Fifty Years of Scientific Investigation: The Importance of Scholarship and the Influence of Politics and Controversy

Robert L. Brent MD, Ph.D., D.Sc.(Hon)
Thomas Jefferson University
duPont Hospital for Children
Wilmington, DE
Welcome to Delaware
SMALL WONDER
THE FIRST STATE
Home of Tax - Free Shopping
Radiation Research Projects

Neoplasia induced in developing embryos by X-irradiation
Carbon 14 Transmutation Effect ('49-53)
Induction of Unbalanced Translocations ('48-52)
Comparison of Mouse and Human Development ('54)
Spectrum of Cosmic Rays entering the Atmosphere ('50)

Studies with Radioactive Rose Bengal. '60s
Fetal Thyroid Development Using I-131 ('55-57)
Indirect Effect of Ionizing Radiation on the Developing
Mammalian Embryo. ('55-68)
"The All-or None Phenomenon" ('50-92)
Radiation Teratogenesis and the Threshold Concept ('68-92)
The Importance of Dose-rate in Radiation Embryology Studies ('68)
Transplacental Carcinogenesis following Embryonic Irradiation. '50s-
'90s

Intrauterine Radiation, Mental Retardation and
Neurobehavioral Effects ('84-92)
Astatine Radiation of the Rat Yolk Sac. ('72)
Neutron Irradiation of the Embryo. Experiments on
Relative Biological Effect. ('72-92)
Cytogenetic changes in the Preimplantation Embryo ('82)
Embryonic Effects of Ultrasound and Microwave Exposure.
Reproductive Risks of low frequency EMF exposures.
The risks of ionizing radiation to the developing embryo. The use of animal and human studies to determine these risks in order to provide counseling to exposed individuals.

1. The NOAEL for congenital malformations.
2. The “all or none phenomenon”.
3. The sensitivity of the central nervous system; the risk of mental retardation and neurobehavioral effects.
4. The impact of fractionation and protraction on embryonic radiation risks.
5. The risk of congenital malformations (teratogenesis) following maternal radiation when the embryo is not exposed.
6. The risk of leukemia following embryonic irradiation
7. The need for compassionate, objective, scholarly counseling of exposed individuals.
What do we want to emphasize?

1. The importance of resolving scientific controversy
2. The impact of politics on science and scientists
3. Utilization of biological plausibility in evaluating scientific research, conclusions and interpretations based on in depth knowledge of biochemistry, physiology, pathology, embryology, neuroanatomy, etc.
4. The reluctance for some scientists to say:
   “I don’t know”
   “I was wrong”
What do we know about the qualitative and quantitative effects of ionizing radiation on the developing embryo?

**Congenital malformations**

The NOAEL for congenital malformations is >0.2 Gy at the most sensitive stage of development (9 days p.c. in the rat) (22 days p.c. in the human). The NOAEL on the 10th day p.c. is 0.4-0.5 Gy.

The threshold is much higher at later stages of pregnancy.

During pre-organogenesis the embryos that survive are not growth retarded nor do they have a higher incidence of malformations.
Ocular anomalies in 90% of 9-day animals given 100 r.

Encephalocele

Exencephaly

Brain anomalies in 41% of 9-day animals given 100 r.
What do we know about the qualitative and quantitative effects of ionizing radiation on the developing embryo?

**Embryonic death**

The NOAEL for the lethal effects of radiation is lowest during the pre-implantation, pre-organogenesis stages and is approximately 0.1-0.2 Gy (mouse and rat) (0-8 days p.c. rat) (0-14 days p.c. in the human).

The NOAEL for increased risk of embryonic death increases throughout gestation and is similar to the mother’s risk in late gestation.
<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Litters</th>
<th>Embryos</th>
<th>Resorptions</th>
<th>Fetal weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>77</td>
<td>902</td>
<td>4.77%</td>
<td>5.264 g</td>
</tr>
<tr>
<td>0.05</td>
<td>58</td>
<td>699</td>
<td>6.49%</td>
<td>5.199 g</td>
</tr>
<tr>
<td>0.10</td>
<td>76</td>
<td>944</td>
<td>7.75%</td>
<td>5.207 g</td>
</tr>
<tr>
<td>0.20</td>
<td>71</td>
<td>851</td>
<td>11.41%</td>
<td>5.148 g</td>
</tr>
<tr>
<td>0.30</td>
<td>43</td>
<td>490</td>
<td>18.57%</td>
<td>5.015 g</td>
</tr>
</tbody>
</table>
What do we know about the qualitative and quantitative effects of ionizing radiation on the developing embryo?

