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No One Escapes Harm: The Essential Story of In-Utero Irradiation

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The title of this CNR paper, "No One Escapes Harm," was a speculation a few years ago. Today, there is some real-world human evidence to support it. The nature of this evidence, and some of its important implications with respect to accidental and deliberate nuclear pollution and to other sources of radiation exposure, are the subjects of this "story." The details are in Chapter 6 of CNR's next book (CNR 1993, *Radiation Consequences from Chernobyl and Comparable Exposures*).

1 * The Early Story about Severe Mental Retardation

There are some human data on "birth defects" following in-utero irradiation received during radiation-therapy of pregnant women for uterine cancer, and there are some human data following the use of high-dose radiation to induce abortions. These

types of data are at doses too high to be relevant to members of the general population.

By contrast, the Atomic-Bomb Survivor Study includes a sample of children who were irradiated in-utero by the bombings, at various gestational ages and at various dose-levels ranging from about 4 rads to over 150 rads. Thus, almost all analysts rely on the A-Bomb Study for evidence about "birth defects" induced by in-utero irradiation of humans. The A-Bomb Study is controlled by the Radiation Effects Research Foundation (RERF), which is jointly sponsored by the U.S. Department of Energy and the Japanese Ministry of Health. RERF is the successor to the ABCC (Atomic Bomb Casualty Commission).

In the summer and autumn of 1950, the ABCC undertook a search for radiation-induced abnormalities in Hiroshima children exposed to bomb radiation during the first 20 weeks of gestation. The investigator, George Plummer, reported as follows (1952, *Pediatrics* Vol.10: p.687, 692):

". . . 205 such children were discovered and studied in the summer and autumn of 1950 . . . Eleven were exposed within 1200 meters of the bomb hypocenter . . . Seven of these 11 children exposed within 1200 meters had microcephaly [small head circumference] with mental retardation. This diagnosis was not made on any of the 194 children exposed at greater distances." Since 1950, the radiation community has done additional studies of mental retardation involving un-utero survivors of both Hiroshima and Nagasaki.

The Operative Definition of "Severe Mental Retardation"

All the RERF reports use the same criteria to identify severe mental retardation: "Judgments of severe mental retardation were based on clinical impressions and not on an IQ score, if such existed. A child was deemed to be severely mentally retarded if he or she was `unable to perform simple calculations, to make simple conversation, to care for himself or herself, or if he or she was completely unmanageable or had been institutionalized'" (Otake 1987 in RERF Technical Report TR-16-87, p.4).

The 30 Unluckiest Children

The study-sample used by RERF in 1987 consists of a total of 1598 individuals: 513 were exposed to un-utero radiation by the bombs, and 1085 are non-exposed controls. In this study-sample, there are a total of 30 cases of severe mental retardation: 21 in the exposed groups and 9 in the non-exposed controls. The rate of severe retardation in the exposed is (21 cases / 513 children) = 0.041, while the rate in the non-exposed controls = (9 cases / 1085 children) = 0.008 --- 5-fold lower.

Readers may have noticed that the rate of 0.041 (or 4.1 percent) in the exposed

group means that 95.9% of the exposed study-sample did *escape* severe mental retardation. How is this consistent with our title? The "story" is just beginning.

The Effect of Gestational Period

RERF analysts have shown, and our independent analysis agrees, that the hazard varies with gestational age at time of irradiation. This was learned by dividing the study-sample unto four groups: Survivors who were irradiated 0-7 weeks after fertilization, 8-15 weeks, 16-25 weeks, and 26+ weeks. The four zero-dose groups were conceived at comparable times relative to the bombings, but they were not irradiated. A sample of the raw data is shown in the box below.

