Association

American Radium Society
American Roentgen Ray Society
American Society for Radiation Oncology
American Society of Emergency Radiology
American Society of Health-System Pharmacists
American Society of Nuclear Cardiology
American Society of Radiologic Technologists
American Thyroid Association
Association of Educators in Imaging and Radiological Sciences
Association of University Radiologists
Bioelectromagnetics Society
Campus Radiation Safety Officers
College of American Pathologists
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Nuclear Energy Institute
Office of Science and Technology Policy
Paper, Allied-Industrial, Chemical and Energy Workers International Union
Product Stewardship Institute
Radiation Research Society
Radiological Society of North America
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NCRP has found its relationships with these organizations to be extremely valuable to continued progress in its program.

Another aspect of the cooperative efforts of NCRP relates to the Special Liaison relationships established with various governmental organizations that have an interest in radiation protection and measurements. This liaison relationship provides: (1) an opportunity for participating organizations to designate an individual to provide liaison between the organization and NCRP; (2) that the individual designated will receive copies of draft NCRP reports (at the time that these are submitted to the members of the Council) with an invitation to comment, but not vote; and (3) that new NCRP efforts might be discussed with liaison individuals as appropriate, so that they might have an opportunity to make suggestions on new studies and related matters. The following organizations participate in the Special Liaison Program:

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Canadian Association of Medical Radiation Technologists
Canadian Nuclear Safety Commission
Central Laboratory for Radiological Protection (Poland)
China Institute for Radiation Protection
Commissariat a l'Energie Atomique (France)
Commonwealth Scientific Instrumentation Research Organization (Australia)
European Commission
Heads of the European Radiological Protection Competent Authorities
Health Council of the Netherlands
Health Protection Agency
International Commission on Non-Ionizing Radiation Protection
International Commission on Radiation Units and Measurements
International Commission on Radiological Protection
International Radiation Protection Association
Japanese Nuclear Safety Commission
Japan Radiation Council
Korea Institute of Nuclear Safety
Russian Scientific Commission on Radiation Protection
South African Forum for Radiation Protection
World Association of Nuclear Operators
World Health Organization, Radiation and Environmental Health

NCRP values highly the participation of these organizations in the Special Liaison Program.

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American Healthcare Radiology Administrators
American Industrial Hygiene Association
American Insurance Services Group
American Medical Association
American Nuclear Society
American Osteopathic College of Radiology
American Podiatric Medical Association
American Public Health Association
American Radium Society
American Roentgen Ray Society
American Society for Radiation Oncology
American Society for Therapeutic Radiology and Oncology
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NCRP seeks to promulgate information and recommendations based on leading scientific judgment on matters of radiation protection and measurement and to foster cooperation among organizations concerned with these matters. These efforts are intended to serve the public interest and the Council welcomes comments and suggestions on its reports or activities.

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NCRP Reports

No.	Title
8	*Control and Removal of Radioactive Contamination in Laboratories* (1951)
22	*Maximum Permissible Body Burdens and Maximum Permissible Concentrations of Radionuclides in Air and in Water for Occupational Exposure* (1959) [includes Addendum 1 issued in August 1963]
25	*Measurement of Absorbed Dose of Neutrons, and of Mixtures of Neutrons and Gamma Rays* (1961)
27	*Stopping Powers for Use with Cavity Chambers* (1961)
30	*Safe Handling of Radioactive Materials* (1964)
32	*Radiation Protection in Educational Institutions* (1966)
35	*Dental X-Ray Protection* (1970)
36	*Radiation Protection in Veterinary Medicine* (1970)
37	*Precautions in the Management of Patients Who Have Received Therapeutic Amounts of Radionuclides* (1970)
38	*Protection Against Neutron Radiation* (1971)
40	*Protection Against Radiation from Brachytherapy Sources* (1972)
41	*Specification of Gamma-Ray Brachytherapy Sources* (1974)
42	*Radiological Factors Affecting Decision-Making in a Nuclear Attack* (1974)
44	*Krypton-85 in the Atmosphere—Accumulation, Biological Significance, and Control Technology* (1975)
46	*Alpha-Emitting Particles in Lungs* (1975)
47	*Tritium Measurement Techniques* (1976)
49	*Structural Shielding Design and Evaluation for Medical Use of X Rays and Gamma Rays of Energies Up to 10 MeV* (1976)