**Neurobehavioral effects**

The NOAEL for neurobehavioral effects is 0.2 Gy at the most sensitive stage of development (17 to 20 days p.c. in the rat) (mid-gestation in the human).

Mental retardation is not a stochastic phenomenon. It is a deterministic effect.

If these data are our best estimates of the risk of irradiation in pregnancy, why did Handbook 54 (1977) of the NCRP establish .05 Gy as the embryonic exposure not to exceed when exposing pregnant women or women of reproductive age?
The All or None Phenomenon

Use my data To counsel humans vs.
<table>
<thead>
<tr>
<th>Pre differentiation Period</th>
<th>Usually Not Susceptible to Teratogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of Early Differentiation</td>
<td>Highly Susceptible to Teratogenesis</td>
</tr>
<tr>
<td>Period of Advanced Organogenesis</td>
<td>Increasingly Resistant to Teratogenesis With Increasing Age</td>
</tr>
</tbody>
</table>
"The All or None Phenomenon"

"Surviving embryos have malformation rates similar to those of the controls, not because malformations cannot be produced at this stage; however, at high exposures significant induced cell loss or chromosome abnormalities are most likely to result in zygote death or malformations that are lethal."

<table>
<thead>
<tr>
<th>Post-conception Exposure Day (2 Gy)</th>
<th>Control</th>
<th>2.5 days</th>
<th>5.5 days</th>
<th>7.5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>7%</td>
<td>66%</td>
<td>22%</td>
<td>45%</td>
</tr>
<tr>
<td>Term weight</td>
<td>1.59g</td>
<td>1.61g</td>
<td>1.33g</td>
<td>1.26g</td>
</tr>
<tr>
<td>Defects (%)</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td>77</td>
</tr>
</tbody>
</table>
All or None Phenomenon

Exceptions to the rule

Rugh irradiated pregnant C57 mice on the first day of pregnancy and reported an increase in the incidence of exencephaly. In Rugh’s studies there was no dose-response relationship. Argonne laboratories reported that the incidence of exencephaly in 1000 consecutive C57 litters was similar to the incidence in Rugh’s radiated litters.
All or None Phenomenon
Exceptions to the rule (epigenetic effects) following high doses of radiation

Streffer et al have utilized the Heiligenberger Stamm strain referred to as the HLG/Zte strain in their radiation studies. It is a strain with a 1-4% spontaneous incidence of gastroschisis. Irradiation of this strain on the first day of pregnancy with high exposures results in an increase in embryonic mortality and an increase in the incidence of gastroschisis.

C57Bl mice or HLGxC57Bl hybrids in their laboratory, when irradiated, have an increase in mortality, but no increase in congenital malformations.
The All or None Phenomenon
Dogma

In many of Streffer’s and his colleague’s papers they repeat the mantra:
“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.”
The “all or none phenomenon concept indicates that the predominant effect of embryotoxic exposures during the pre-implantation period is embryonic death. It also indicates that even in susceptible mouse strains, the risk is very low, even at high doses,

And most important there are no developmental risks below 0.2 Gy, even in the genetically susceptible strains.
What to do with the mouse data?

The fact that the reported malformations are specific for susceptible strains of mice indicates that these are genetically susceptible strains (epigenetic effect), resulting in an increase in the specific malformation from many forms of stress.

In some experiments, cross-transfer has indicated that radiation of the uterus has been responsible for the epigenetic effect.

Induced genetic changes in the one cell embryo would not result in an increase in only one type of abnormality, such as gastroschisis or exencephaly.

It is not biologically plausible.
Use My Data to Counsel Humans Please!

No thanks!
Is there an increased risk of mental retardation from radiation exposures in the diagnostic range (<05 Gy)?
15 week to birth exposure
<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>Pathology</th>
<th>Site</th>
<th>Diseases</th>
<th>Risk</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stochastic</td>
<td>Damage to a single cell may result in disease</td>
<td>DNA</td>
<td>Cancer, germ cell mutation</td>
<td>Some risk exists at all doses; at low doses, risk is usually less than the spontaneous risk</td>
<td>Incidence of the disease increases but the severity and nature of the disease remain the same</td>
</tr>
<tr>
<td>Threshold</td>
<td>Multiple cell and tissue injury</td>
<td>Multiple, variable etiology, affecting many cellular and organ functions</td>
<td>Birth defects, growth retardation, death, toxicity, mental retardation etc.</td>
<td>No increased risk below the threshold dose</td>
<td>Both the severity and incidence of the disease increase with dose</td>
</tr>
</tbody>
</table>