8-15 WEEK PERIOD		8-15 WEEK PERIOD	
Avg. Fetal Dose	Percent of Sample with Severe Mental Handicap	Avg. Fetal Dose	Number of Children and Mean School Score
0 rad	(2 / 257) = 0.78 %	0 rad	170 with score = 2.80
4 rads	(3 / 69) = 4.35 %	4 rads	60 with score = 2.79
23 rads	(4 / 50) = 8.00 %	24 rads	26 with score = 2.4
72 rads	(4 / 13) = 30.77 %	73 rads	5 with score = 1.6
146 rads	(6 / 8) = 75.00 %	129 rads	2 with score = 1.1

Numerators are the severely retarded cases; denominators are the total sample. Data are from Otake 1987, Table 2a. We show the unaltered, complete sample. (best=5)

Data are from Otake 1988, plus readings off Otake's We show the unaltered, complete sample for first-grade school-scores (scale 1-5; best=5)

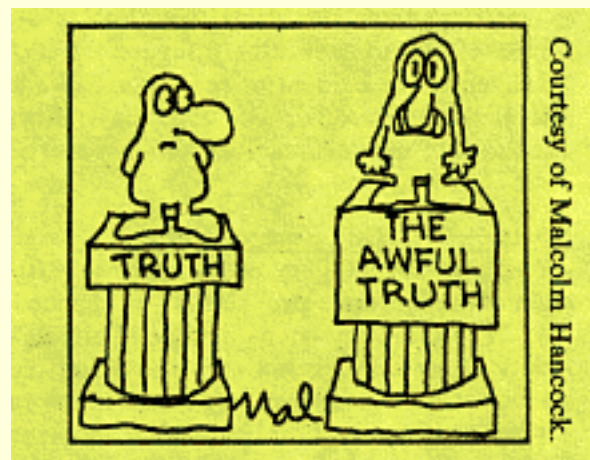
The data indicate that, if 100 rads are received in-utero during the 8-15 week period, almost 50 % of all liveborn children will be *severely* mentally retarded (see the criteria above). If the same dose is received during the 16-25 week gestational period, about 14 % (one out of every seven) of all liveborn children will be *severely* mentally retarded. The percent of each sample which is severely retarded rises as dose rises, in both of the vulnerable periods. The positive dose-response is strong evidence in favor of radiation as *causal*, so causation is not in dispute.

Within the data, there is no observable effect in the 0-7 week and 26+ week periods, but "no effect observed" is not the same as "no effect occurred." Analysts should be very cautious about drawing important conclusions from small numbers, which are subject to random fluctuations. How small are the numbers here? When the 30 severely retarded cases (exposed plus non-exposed) are subdivided by gestational age at irradiation, just *one* case falls into the 0-7 week period. (It occurred in the non-exposed group.)

2 * A Call for *more* of the "Story"

For over thirty years, the total "story" about mental retardation from un-utero irradiation rested on the severely retarded cases. It was possible to imagine that, aside from a few tragic cases, no one else suffered --- even at high doses.

In Gofman 1981 (*Radiation and Human Health*, p.735), we analyzed the data on the severely retarded cases, and we commented ". . . it would be sad indeed if our concern were only for those who were so seriously retarded [that they were unable] to perform simple calculations, to carry on a simple conversation, to care for himself' or [they had a record of] complete unmanageability or institutionalization at any time. If we do not concern ourselves with radiation until these effects are present, there will likely be no human beings left who can care for themselves."



Where Was the Rest of the Story?

"Obviously, we should really be concerned about grossly smaller effects than those looked for in the Hiroshima and Nagasaki infants exposed in-utero . . . It seems as though some more sophisticated study of mental development could have been made that would have given meaningful information about lesser degrees of mental retardation" (Gofman, 1981, p.735).

We predicted in the same chapter (p.708) that the severity of radiation-induced mental handicap and other birth defects would vary "from exceedingly mild effects to exceedingly severe effects, the degree being in some way related to the amount of radiation." We explained the difference between radiation-induced cancer which is a "stochastic effect" and radiation-induced loss of mental function, which we expected to be a "non-stochastic effect."

Non-Stochastic Effects --- No One Escapes Harm

"Certain effects fall into the category of 'all or none' effects, in which a given amount of radiation confers a probability, or chance, of developing the effect. These are known as stochastic effects of ionizing radiation. The severity of the effect is not at issue, rather the probability that the effect will occur at all is what we may relate to the radiation dose. Two outstanding examples of stochastic effects of radiation are cancer and leukemia . . . The radiation increases the probability of developing the cancer, but does not influence the severity of its clinical manifestations" (Gofman 1981, p.708).

Non-stochastic in-utero effects are effects whose severity in a single fetus rises with dose. When radiation acts non-stochastically on the central nervous system of fetuses in-utero, every fetus is injured according to the particular dose. None completely escapes injury. However, equal in-utero doses do not result in equal mental function in liveborn children because radiation is acting upon a future function whose natural, pre-radiation levels vary in any general population from fetus to fetus.