50 *Environmental Radiation Measurements* (1976)
52 *Cesium-137 from the Environment to Man: Metabolism and Dose* (1977)
54 *Medical Radiation Exposure of Pregnant and Potentially Pregnant Women* (1977)
55 *Protection of the Thyroid Gland in the Event of Releases of Radioiodine* (1977)
57 *Instrumentation and Monitoring Methods for Radiation Protection* (1978)
58 *A Handbook of Radioactivity Measurements Procedures*, 2nd ed. (1985)
60 *Physical, Chemical, and Biological Properties of Radiocerium Relevant to Radiation Protection Guidelines* (1978)
61 *Radiation Safety Training Criteria for Industrial Radiography* (1978)
62 *Tritium in the Environment* (1979)
63 *Tritium and Other Radionuclide Labeled Organic Compounds Incorporated in Genetic Material* (1979)
64 *Influence of Dose and Its Distribution in Time on Dose-Response Relationships for Low-LET Radiations* (1980)
65 *Management of Persons Accidentally Contaminated with Radionuclides* (1980)
67 *Radiofrequency Electromagnetic Fields—Properties, Quantities and Units, Biophysical Interaction, and Measurements* (1981)
68 *Radiation Protection in Pediatric Radiology* (1981)
69 *Dosimetry of X-Ray and Gamma-Ray Beams for Radiation Therapy in the Energy Range 10 keV to 50 MeV* (1981)
70 *Nuclear Medicine—Factors Influencing the Choice and Use of Radionuclides in Diagnosis and Therapy* (1982)
72 *Radiation Protection and Measurement for Low-Voltage Neutron Generators* (1983)
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78 *Evaluation of Occupational and Environmental Exposures to Radon and Radon Daughters in the United States* (1984)
79 *Neutron Contamination from Medical Electron Accelerators* (1984)
80 *Induction of Thyroid Cancer by Ionizing Radiation* (1985)
81 *Carbon-14 in the Environment* (1985)
82 *SI Units in Radiation Protection and Measurements* (1985)
83 *The Experimental Basis for Absorbed-Dose Calculations in Medical Uses of Radionuclides* (1985)

84 *General Concepts for the Dosimetry of Internally Deposited Radionuclides* (1985)
86 *Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields* (1986)
87 *Use of Bioassay Procedures for Assessment of Internal Radionuclide Deposition* (1987)
88 *Radiation Alarms and Access Control Systems* (1986)
89 *Genetic Effects from Internally Deposited Radionuclides* (1987)
90 *Neptunium: Radiation Protection Guidelines* (1988)
92 *Public Radiation Exposure from Nuclear Power Generation in the United States* (1987)
93 *Ionizing Radiation Exposure of the Population of the United States* (1987)
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97 *Measurement of Radon and Radon Daughters in Air* (1988)
99 *Quality Assurance for Diagnostic Imaging* (1988)
100 *Exposure of the U.S. Population from Diagnostic Medical Radiation* (1989)
101 *Exposure of the U.S. Population from Occupational Radiation* (1989)
102 *Medical X-Ray, Electron Beam and Gamma-Ray Protection for Energies Up to 50 MeV (Equipment Design, Performance and Use)* (1989)
103 *Control of Radon in Houses* (1989)
104 *The Relative Biological Effectiveness of Radiations of Different Quality* (1990)
105 *Radiation Protection for Medical and Allied Health Personnel* (1989)
106 *Limit for Exposure to "Hot Particles" on the Skin* (1989)
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122 *Use of Personal Monitors to Estimate Effective Dose Equivalent and Effective Dose to Workers for External Exposure to Low-LET Radiation* (1995)
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124 *Sources and Magnitude of Occupational and Public Exposures from Nuclear Medicine Procedures* (1996)
125 *Deposition, Retention and Dosimetry of Inhaled Radioactive Substances* (1997)
126 *Uncertainties in Fatal Cancer Risk Estimates Used in Radiation Protection* (1997)
127 *Operational Radiation Safety Program* (1998)
128 *Radionuclide Exposure of the Embryo/Fetus* (1998)
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NCRP Commentaries