*Brent, 1987, 1990, 1999
Brain growth and total growth retardation most sensitive to environmental toxicants during midgestation as reported by Rugh in research using mice (1956).
Thalidomide was teratogenic for only two weeks during the first trimester (Lentz 1963)
1.5 Gy 17th day p.c., Control

Ocular anomalies in 90% of 9-day animals given 100r

Encephalocele
Exencephaly

Brain anomalies in 41% of 9-day animals given 100r
Golgi-Cox stains of outer cerebral cortex of adult rats. The surfaces are at the top. A, normal. B, large irregular neurons resulting from exposure to 200 r on the 17th day of foetal life. C, bizarre outer neurons resulting from 200 r on the 22nd foetal day.
Control 20 rad on 18th day pc at 3.5 weeks of age

Paucity of neurons (right) in the outer cortex of 18-day fetal rat exposed to 20 rad. It was an 18-day fetus compared with a normal (left). Cresyl violet, ×200
Postnatal Developmental Markers and Reflexes Evaluated in Offspring Irradiated Inutero

- Pinna detachment
- Eye opening
- Testes descent
- Vaginal opening
- Surface righting
- Negative geotaxis
- Auditory startle
- Air righting
- Visual placing
## EFFECT OF IN UTERO IRRADIATION ON GROWTH, REFLEXES AND DEVELOPMENTAL PARAMETERS

<table>
<thead>
<tr>
<th>Dose of X-ray (Gy):</th>
<th>0.1</th>
<th>0.2</th>
<th>0.4</th>
<th>0.6</th>
<th>0.1</th>
<th>0.2</th>
<th>0.4</th>
<th>0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect Growth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retardation at</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth Retardation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postpartum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parameters (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflexes (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Post Conception Day of Irradiation**

- Day 9
- Day 17

- **+(1)**
- **+(1)**
- **+(2)**
- **+(2)**
- **+(1)**
- **+(1)**
- **+(1)**
- **+(2)**
- **+(2)**
- **+(1)**
- **+(1)**
- **+(1)**
<table>
<thead>
<tr>
<th>Dose in Sv</th>
<th>No. with MR</th>
<th>No. at Risk</th>
<th>Rate of MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00 +</td>
<td>12</td>
<td>26</td>
<td>1 in 2</td>
</tr>
<tr>
<td>0.50-0.99</td>
<td>4</td>
<td>43</td>
<td>1 in 11</td>
</tr>
<tr>
<td>0.10-0.49</td>
<td>2</td>
<td>215</td>
<td>1 in 100</td>
</tr>
<tr>
<td>0.005-0.09</td>
<td>3</td>
<td>212</td>
<td>1 in 70</td>
</tr>
<tr>
<td>&lt;0.005</td>
<td>9</td>
<td>1069</td>
<td>1 in 118</td>
</tr>
</tbody>
</table>
Mental Retardation

Miller’s (1999) discussion of the issue of radiation induced mental retardation indicated that when the exposure is less than 0.5 Gy, the risk of severe mental retardation is similar to the unexposed population.

A recalculation estimates the threshold to be 0.57 Gy (CI 95% = 0.35 to 0.66 Gy)
Basic Science Plausibility of Why 1 Rad (.01 Gy) Does Not Double the Incidence of Mental Retardation

1. Teratogenesis is a threshold phenomenon.
2. In-utero exposure to ionizing radiation indicate that there is approximately a 30 point IQ loss per Gy during the most sensitive period of human brain development, indicating that severe mental retardation would not occur at 0.01 Gy, even if there were not a threshold effect.
3. At .01 Gy there are no observable histological effects in the developing brain that could account for severe CNS effects.
4. Neurobehavioral evaluations of animals exposed in-utero demonstrate a threshold for behavioral effects at the same dose as for other teratologic effects (>0.2 Gy).
The Importance of Dose-Rate, Fractionation and Protraction in Determining the Effect of Ionizing Radiation on the Developing Embryo

Exposure of pregnant women to diagnostic radiological procedures or other radiation exposures frequently:

- occur over a period of a few hours or days
- may involve the use of radionuclides
- may involve an elevation in background radiation from flying or a particular location
- may involve occupational exposures
The Indirect Effect of Irradiation on Embryonic Development

Does maternal radiation exposure to the mother without directly exposing the embryo result in an increased risk for congenital malformations?
### Fetal Growth and Mortality Following Maternal Irradiation on 9th Day

