RESEARCH PROGRAMS OF THE ATOMIC ENERGY COMMISSION'S DIVISION OF BIOLOGY AND MEDICINE RELEVANT TO PROBLEMS OF HEALTH AND POLLUTION

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1. Introduction

The program of the Division of Biology and Medicine has the major long term objective to measure and to evaluate the effects of radiations on man. Meeting this obligation is not a simple task. Many of the reasons for this will be obvious to you. Human experimentation is quite properly proscribed; we can make observations on man's responses to radiations only following exposure for reasons other than our need for radiobiological information, reasons such as accident, medical usage of radiations, and so on. We overcome this in part by resorting to the use of human cells in tissue culture. However, the responses of these may not give us a fair picture of what happens in a human being. Hence, we also use experimental animals and attempt to extrapolate the results of those studies to the human situation. Again, a mouse or a dog is not a man, and we need to find ways to improve confidence in our abilities to translate animal data into reliable estimates of hazards to man.

As with any presumably deleterious environmental contaminant, we have the problem of measuring dosages and of relating the magnitudes of observed effects to the dose. This involves not only measurements of external radiation, but the tracing of radionuclides through whatever environmental pathways they may follow in getting into man, determining localizations in human cells and tissues, measuring rates of turnover (biological half-life), and using this information to determine radiation dosages that can be ascribed to such internal emitters.

Except in case of accident, nuclear warfare, and so forth, the radiation doses that we are concerned with are quite small, and this leads to the problem that I do not need to detail to an audience of statisticians: when dosages are small, effects are small, hence difficult to measure because of the sheer magnitude of the observations that must be carried out to obtain samples large enough to permit establishing the statistical significance of differences that may be found. In addition, the effects produced by radiation are indistinguishable from those

arising spontaneously; consequently, small effects may be lost in the background noise.

We have a great need to know the effects of low, protracted doses of radiation to man, but we must depend on experiments with animals exposed to radiation doses that are higher by orders of magnitude, supplementing this by salvaging whatever bits of information can be gleaned from the very few human individuals or populations that have been exposed to sufficient radiation to produce observable changes. Thus, for example, the Commission and its contractors have cooperated in the studies of the Atomic Bomb Casualty Commission in Japan, a study of a Brazilian population living in a high radiation background area of monazite sands and studies of radium dial painters.

What kinds of effects are we concerned with? Effects on somatic (body) cells are of concern because these are the basis of damage to the exposed individuals; deleterious effects on germ (reproductive) cells may be transmitted to and result in damage to some subsequent generation. Most of these inherited changes (mutations) are known to be deleterious, and since they may be passed on from generation to generation, perhaps only occasionally resulting in a damaging effect when they occur in a suitable genetic combination, they are quite appropriately regarded as a threat not only to the individual who inherits them, but also to the population as a whole.

2. Genetic effects

With the advent of the nuclear age, it became mandatory that we learn more about the nature and magnitude of the genetic damage that could result from exposure to ionizing radiations. Initially this information came from studies on the spermatozoa (mature male germ cells) of the fruit fly, *Drosophila*. The knowledge of the mutagenicity of X-rays had been obtained by the pioneering work of the late Professor H. J. Muller [1], and the major genetic and cytogenetic effects (chromosomal aberrations, such as deletions, inversions, translocations) were well documented during the ensuing 10 to 12 years. Experiments by W. P. Spencer and C. Stern [2] under the auspices of the Manhattan District, showed that the earlier observations of proportionality of mutation yield to radiation dosage in *Drosophila* sperm that had been reported in the early 1930's held true even for doses as low as 25 Roentgens (R).

It was realized, however, that human germ cells might differ considerably from those of the fruit fly, and that attention should be centered on the immature germ cells, on the cells that are at risk for the major portion of the life cycle. Ideally, this information should come from a mammalian species. Hence, in 1956 an experiment was initiated by Dr. W. L. Russell at the Oak Ridge National Laboratory (ORNL) to measure the mutation rate in spermatogonia (immature germ cells of the male) of the mouse, using seven specific loci. The results of this experiment showed that mouse spermatogonia are some fifteen times more sensitive to radiation than similar cells in the fruit fly [3]. On the basis of these

early mouse data, the various standards-setting bodies decided that the then current permissible occupational exposure levels were too high, and the maximum permissible annual dose for occupational exposure was lowered from 50 to 5 roentgens and for the first time a population permissible dose set at one-tenth this lower level. Subsequently, for a suitable sample 170 mR per year was given as a standard. This permissible exposure has not been changed up to the present. It gives a total genetically effective dose of 5 R per 30 year generation from man-made sources, exclusive of the medical usage and natural background radiation for the general population.