3 * More of the Story Is Released

Does the degree of radiation-induced mental handicap in an individual who was irradiated in-utero depend on the amount of the individual's radiation dose? The question can not be addressed by the thirty cases of severe mental retardation because the data cover only *one* degree of mental handicap.

In 1986 and 1988, RERF released data which were collected decades earlier. These "exhumed" data cover "IQ" tests of intelligence at ages 10-11 years, and records of school performance in grades 1-4, in samples of in-utero irradiated A-bomb survivors (Schull 1986 = RERF TR-7-86, and Otake 1988 = RERF TR-2-88). The radiation effect is non-stochastic. The exhumed evidence leads Schull et al to conclude (Schull 1990 in *Neurotoxicology and Teratology* Vol.12: p.257):

"These data suggest a continuum of effects on the developing brain of exposure to ionizing radiation; indeed, the downwards shift seen in the distribution of IQ scores with increasing exposure predicts reasonably well the increase in severe mental retardation actually observed. This suggests, in turn, that the impact of exposure to ionizing radiation will be related to where in the normal continuum of cortical function an individual would have resided if unexposed."

Elsewhere, the RERF analysts report that both effects (reduced school scores and reduced IQ scores) seem to be proportional to fetal radiation dose --- the linear dose-

response, with no suggestion of a threshold. Also, they report no detectable effects in the 0-7 week and 26+ week periods of gestation.

An Independent Analysis Performed

Do we concur that the data support their conclusions? Both sets of data are independent!y analyzed in CNR 1993, Chapter 6. We do agree. One sample of the data is provided in the right side of the above so that readers can see how the newer data differ from the data for severe mental retardation. Instead of showing how the frequency of a *single* level of mental function (severe retardation) changes with fetal radiation dose, the school-performance data show how the average level of mental function *varies* with fetal radiation dose. Hiroshima school scores combine achievement-data for language, social studies, arithmetic, science, music, drawing plus handicrafts, and gymnastics.

The exhumed data are the human data which happen to exist in this world on degrees of brain damage from in-utero irradiation. No one asserts that there is a one-to-one relationship between school performance and either structural or biochemical evaluation of brain function. No such assertion is made for IQ scores either. However, we share with RERF the opinion that each set of scores is *one* meaningful way to assess functional damage in the CNS (central nervous system).

Severely Retarded Cases: One Extreme of a Continuum

The school-score data include some of the 30 severely retarded cases. Thirteen attempted the first grade; only one made it into the fourth grade. Otake et al perform extensive statistical testing on the effect of excluding these cases from school-score analysis (Otake 1988, Table 7a), and these analysts find that a radiation effect is present with and without these cases. This supports the presumption that the severe cases of mental retardation are an integral part of the non-stochastic effect of un-utero irradiation upon mental function, and should be *included* in the analyses. The inclusion does not appear to be in dispute.

4 * Warning about the First Week of Pregnancy

Reports that the A-bomb study-sample shows no radiation-induced mental handicap among embryos irradiated during the first seven weeks of development may lead some women and some physicians to become more careless about irradiation during the first week of pregnancy.

Findings from the A-Bomb Study would be an exceedingly poor reason to become casual. In the study, there were a total of 85 bomb-exposed survivors who were between 0-

7 weeks of their development at the time of the bombing. If their conception occurred with equal frequency in each week, then the entire study consists of only (85 / 7), or 12 children exposed during the first week of development. On the basis of such a small sample, it would be reckless indeed to become careless about avoidable exposures and thus to gamble with the future of any family.

When radiation exposure occurs during the second or third day after fertilization, there are only about 2 to 16 cells present in the developing embryo. Additional cell-divisions occur during days 4-6, when the cells of the developing embryo (now called a blastocyst) are arranged in a single layer which forms a hollow ball. If, during the first week, radiation induces a chromosome aberration in one of the cells, what will happen?

The evidence stares at us, from the mosaic cases of birth defects in the Clinical Atlas of Human Chromosomes (Grouchy+Turleau 1984), that embryos at these early stages do *not* always discard a cell with a chromosomal aberration. A mosaic case is a child with most cells chromosomally normal but a fraction chromosomally abnormal. The known mosaics prove that a single aberrant cell, probably injured before an embryo has even 100 total cells, can develop into a very large clone of cells with the same chromosomal defect. These known mosaics also prove that the health consequences can be devastating --- and they almost always include mental retardation (CNR 1993, Chapter 5).