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Whole Body 400 rad</th>
<th>Partial Body 1,000 rad</th>
<th>Partial body 1400 rad</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Fetal deaths</td>
<td>13.2</td>
<td>22.1</td>
<td>20.4</td>
<td>39.0</td>
</tr>
<tr>
<td>Fetal wt. at term</td>
<td>4.70 g</td>
<td>4.84 g</td>
<td>4.57 g</td>
<td>3.86 g</td>
</tr>
<tr>
<td>Fetal length (cm.)</td>
<td>3.77</td>
<td>3.76</td>
<td>3.83</td>
<td>3.60</td>
</tr>
<tr>
<td>Malformations</td>
<td>1.8%</td>
<td>2.2%</td>
<td>1.4%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>4%</td>
<td>21%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>% Increase in maternal weight</td>
<td>31.3%</td>
<td>35.8%</td>
<td>17.9%</td>
<td>10.8%</td>
</tr>
</tbody>
</table>
Hujoel et al published a report in the 2004 April JAMA (291:1987-1993) indicating that dental X-rays averaging 0.4 mGy in pregnant women may be responsible for babies being born with low birth weight due to irradiation of the maternal thyroid and/or pituitary.

The risks of the vast majority of most diagnostic radiological procedures do not represent significant reproductive risks and do not warrant the interruption of wanted pregnancies.

Therapeutic radiation and radionuclide procedures do represent potential reproductive risks, however, each case has to be evaluated because frequently the risks are also not increased.

Evaluation of the allegation of radiation-induced malformations necessitates detailed analysis and cannot be performed superficially.

There is not always enough information to draw definitive conclusions about whether there is an increased risk for developmental or reproductive effects.
Health Physics Pregnancy Website, Ask the Expert (ATE)

In 2005 there were a total of 88,000 hits on the pregnancy website.

Based on the first two months of 2006, Dr. Roessler projects 154,000 hits on the pregnancy website.

In 2005, one thousand and nine (1009) individuals made direct contact with me personally.
Rare And Common Questions On The Pregnancy Ask The Experts Web Site

✓ Exposure of the abdomen or pelvis to diagnostic or therapeutic radiation during pregnancy.
✓ Exposure of the chest, head, neck, or extremities during pregnancy.
✓ Exposure to diagnostic or therapeutic ultrasound.
✓ Exposure to EMF (from power lines to MRI).
✓ Preconception radiation to the ovary or testes. Concern about genetic risks.
✓ Inadvertently being in a room when an x ray was taken.
✓ Being near a patient who received radiation therapy.
✓ Proximity to an individual who has been given a radionuclide for diagnostic or therapeutic purposes.
Rare And Common Questions On The Pregnancy Ask The Experts Web Site

- Laser hair removal
- Tanning salon exposure
- Use of an ultrasound tissue sonicator
- Hair dryer, computer, cell phone, microwave oven
- Airport scanner or x-ray baggage checker
- Flying in general; and flying during solar flares
- Living near a building with a microwave dish
- Computer screen exposure
- Taking of dental x rays by a dental assistant
Thank you so much. You are doing a priceless job by reaching out to people. God bless you.
Letter from Nancy Joerg, 2006

I sometimes think back to 1975 and wonder what my life would have been like if Jeanette had not been born. Not only would I not have my beautiful daughter Jeanette and no granddaughters in my life, I would have a lifetime of sadness and loss because I had followed the advice of three doctors who knew nothing about the risks of radiation.

That is what was tormenting me when I called you in 1975. On what scientific or medical data was the decision to terminate the pregnancy based? The incredibly important scientific and medical work of you and your colleagues has had a direct and personal impact on me and my family.

I can never thank you enough. The enormity of what you have contributed to me and my family and future generations of my family is beyond description.
Epilogue
Laboratory scientists who work with animals may never see their research benefit a single patient in their lifetime, although their research may be conceptually important. Yet our laboratory has been able to see that the lives of thousands of families have benefited from radiation embryological research studies.

Just as important, is the willingness and persistence to debate the controversial issues, attempt to resolve the controversies and then apply the best science to assist patients in turmoil, about the risks of radiation to their offspring.

As a physician, I must thank the thousands of patients who have contacted a stranger that they have never met to reveal the intimate details of their reproductive problems.

I have had the good fortune to experience a most memorable and exciting lifetime scientific journey with rewards that would be priceless to any physician; to be permitted the opportunity to change the lives of thousands of patients.
My wife Lillian and I look forward to greeting all the attendees at the reception.

The End