Following are five examples of some of the studies developed to investigate these important issues:

1. *Relation of Human and Animal Effects of Bone-Seeking Radionuclides.* The radium-dial-painters study provided a quantitative epidemiological data base for humans exposed to, and carrying gradedbody burdens of, the natural bone-seeking radionuclide radium-226. By obtaining comparable data for radium-226 in a long-lived animal species (dog), a radiation effects ratio (RER) for radium-226 can becalculated as follows:

$$\text{RER} = \frac{^{226}\text{Ra-effects (man)}}{^{226}\text{Ra-effects (dog)}} .$$

Assuming the same interspecies relation holds true for other bone-seeking radionuclides, such as plutonium-239, and using the following expression, the data from the dog studies can be used to estimate the potential hazards from these radionuclides to humans:

$$^{239}\text{Pu-effects (man)} = \text{RER} \times {}^{239}\text{Pu-effects (dog)}.$$

These studies provide vital data for predicting human risks of radiogenic bone cancer from important man-made radionuclides, which are already present in our biosphere. The data derived from these experiments have demonstrated that the present guidelines are scientifically defensible for radiation exposure by workers and the general population.

2. *Determination of Dose-Rate Effects of External Sources on Radiation Risks.* Most of the early data on radiation risk estimation were derived from studies of people involved in diagnostic and therapeutic medical X-ray exposure. Although there was strong evidence that low dose rates or protracted radiation exposure was less harmful than high-dose-rate single exposures, no systematic assessment and measurement of the magnitude of the dose-rate effectiveness factors had been made for either heritable or genetic effects or for delayed toxicological effects and cancer induction. OHER-supported studies showed that genetically different mouse strains responded similarly to the varying dose rates. These findings prompted studies in which gamma and neutron irradiation would be compared as a function of dose rate.

3. *Potential Health Risks in Nuclear Research, Weapons Programs, and Power Production.* Multispecies animal experiments were initiated in several laboratories to validate the acceptability of standards and guidelines for radionuclides produced by nuclear fission. Priority among the fission products was established based on their relative fission yields, their half-lives, and their propensity, due to the metabolic characteristics of the exposed animal, to be deposited and retained in specific organs of the body. These studies showed that radiation responses could be altered by different routes of exposure, by differences in localized dose and dose rate, and by other variables such as the chemical characteristics of the radioactive compound and the type of radiation produced by its decay products. Development of nuclear power reactors led to expansion of the OHER effort to include evaluation of important radionuclides encountered at each significant stage of the nuclear fuel cycle, from uranium mining through storage and disposal of nuclear waste.

A major fraction of OHER's research has involved animal exposures by inhalation, one of the most significant routes of exposure for products of the fission process, especially plutonium. These animal studies were instrumental in developing models describing the distribution and fate of various soluble and insoluble aerosols in the lungs, including movement to remote critical organs at different times after exposure.

4. *Determination of the Genetic Effects of Radiation in Mice.* Until 1947 estimates of the genetic hazards of radiation were based entirely upon the data derived from the fruit fly (Drosophila). Because it was essential to obtain information on a mammalian species to provide a closer correlation with man and because a genetic study requires data over many generations, a long-term, very large-scale study of radiation-induced genetic effects in mice was begun. Pending definitive results from the epidemiological studies discussed earlier, the results of the mouse studies still provide the basis for our estimation of genetic risk to humans.

The large mouse study required the development of new techniques and methods for detecting radiation-induced mutation. One of these, the specific locus method, has found wide application in determining how mutation rate varies with changes in radiological and biological parameters such as dose rate, dose fractionation, total dose, radiation quality, sex, stage in the cell life cycle, and age at exposure. The specific locus method is also being applied to the study of the processes by which some chemicals cause mutations, called chemical mutagenesis, and to the possible effects of energy-related and other environmental pollutants.

It was found that the mouse was considerably more sensitive than the fruit fly to the induction of mutations by large, rapidly administered (acute) doses of radiation. This result was an important factor in the subsequent lowering of recommended permissible levels for human exposure to radiation. Additionally, it was discovered that the level of mutations produced in male and female mice was different over a range of dose rates. In males this was manifested by a one-third reduction in mutation rate when the same dose was absorbed at a low, as compared with a high,