No.	Title
1	*Krypton-85 in the Atmosphere—With Specific Reference to the Public Health Significance of the Proposed Controlled Release at Three Mile Island* (1980)
4	*Guidelines for the Release of Waste Water from Nuclear Facilities with Special Reference to the Public Health Significance of the Proposed Release of Treated Waste Waters at Three Mile Island* (1987)
5	*Review of the Publication, Living Without Landfills* (1989)
6	*Radon Exposure of the U.S. Population—Status of the Problem (1991)*
7	*Misadministration of Radioactive Material in Medicine—Scientific Background* (1991)
8	*Uncertainty in NCRP Screening Models Relating to Atmospheric Transport, Deposition and Uptake by Humans* (1993)
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10	*Advising the Public about Radiation Emergencies: A Document for Public Comment* (1994)
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12	*Radiation Exposure and High-Altitude Flight* (1995)
13	*An Introduction to Efficacy in Diagnostic Radiology and Nuclear Medicine (Justification of Medical Radiation Exposure)* (1995)
14	*A Guide for Uncertainty Analysis in Dose and Risk Assessments Related to Environmental Contamination* (1996)
15	*Evaluating the Reliability of Biokinetic and Dosimetric Models and Parameters Used to Assess Individual Doses for Risk Assessment Purposes* (1998)
16	*Screening of Humans for Security Purposes Using Ionizing Radiation Scanning Systems* (2003)
17	*Pulsed Fast Neutron Analysis System Used in Security Surveillance* (2003)
18	*Biological Effects of Modulated Radiofrequency Fields* (2003)
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20	*Radiation Protection and Measurement Issues Related to Cargo Scanning with Accelerator-Produced High-Energy X Rays* (2007)
21	*Radiation Protection in the Application of Active Detection Technologies* (2011)
22	*Radiological Health Protection Issues Associated With Use of Active Detection Technology Systems for Detection of Radioactive Threat Materials* (2011)

Proceedings of the Annual Meeting

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1	*Perceptions of Risk,* Proceedings of the Fifteenth Annual Meeting held on March 14-15, 1979 (including Taylor Lecture No. 3) (1980)
3	*Critical Issues in Setting Radiation Dose Limits*, Proceedings of the Seventeenth Annual Meeting held on April 8-9, 1981 (including Taylor Lecture No. 5) (1982)
4	*Radiation Protection and New Medical Diagnostic Approaches,* Proceedings of the Eighteenth Annual Meeting held on April 6-7, 1982 (including Taylor Lecture No. 6) (1983)
5	*Environmental Radioactivity,* Proceedings of the Nineteenth Annual Meeting held on April 6-7, 1983 (including Taylor Lecture No. 7) (1983)
6	*Some Issues Important in Developing Basic Radiation Protection Recommendations*, Proceedings of the Twentieth Annual Meeting held on April 4-5, 1984 (including Taylor Lecture No. 8) (1985)
7	*Radioactive Waste*, Proceedings of the Twenty-First Annual Meeting held on April 3-4, 1985 (including Taylor Lecture No. 9)(1986)
8	*Nonionizing Electromagnetic Radiations and Ultrasound,* Proceedings of the Twenty-Second Annual Meeting held on April 2-3, 1986 (including Taylor Lecture No. 10) (1988)
9	*New Dosimetry at Hiroshima and Nagasaki and Its Implications for Risk Estimates*, Proceedings of the Twenty-Third Annual Meeting held on April 8-9, 1987 (including Taylor Lecture No. 11) (1988)
10	*Radon*, Proceedings of the Twenty-Fourth Annual Meeting held on March 30-31, 1988 (including Taylor Lecture No. 12) (1989)
11	*Radiation Protection Today—The NCRP at Sixty Years*, Proceedings of the Twenty-Fifth Annual Meeting held on April 5-6, 1989 (including Taylor Lecture No. 13) (1990)
12	*Health and Ecological Implications of Radioactively Contaminated Environments*, Proceedings of the Twenty-Sixth Annual Meeting held on April 4-5, 1990 (including Taylor Lecture No. 14) (1991)
13	*Genes, Cancer and Radiation Protection,* Proceedings of the Twenty-Seventh Annual Meeting held on April 3-4, 1991 (including Taylor Lecture No. 15) (1992)
14	*Radiation Protection in Medicine,* Proceedings of the Twenty-Eighth Annual Meeting held on April 1-2, 1992 (including Taylor Lecture No. 16) (1993)
15	*Radiation Science and Societal Decision Making,* Proceedings of the Twenty-Ninth Annual Meeting held on April 7-8, 1993 (including Taylor Lecture No. 17) (1994)
16	*Extremely-Low-Frequency Electromagnetic Fields: Issues in Biological Effects and Public Health*, Proceedings of the Thirtieth Annual Meeting held on April 6-7, 1994 (not published).
17	*Environmental Dose Reconstruction and Risk Implications,* Proceedings of the Thirty-First Annual Meeting held on April 12-13, 1995 (including Taylor Lecture No. 19) (1996)

18 *Implications of New Data on Radiation Cancer Risk*, Proceedings of the Thirty-Second Annual Meeting held on April 3-4, 1996 (including Taylor Lecture No. 20) (1997)

