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IRB

A Review of Human Subjects Research

Volume 4 Number 1 January 1982

Evaluating Risk from Radiation for Research Subjects by Naomi Alazraki 1

The Ethics of Research involving Radiation by Robert M. Veatch 3

Do Researchers and Subjects Have a Fiduciary Relationship? by Angela R. Holder 6

More on Making Consent Forms More Readable by T.M. Grundner with comments by Robert J. Levine and Alan Meisel 8

LETTERS 10

UPDATE 11

ANNOTATIONS 12

Evaluating Risk from Radiation for Research Subjects by Naomi Alazraki

IRBs are called upon to review a wide variety of research subject matter. Radiation exposure represents one very specialized area that IRBs must evaluate in approximately 15%* of research projects at a university with a medical school. Although those medical centers also have radiation safety and medical radioisotope committees that evaluate the radiation risks of research, the IRB members need some additional background in order to evaluate competently the risk-benefit ratio of a given research project.

The general public regards the phenomenon of radiation as a mystery, which only a few experts understand. Yet there is still a huge amount even the experts don't know. For example, there is "expert dissensus" (rather than consensus) in our efforts to evolve guidelines for basic radiation protection. Controversy surrounds even the most fundamental concepts upon which radiation protection measures depend. Is there a threshold for radiation below which no harmful effect occurs? We do not know. The National Council for Radiation Protection has decided to assume that there is no such threshold, i.e., that there is no absolutely safe radiation dose, except zero.

Yet life on earth is bathed in naturally occurring radiation. We are constantly exposed to radiation from various sources in our environment, including terrestrial radiation, cosmic radiation, and radioactive elements present in our bodies.[1] Approximately 3% of body potassium is in the form of potassium 40, which is radioactive. At sea level, each individual gets an average radiation dose of approximately 100 millirem (mrem) per year.

One of the major problems in discussing radiation is the prevalence of "radioactive ignorance." Athough it is approximately 36 years after Hiroshima and approximately 86 years after the discovery of x-radiation by Roentgen, most people don't know what radiation is. The units of measurement—curie, rad, and rem—are meaningless terms. This form of ignorance, as has been pointed out in a *Washington Post* editorial, is risky. Thus, a major educational effort for both lay and professional groups on what radiation is all about is definitely needed.

The electromagnetic spectrum encompasses categories of radiation of varying wave lengths and energies, ranging from cosmic radiations (shortest wave length and highest energy) to radiowaves (longest wave length and lowest energy). Of intermediate wave lengths and energies on the electromagnetic spectrum, other forms of radiation include gamma and x-radiation, ultraviolet radiation, visible light, infrared radiation, and microwaves. All radiation forms are characterized by an exchange of energy upon interaction with some material, for example, body tissues. Gamma radiation and x-radiation are of great importance in diagnostic medicine. In addition to x- and gamma radiation, in therapeutic medicine we are also interested in other particulate radiation forms, including alpha and beta radiation.

Over the past 50 years, several national and international conferences have been held to establish uniformity in measuring radiation.[2] The "quantity of radiation" has been called "exposure"; quantification of radiation energy deposition has been called "absorbed dose." Absorbed dose refers to the deposition of energy from the radiation source. For purposes of evaluating human exposures, measurements of absorbed dose are most relevant. The units of radiation dose are the rad, the radiation absorbed dose unit, and the rem, the Roentgen equivalent man unit. The Roentgen, the earliest unit of radiation measurement, represents the absorption of energy in air. It is used only for x-rays and gamma rays. The rad is more precisely defined as the absorption of 100 ergs of energy per gram of material. The rem is the same as the rad, except that it takes into account the efficiency of the radiation in producing damage, in addition to the amount of energy absorbed in the material.

For x-rays, gamma rays, and beta rays, the efficiency of radiation in producing damage is approximately the

*Based on data from the records of the IRB at the University of California, San Diego.

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same and has a unit value of one. Thus, for x-rays, gamma rays, and beta particles, the rem and rad are equivalent and are used interchangeably. Alpha particles and neutrons, however, have a very different efficiency in producing damage (quality factor), which is much higher than the unit one of x-rays, gamma rays, or beta rays. The quality factor for neutrons is two to ten times the damage caused by the same energy exchange from x-, gamma, or beta, and the quality factor for alpha particles is a factor of ten to twenty times that of x-, gamma, or beta rays. The efficiency of different radiation forms in producing damage, the quality factor, or the LET (Linear Energy Transfer factor) depends upon the density of ion pairs (pairs of free negative electrons and positive-charged atoms) produced from the radiation interaction with tissue. More sparsely ionizing radiation which results in lightly concentrated numbers of ion pairs, produces less tissue damage.