An Emphatic Warning

CNR emphatically warns against unnecessary radiation exposure at *any* stage of pregnancy. Quite aside from the menace of reduced mental function, there is a radiation-induced stochastic risk of both childhood cancer (including leukemia) and adult cancer--- details in CNR 1990 [Radiation-Induced Cancer](#). Moreover, there are good reasons to think that in-utero irradiation can permanently injure organs *additional* to the brain. These reasons are thoroughly presented in CNR 1993.

5 * "The Essential Story of In-Utero Irradiation"

The evidence from the school scores and the IQ scores indicates that, during the combined 8-25 week period of gestation, **(a)** the mental function of each fetus is injured in proportion to radiation dose (the linear dose-response), **(b)** severe retardation induced by radiation is part of a continuum of injury, and **(c)** there is no threshold-dose which must be reached before radiation starts inflicting permanent CNS injury.

Injury is a *certAinty* rather than a *risk* during the 8-25 week period. No one who is thus irradiated in-utero completely escapes some loss of mental function. These are

reasonable conclusions from the only existing human evidence, but of course, they might someday be modified by additional human evidence.

How Many People Are Mentally Retarded?

We are going to assume that mental function in a general population has a normal distribution or bell-shaped curve, like [Figure-A](#). Levels of mental function are shown in Standard Scores along the horizontal axis and the height of the curve indicates the relative frequency. The crest of the curve represents the most frequent or typical level of mental function, at Std.Score = 0. The curve is exceedingly low at Std.Score 4+, and also exceedingly low at Std.Score -4, because only a very small percent of a general population has either such brilliant or such poor mental function.

In any curve like [Figure-A](#), the Std.Scores of 50 % of the population lie to the *left* of the crest ("below average"), scores of 15.87 % lie at or below the Std.Score -1, and scores of 2.28 % lie at or below Std.Score -2.

Either school scores or IQ scores can be converted to Standard Scores (as shown in CNR 1993, Chapter 6).

It is self-evident that mental function is a continuum of levels, and that any score dividing "mental retardation" from "normal" is an arbitrary choice. Like Schull et al (1990, p.255), we use a Std.Score of -2 as the dividing line. Individuals with Std.Scores of -2 or lower "qualify" as mentally retarded. And so [Figure-A](#) shows a heavy vertical line at -2. By definition, then, 2.28 % of a general population is mentally retarded, and a smaller percent is *severely* mentally retarded.