19 *The Effects of Pre- and Postconception Exposure to Radiation*, Proceedings of the Thirty-Third Annual Meeting held on April 2-3, 1997, Teratology **59**, 181–317 (1999)

20 *Cosmic Radiation Exposure of Airline Crews, Passengers and Astronauts*, Proceedings of the Thirty-Fourth Annual Meeting held on April 1-2, 1998, Health Phys. **79**, 466–613 (2000)

21 *Radiation Protection in Medicine: Contemporary Issues*, Proceedings of the Thirty-Fifth Annual Meeting held on April 7-8, 1999 (including Taylor Lecture No. 23) (1999)

22 *Ionizing Radiation Science and Protection in the 21st Century*, Proceedings of the Thirty-Sixth Annual Meeting held on April 5-6, 2000, Health Phys. **80**, 317–402 (2001)

23 *Fallout from Atmospheric Nuclear Tests—Impact on Science and Society*, Proceedings of the Thirty-Seventh Annual Meeting held on April 4-5, 2001, Health Phys. **82**, 573–748 (2002)

24 *Where the New Biology Meets Epidemiology: Impact on Radiation Risk Estimates*, Proceedings of the Thirty-Eighth Annual Meeting held on April 10-11, 2002, Health Phys. **85**, 1–108 (2003)

25 *Radiation Protection at the Beginning of the 21st Century–A Look Forward*, Proceedings of the Thirty-Ninth Annual Meeting held on April 9–10, 2003, Health Phys. **87**, 237–319 (2004)

26 *Advances in Consequence Management for Radiological Terrorism Events*, Proceedings of the Fortieth Annual Meeting held on April 14–15, 2004, Health Phys. **89**, 415–588 (2005)

27 *Managing the Disposition of Low-Activity Radioactive Materials*, Proceedings of the Forty-First Annual Meeting held on March 30–31, 2005, Health Phys. **91**, 413–536 (2006)

28 *Chernobyl at Twenty*, Proceedings of the Forty-Second Annual Meeting held on April 3–4, 2006, Health Phys. **93**, 345–595 (2007)

29 *Advances in Radiation Protection in Medicine*, Proceedings of the Forty-Third Annual Meeting held on April 16-17, 2007, Health Phys. **95**, 461–686 (2008)

30 *Low Dose and Low Dose-Rate Radiation Effects and Models*, Proceedings of the Forty-Fourth Annual Meeting held on April 14–15, 2008, Health Phys. **97**, 373–541 (2009)

31 *Future of Nuclear Power Worldwide – Health, Safety, and Environment*, Proceedings of the Forty-Fifth Annual Meeting held on March 2–3, 2009, Health Phys. **100**(1), 2–112 (2011)

32 *Communication of Radiation Benefits and Risks in Decision Making*, Proceedings of the Forty-Sixth Annual Meeting held March 8–9, 2010, Health Phys. **101**(5), 497–629 (2011)

33 *Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions*, Proceedings of the Forty-Seventh Annual Meeting held on March 7–8, 2011, Health Phys. **103**(5), 529–684 (2012)

Lauriston S. Taylor Lectures

No.	Title
1	*The Squares of the Natural Numbers in Radiation Protection by* Herbert M. Parker (1977)
2	*Why be Quantitative about Radiation Risk Estimates?* by Sir Edward Pochin (1978)
3	*Radiation Protection—Concepts and Trade Offs* by Hymer L. Friedell (1979) [available also in *Perceptions of Risk*, see above]
4	*From "Quantity of Radiation" and "Dose" to "Exposure" and "Absorbed Dose"—An Historical Review* by Harold O. Wyckoff (1980)
5	*How Well Can We Assess Genetic Risk? Not Very* by James F. Crow (1981) [available also in *Critical Issues in Setting Radiation Dose Limits*, see above]
6	*Ethics, Trade-offs and Medical Radiation* by Eugene L. Saenger (1982) [available also in *Radiation Protection and New Medical Diagnostic Approaches*, see above]
7	*The Human Environment—Past, Present and Future* by Merril Eisenbud (1983) [available also in *Environmental Radioactivity*, see above]
8	*Limitation and Assessment in Radiation Protection* by Harald H. Rossi (1984) [available also in *Some Issues Important in Developing Basic Radiation Protection Recommendations*, see above]
9	*Truth (and Beauty) in Radiation Measurement* by John H. Harley (1985) [available also in *Radioactive Waste*, see above]
10	*Biological Effects of Non-ionizing Radiations: Cellular Properties and Interactions* by Herman P. Schwan (1987) [available also in *Nonionizing Electromagnetic Radiations and Ultrasound*, see above]
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