The average annual natural background radiation in the United States under the most favorable environmental conditions is approximately 80 to 100 mrem per year. The sources of this radiation are approximately one-third from cosmic radiation, one-third from terrestrial radiation including radiation from potassium-40, uranium-238, and thorium 232, and one-third from radionuclides present in the body, including potassium-40, carbon-14, rubidium-87, and tritium. In addition, inhaled radionuclides, for example, radon-222 and its daughters, expose the lungs to an additional 100 mrem per year. Thus, gonadal exposures may be approximately 80-100 mrem per year, but lung exposures, in some geographic regions,may be considerably higher because of the inhaled radionuclides, 180-200 mrem per year.[3]

Depending upon the location, terrestrial exposures vary considerably. For example, although the average best case exposure from terrestrial radiation in the United States is approximately 30 mrem per year, in Brazil there are areas where the terrestrial exposures are estimated to be 500 to 1000 mrem per year, and other areas in Brazil where the exposures are even higher, 1600 to 12,000 mrem per year. In some regions of India, exposures are measured at 1300 mrem per year. In France, exposures are measured at 180-350 mrem per year from terrestrial sources.[3]

Another variable that affects radiation exposure is altitude. For example, regions at higher altitude get more background radiation from cosmic sources than locations at sea level. La Paz, Bolivia, at an altitude of 3,630 meters, shows 270 mrem per year of background cosmic radiation level, while at sea level, exposures are approximately 30 mrem per year.

Within the United States, cosmic radiation measured in Florida is approximately 30 mrem per year; in Denver, the exposures are in the range of 70 mrem per year. Radiation within the ground measured in Dallas is approximately 30 mrem per year, while in Denver, measurements range up to 130 mrem per year. Radiation from building materials is estimated to be approximately 55 to 60 mrem per year. Natural radiation from internal sources reflecting radioactive materials in food, water and air is in the neighborhood of 25 mrem per year.

Radiation from medical procedures is an additional source of radiation exposure to the general public. This is estimated for the whole population to average approximately 50 to 70 mrem per person per year. The average annual genetically significant dose (GSD) from diagnostic medical studies is estimated at 55 mrem per year in the United States. Dental exams contribute an additional 0.15 mrem per year; and radiation therapy, when averaged over the general population, contributes approximately 10 mrem per year per person. Occupational irradiation contributes to public exposure and averages about 1% of the natural radiation exposures.

Air travel is another source of radiation exposure to the public. At 30,000 feet, polar flights expose passengers to 1 mrem per hour, while mid-latitude flights expose passengers to 0.5 mrem per hour.

The risks from low-level radiation (1 to 25 rads) include cancer and genetic problems.[4] Cancer is a late effect of radiation, typically occurring anywhere from ten to twenty-five years after the irradiation, except for leukemia, which characteristically occurs somewhat earlier, between two to fifteen years after the irradiation. This risk of fatal cancer is estimated at one extra death in 10,000 persons irradiated by 1 rem. The leukemia risk is estimated at one extra death in 50,000 persons getting 1 rem. Of 10,000 persons, 1700 will normally die from cancer; thus the cumulative expected death rate plus the imposition from 1 rem of radiation is 1701 deaths per 10,000 persons. This estimate of 1 death per 10,000 or per 50,000 from 1 rem of radiation is arrived at indirectly. Based on data of cancer incidence and death rates in populations that have been exposed to high doses of radiation, for example, Hiroshima, atom-bomb test accidents, and other radiation accidents, mathematical functions can be fitted to the plotted curves of the absorbed do versus cancer incidence. Those curve take the form of linear quadratics, although pure quadratics have also been applied. Extrapolating down to low-dose exposures of 1 to 25 rads from the high dose data, an estimate of the death rate based on 1 rem of exposure can be calculated.

Whether or not 1 rem of exposure actually results in that additional incidence of cancer has not been documented definitely. It is difficult to determine whether 1 rem of radiation results in cancer because biological damage resulting from radiation does not produce unique diseases. Ionizing radiation produces effects indistinguishable from spontaneous disease or those of chemical mutagens or carcinogens.

Radiation effects on the fetus are another area of concern. Malformation and defects of organs, particularly in those organs developing at the time of irradiation, have been identified. Cancer developing early in childhood has been related to radiation exposure *in utero*. The risk is estimated to be about 25 cases per year of leukemia and 25 cases per year of solid cancer in or million children irradiated by 1 rem radiation. This risk represents approximately five to 10 times the apparent adult risk. Without doubt the fetus is more sensitive than fully developed humans to the effects of radiation.

Genetic effects from low-level radiation become manifest in subsequent generations.[4] Thus, genetic effects are probably more difficult to establish than cancer. It is estimated that 1 rem of radiation results in 25 defective children per million of the next generation. Normally, 100,000 per million children are born with a genetic defect.