However, these results were for large doses administered acutely (that is, at high dose rates), whereas our major concern is for the low level, chronic exposures that might occur from various kinds of environmental radiation contamination. In view of the difficulty in carrying out low dose experiments as mentioned above, the question became what would be the effect of exposing the mice chronically (that is, at low dose rates), where the total radiation dose would be the same? In these subsequent experiments Dr. Russell [4] obtained the answer that at high doses, 300–600 R delivered at dose rates of 0.8 R per minute only one-third to one-fourth as many mutations were produced as compared to that induced by a similar dose administered at a rate of 90 R per minute. Lower dose rates down to 0.001 R per minute (normal background rate is approximately .001 R per 3.65 days) did not produce an additional sparing effect on mutation induction in irradiated spermatogonia.

When similar experiments were carried out in which oocytes (egg precursors) in female mice were irradiated, again a dose rate effect was found [5]. This effect was even more striking than that observed for irradiated spermatogonia. Mutation induction diminished as dose rate decreased from 90 R per minute down to 9×10^{-3}R per minute, such that there was a limiting dose rate below which few or no mutations were detected. Similarly, even with acute treatments, low doses of radiation (for example, 50 R) give fewer mutations than are expected on the basis of simple proportionality to dose ("linearity") [6]. In addition, there is every indication that as time from irradiation to conception increases, the premutational damage that is produced with acute exposures is completely eliminated [7].

Why is this so? We know of the existence of repair systems for the repair of damage to DNA, the genetic material, and, in a variety of organisms, can show the effects of repair of potential mutational damage, leading to a reduction in the yield of mutated genes. It is Dr. Russell's view that the effect of low level radiation exposure as well as time from exposure to conception is to permit much more effective repair of damage than is possible when the total damage is produced in a short period of time.

Again, why not get this information from man? You may be surprised to learn that to date no radiation induced mutations of any kind have been demonstrated to occur in man. You should not take this to mean that none have been produced by radiation, rather that genetic techniques have not yet been devel-

oped and used to detect such changes. The only rigorously treated genetic information available to date, obtained from human studies, is that reported on the progeny of the survivors of the atomic bombs at Hiroshima and Nagasaki. These studies indicated that genetic effects of the exposure to acutely delivered, high doses of radiation, which included both gamma rays and biologically more effective fast neutrons, could not be detected in these populations with the genetic endpoints available at that time (sex ratio, morbidity, mortality, presence of congenital abnormalities, and so forth, of children of the survivors) [8]. These negative results indicate that man is, in all probability, not much more sensitive to radiation than is the mouse (and he may be less sensitive).

There are many factors that must be known before we can be completely confident of our extrapolation from experimental animals to man. Recognizing this, the Atomic Energy Commission (AEC) has, for many years, maintained an active program in basic radiation genetics, including studies of somatic cell genetics, repair processes, the structure and function of the genetic material, and variations in response to radiation of different species.

Another important problem of concern is the behavior and expression of mutations in populations. A number of experiments have been carried out with mice, in which the spermatogonia of males and in some experiments both spermatogonia of the males and oocytes of the females have been irradiated with large acute doses of radiation in each generation, with the purpose of measuring accumulated genetic damage, where the damage was to be measured by the reduction in reproductive or Darwinian fitness—that is, effects on morbidity and mortality, fecundity (litter size), and so forth. A striking, common feature of these experiments is their failure to show evidence of significant cumulative damage [9].

2.1. *Early and late somatic effects of external radiation.* In a logical way the program of the Division of Biology and Medicine has evolved to assess three main potential exposures of individuals or large human populations; (1) possible exposure of one or few individuals to high doses as might result from an accident, (2) possible exposure of a small group of individuals to moderate doses in their occupation, and (3) possible exposure of a large population to minute amounts of radioactivity released to the environment by a nuclear industry.

The last possibility is the one of primary concern at present and differs very little from the overall problem of release of small amounts of any potentially toxic material by any industry to the environment.

Very early in the biological research program studies relevant to these considerations were being conducted since only the potential sources of radioactivity have changed from nuclear weaponry to nuclear power for peacetime application.

The three modes of potential exposure require the understanding of several variables, among which are total dose, dose rate, and quality of the radiation, which are potential determinants of both the qualitative and quantitative aspects of possible biological effects.

It was decided quite early in the Division of Biology and Medicine (DBM)

program that prospective or retrospective epidemiological studies on accidentally or purposely exposed human populations would not be sufficient for evaluation of human hazards. Moreover, it was concluded that such studies would contribute little to a basic understanding of how the biological effects were produced or how the human body reacts to the damage produced by normal recovery and repair processes.