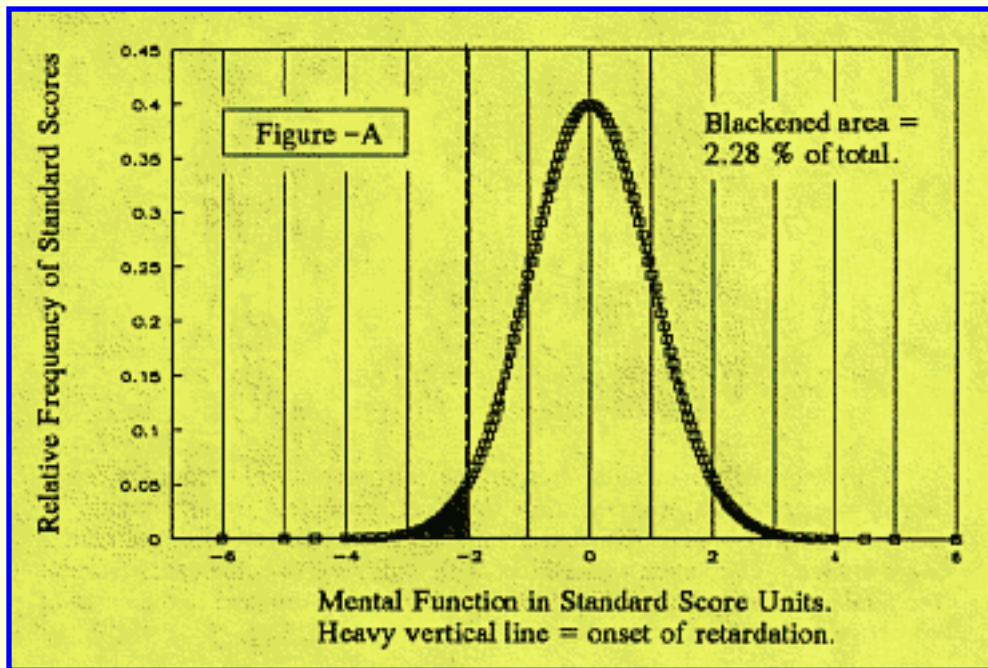


Figure - A

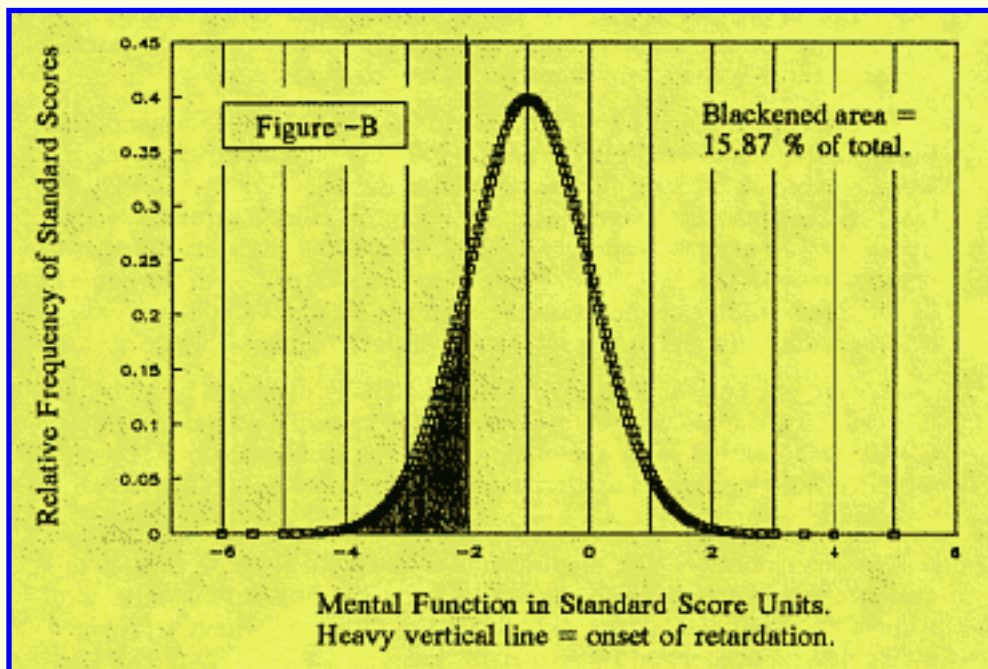


Figure - B

Pushing the Entire Curve to the Left by In-Utero irradiation

The data shown in the box for school scores illustrates the finding that the average mental function in the non-irradiated group was better than the average in any of the

irradiated groups, and that average performance deteriorated as radiation dose increased.

Let us consider one irradiated group at a time: The 24-rad group. Without in-utero irradiation, the average score would have been 2.80, like the non-exposed group. The average score is calculated from *all* the scores, including the ones which are way below average and way above average (near the extremes of the bell-shaped curve), and all the scores in between.

Exposure to 24 rads in-utero lowered *all* the potential scores. Thus, the single average score found in the study is 2.4 instead of 2.80. And in the same way, *all* the potential scores in the 73-rad group were reduced by the in-utero exposure, so that the single average score found in the study is 1.6 instead of 2.80. And an even greater shift to a lower average is found in the 129-rad group.

In-utero irradiation is pushing the entire curve of mental function in an irradiated group to the left (compare [Figure-A](#) with [Figure-B](#)). But the absolute level of mental performance which we regard as "retarded" is independent of radiation. So the heavy vertical line which denotes the onset of mental retardation does *not* move to the left when the whole curve shifts leftward. If radiation moves the curve to the left by -1 Std.Score, as shown in Figure-B, the fraction of the irradiated group which lies at or below the heavy vertical line becomes 15.87 % instead of 2.28.