In order to provide the public with some guidelines for radiation protection, acknowledging that some radiation exposure may be unavoidable for occupational purposes, the National Council on Radiation Protection has issued what are called "permissible dose standards."[4] These permissible dose standards have been lowered progressively over the years; the last permissible dose standard issued in 1956 was 5 rems per year for an occupational worker. Five rems in any one year refers to combined whole body occupational exposure and represents a suggested annual limit. Additional dos limiting recommendations are spec ified for individual areas of the body;

for example, the skin has a maximum permissible dose limit of 15 rem in any one year; for the hands it is 75 rems in any one year; the forearms—30 rems; for other organs and tissues, it is 15 rems. Pregnant women have a maximum permissible dose limit of 0.5 rem for the gestation, and for the general public it is 0.5 rem yearly.

In evaluating risk from radiation exposure, we should also take into account the type of exposure, i.e., whole body versus individual organs. But, how can we comprehensibly express the risk from radiation for subjects participating in research projects? One of several suggested approaches to presenting the risk to an individual is to compare the calculated risk of death from radiation with other risk levels occurring in more familiar contexts. For example, a one-in-a-million risk of death has been attributed to[5]:

400 miles by air,
60 miles by car,
¾ of a cigarette,
1½ minutes of rock climbing,
1½ weeks of typical factory work,
20 minutes of being a man aged 60,
drinking half a liter of wine,
spending one hour in a coma.

Another way of expressing the risk in more familiar contexts would be by comparison to the incidences of death per million per year in various occupations. For example, in construction there are 717 deaths per million per year; in mining and quarrying there are 994 deaths per million per year; in agriculture there are 613 deaths per million per year.[5]

The risk from radiation can also be expressed as a comparison with the quantities of radiation exposure which the subject gets from naturally occurring sources. That is, the research subject could be informed that participation in the study will result in a radiation exposure that is approximately twenty times the natural background which he or she gets in one year. Or, a comparison can be presented between the exposure dose from the research and the maximum permissible exposures as suggested by the National Council on Radiation Protection for occupational workers, or hospital workers, in a year. For example, subjects could be told that the radiation exposure from participating in the project is approximately 50% of the maximum permissible exposure for a hospital worker for a year.

Another presentation to a subject might be the comparison with the dose received from common medical x-ray procedures. For example, the subjects could be told that the radiation that they would receive from participating in the research project is approximately equivalent to the radiation they would receive from two chest x-rays. This approach has been criticized as being coercive, since many people consider a chest x-ray harmless.

The real problem is that these expressions do not inform the subject of the real risks of radiation; but then again, the real risk is not truly known. Perhaps, in addition to a comparison presented in one of the forms illustrated above, a sentence should be added to consent forms stating that, although radiation is a fact of our environment, the true risk of low levels of radiation is not known precisely.

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The Ethics of Research Involving Radiation

by Robert M. Veatch

In some ways research protocols involving exposure of subjects to radiation present the same problems for IRB members as those encountered in other research proposals. Risks must be compared with benefits to the subject and others; subjects must be reasonably informed; the usual rights of the subject must be protected; and subjects must be selected equitably. At a practical level, however, proposals involving potential radiation risk raise unique, perplexing issues. Radiation exposure places directly at risk, in addition to consenting subjects, other human beings—bystanders, lab personnel; and even future generations. Not only are potential effects not known, but most IRB members have very little understanding of the mechanisms of action of radiation and even the basic concepts underlying its effects. Because the field of radiation itself is politically and socially controversial, IRB members necessarily find themselves participating in a larger social debate.

Risk Assessment

One major problem facing IRBs is risk assessment. It can honestly be said of most research involving radiation that there is no conclusive evidence that exposures called for in the protocol are harmful. Still the overwhelming consensus is that some risk, however small, remains and must be considered. Under the older DHEW regulations the decision about whether any risk was present made a significant difference to IRBs (because review was triggered by federal regulations only when risk was present). Current DHHS regulations, however, make no such distinction. IRB review is called for in protocols involving radiation exposure whether or not subjects are deemed to be at risk. While certain categories of research are exempt from review and other categories can be given expedited review, any research governed by DHHS regulations involving the exposure of subjects to radiation, no matter how little, certainly does not fall into either of those classes.

In assessing risks of harm and comparing them to potential benefits IRBs face several problems. First, the IRB is normally considering an extremely small probability of harms, many of which, however, if they occur, will be very substantial. Moreover, the IRB is often working with what is at best a rough estimate, often based on an extrapolation from exposures in very different settings at much higher radiation levels. There is theoretical disagreement over the legitimacy of the extrapolation. In such a situation substantial disagreement over the degree of the risk is expected.

Because of the highly technical nature of the data, IRBs will probably have to rely on the testimony of experts, often one or at most two IRB members or consultants. Yet even the experts differ greatly in deciding what the risk level is, whether it is legitimate

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