Experimental animals, chiefly small rodents and beagle dogs have comprised the major organisms used for evaluation of both acute and delayed somatic effects of ionizing radiation. An important aspect of the radiobiology program sponsored by the DBM has been to provide a strong basic research program on cellular and molecular radiobiology to provide fundamental biological principles which strengthen the more applied work and facilitate the often difficult extrapolation of radiation hazards to man. A good example is the case of a collaborative effort between a group at the University of California, Laboratory of Radiobiology, and one at ORNL. Studies at ORNL established that in microorganisms extreme sensitivity to ultraviolet radiation can be attributed to genetic defects which preclude the synthesis of enzymes which are involved in repair of chemical defects produced in the DNA by the radiation. In humans the genetically controlled cancerous disease, known as xeroderma pigmentosum, is characterized by abnormal sensitivity of the skin to sunlight and the irradiated cells become cancerous. A prompt application of the finding on bacteria using similar techniques has led to the conclusion that the cells of the affected humans lack one of the enzymes contained in normal cells that repairs radiation damage to the DNA. While this study does not imply that this is an important aspect of radiation carcinogenesis it does show that normal cells have enzymes for repair of radiation damage.

It will not be possible in this presentation to describe in detail the many important studies which have been carried out over the year as part of the radiobiology program sponsored by the AEC. Results of many individual studies have produced some general principles which will be highlighted, and an effort will be made to describe important new research programs to fill in gaps in our information, especially in the most timely problems of the day which fall mostly in the area of evaluating the potentially hazardous effects of low doses of radiation received at low dose rates. By definition these involve the late somatic effects of radiation which can lead to premature death.

2.2. *Effect of total dose and dose rate.* Although it is tempting to subdivide the important effects of ionizing radiation on animals into immediate and late effects, this subdivision is arbitrary and depends on both the total dose and the dose rate and also on the quality of the radiation.

In model animal systems it has been known for many years that X-rays or gamma rays received at sufficiently high dose rates produce different modes of death as a function of the total dose as shown in Figure 1. Between 300 and 1000 rads, experimental animals die after a latent period of a few days to three weeks predominately from damage to the bone marrow which is reflected in