The Dimming of Intelligence

Everyone is more familiar with IQ scores than Standard Scores, so we will describe the essential story of in-utero irradiation in terms of IQ scores. A score of 100 is considered average. In the absence of evidence to the contrary, it is reasonable to assume that the reduction of intelligence is the same per rad of in-utero irradiation at all underlying (pre-injury) levels of potential intelligence.

If someone is destined, biologically, to have an IQ of 130 on a particular test, and then is shifted due to in-utero radiation by 15 points to an absolute IQ score of 115, then someone else who is destined to have an IQ of 100 will be shifted also by this same 15 points to an absolute IQ score of 85 . . . and 85 will be shifted to 70 . . . and 70 to 55.

In-utero irradiation during the vulnerable period causes the brilliant to become less brilliant, the average to become "below average," and the retarded to become more retarded. And by pushing more people over the heavy vertical line into the realms of mental retardation and severe retardation, such exposure automatically increases the *percent* of a population-sample which is retarded and severely retarded.

6 * Brain-Injury versus Elevated Cancer-Risk

There are some interesting differences between the issues of brain-injury and cancer-risk. With respect to cancer, in-utero irradiation confers an elevated risk of an often fatal disease, which may not occur until late in life. With respect to brain-injury, in-utero irradiation during the 8-25 week period confers a certainty of reduced mental function, an effect which is lifelong. We have shown elsewhere ([CNR 1990](#)) that there is no threshold-dose or safe-dose of radiation with respect to cancer. The risk is approximately proportional to the size of the dose, right down to zero-dose. What about brain-injury?

Some Astonishing Suggestions in Medical Journals and Reports

Some of the RERF analysts (echoed almost verbatim by the BEIR Committee) are suggesting far and wide that high threshold-doses --- in the regions of 10 to 70 rads--- may exist for radiation-induction of severe mental retardation. For example, see Otake et al 1987, p.2, and Schull et al 1990, p.255, 257; and Yamazaki and Schull in *J. Amer. Med. Assn.*, August 1, 1990, p.605, 608, and BEIR 1990 pp.357-58.

Nevermind that, in the very same articles and reports, they present the newer evidence against any threshold-dose. Nevermind that they themselves appear to accept the



premise that *severe* mental retardation is just the extreme end of the continuum of mental function tested by school and IQ scores. Nonetheless, they make elaborate efforts with alternate statistical models to find thresholds within the tiny group of 30 severely retarded cases.

They especially focus attention on the retroactively altered input in which average doses, number of participants, grouping of participants, and percent with severe retardation have all been changed after the results were known. They even experiment with dropping selected cases from the total of 30 (details in CNR 1993). What ever happened to the [rules of objective research](#)?

A Serious Issue for Humanity

Our mind boggles at the very idea of scientists searching so creatively for thresholds

in the meagre supply of cases (19 cases in the 8-15 week period, 6 cases in the 16-25 week period).

The strongest claims about a threshold involve the 16-25 week period. For instance, Schull et al (1990, p.255, 257) say that "A threshold does seem to exist; no increase in cases is seen at doses of less than 0.5 Gy [50 rads] . . . There is still disagreement, however, whether a threshold does truly exist." Yamazaki and Schull (1990, p.608) tell the vast international readership of JAMA that the evidence suggests a threshold in the range of 21 to 70 rads. They characterize the evidence as "the seemingly clear evidence of a threshold at this later stage of development."

We are just amazed that anyone would actually discuss a possible threshold in a sample whose dose-response is based on a total of *six cases* (with only 3 cases above 10 rads). The inadequate size of the sample is not emphasized in these two peer-reviewed papers, however.

It is our opinion that on a serious issue for humanity --- and this is a serious one indeed --- the suggestion of a threshold based upon such thin evidence should simply be dismissed. This would be our opinion even without the positive evidence *against* any threshold which is provided by the data on school and IQ scores.

What about a Fetal Dose of a Half Rad?

The absence of any threshold-dose for brain-injury has different implications than its absence for cancer. For instance, an in-utero dose of a half rad would be of concern with respect to cancer-induction. The available evidence suggests 0.5 rad in-utero can increase the risk of childhood cancer or leukemia by about 35 % (CNR 1993, Chapter 4). By contrast, the evidence from IQ scores suggests a reduction of about one-quarter point per fetal rad, or one-eighth point for 0.5 rad during the 8-25 week period (not applicable to the first week; see [Part 4](#)).

So with respect to brain-injury, a half-rad during the 8-25 week period is not the issue. The issue is claims that no injury may occur unless the fetus receives 10, 20, 50, or 70 rads. We shall see the real-world relevance of such doses in Part 7.

7 * Some Real-World Implications of the Newer Data

People often assume that doses from nuclear pollution will be low. The Chernobyl accident has already shown that such an assumption is mistaken. Some 24,000 residents of Pripyat received average doses estimated at 40 rads each (DOE 1987). In addition, about 600,000 soldiers and other "clean-up: workers may have received average doses like 25

rads or more. These are not low doses. And if the winds and rains had been different during that accident, over 2 million people in the city of Kiev might be dealing with average doses like 10 to 25 rads, too. (For comparison, we remind readers that the background dose from natural radiation is about 0.1 rad whole-body dose per year at sea level, when the lung-dose from radon is omitted.)

Make no mistake. The doses from nuclear accidents come from radio-nuclides. Although most nuclides --- with some famous exceptions --- decay in a few hours, a few days, or a few months, they are nuclear *pollutants* during their short and menacing existence.

Suddenly the speculations and quasi-claims about thresholds for severe retardation, at fetal doses like 10 to 70 rads, take on real-world meaning in terms of the future of nuclear power. We repeat, however: The evidence does not support threshold-suggestions.

One section of the radiation community goes beyond proposing threshold-doses. The proponents of "hormesis" suggest that ionizing radiation improves the general health. The leading hormetic is Thomas Luckey, who proposes in his 1991 book (p.236): "The theme of future research and practice in radiation safety should be supplementation of background radiation for health." Luckey worries about "radiation deficiency syndrome," and suggests that "optimum exposures" appear to be about 10 rads per year (p.229, 233).

Hormesis is a routine topic in such radiation journals as *Health Physics*. A notable example was the hormetic suggestion from J. A. Izatt of the Scottish Universities Research and Reactor Centre that doses up to 50 rads may protect people against cancer (Izatt 1991; Gofman 1991).

Mental Handicap from Nuclear Pollution (or from Hormetic Dose)

Again we will use the approximation that 2.28 % of a general population is mentally retarded ([Part 5](#)). This means that every mother has a 2.28 % chance (about 1 in 50) that she will give birth to a mentally retarded child. Our work in CNR 1993 makes it possible for anyone to obtain a "ballpark" estimate of how the percent (and thus a mother's individual risk) rises with fetal irradiation during the 8-25 week period.

Some examples follow. They use dose which are already in the tabulations of CNR 1993. The work derives from the exhumed data on school and IQ scores.

Average Fetal Dose	New Percent / Old Percent	Percent Increase in Rate of Mental Retardation
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4 rads	(2.63 / 2.28) = 1.15	15 % increase
10 rads	(3.13 / 2.28) = 1.37	37 % increase (at the optimum "hormetic" dose)
15.4 rads	(3.77 / 2.28) = 1.65	65 % increase
23.0 rads	(4.75 / 2.28) = 2.08	2.08-fold increase
30.8 rads	(6.00 / 2.28) = 2.63	2.63-fold increase
46.2 rads	(9.12 / 2.28) = 4.00	4-fold increase
61.5 rads	(13.36 / 2.28) = 5.86	5.86-fold increase
72.0 rads	(16.85 / 2.28) = 7.39	7.39-fold increase

The tabulation speaks chillingly for itself. Surely there is a moral issue as well as a scientific issue here. Even the lowest entry --- a 15 % increase in the number of babies born retarded among the exposed mothers --- is not acceptable. Yet the tabulation covers only the increase in the frequency of full-blown mental retardation. Full-blown mental retardation is certainly not the only issue.

The really *huge* aggregate injury arises because evidence and logic combine to indicate that *everyone* who receives extra in-utero radiation during the 8-25 week period loses some mental function, in proportion to the extra dose. Those who are *not* pushed over the arbitrary dividing line into full-blown mental retardation are injured too. At each dose-level, those who were destined to be mentally retarded anyway become more retarded, those who were destined for average function become below-average, and those who were destined for brilliant mental function become less brilliant.

In national and international policies toward ionizing radiation, we are dealing with a toxic agent which will lower the mental function of every developing infant who gets in its way.

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