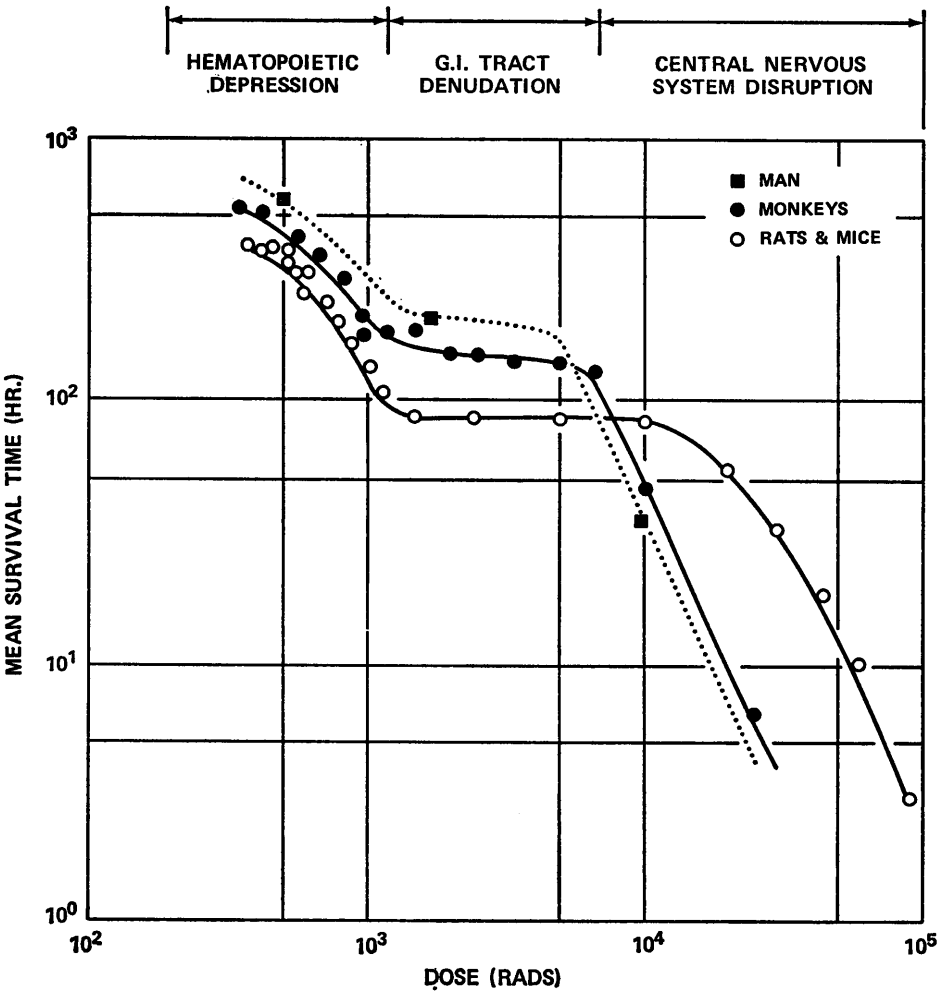

FIGURE 1

Survival time and associated mode of death in relation to dose of acute whole-body irradiation [15].

a marked depression in the production of red and white blood cells. At doses between 1000 and 10,000 rads, animals die after several days due primarily to loss of the epithelium of the gastrointestinal tract. At higher doses of 10,000 to 100,000 animals may die in minutes to a few hours because of damage produced predominately in the central nervous system.

While this figure was not intended to imply that only three organs or tissues are involved in the lethal radiation syndrome, an impressive quantity of data derived from AEC sponsored research does permit some general conclusions to be reached about the early lethal effects of radiation on a number of mammalian

systems. Without exception the radiation damage that leads to early death involves systems whose function depends on continuous cellular replacement such as the intestinal epithelium or systems that provide stem cells for a variety of important cell functions such as the bone marrow. The marrow, of course, is the continuous source of cells for such vital functions as respiration, maintenance of continuity of capillary function as well as the blood clotting mechanism, maintenance of body defense against infection by way of removing foreign cells from the circulation or by setting up a permanent immunological defense against infectious organisms.

At doses lower than 100 rads, effects on these same important systems can be detected, but through the process of cell replacement from stem cell populations recovery of the irradiated individual seems complete. The survivors of such populations, however, may express latent damage to a variety of cell systems which can be classified as late somatic effects and will be discussed below.

As a result of a number of studies on mice, some generalizations can be made about changing radiosensitivity with age of the irradiated population. Irradiation during embryonic or fetal development presents at least one unique problem and that is formation of morphological abnormalities in the development of the offspring. Figure 2 summarizes some of the findings of studies on experimental

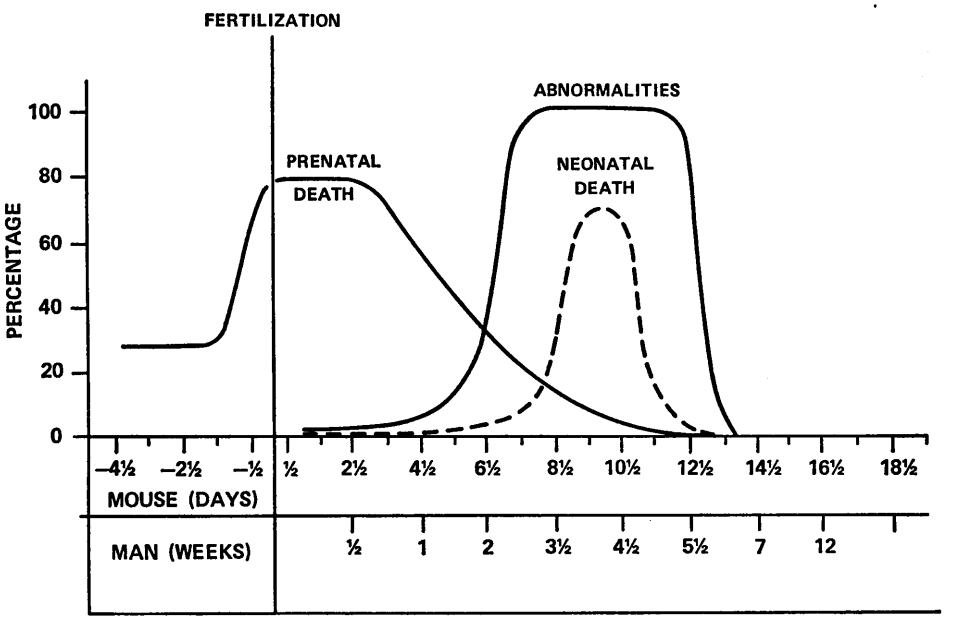

FIGURE 2

Incidence of pre- and neonatal deaths and of abnormal individuals at term after 200 to 400 R X-irradiation of mice at various intervals separated by 24 hours. The corresponding estimated chronology for man is shown [16].

animals and attempts to scale the sensitive periods for man based on the relative time-spans for the two species. It is clear from the data shown that remarkable changes in sensitivity for prenatal and neonatal death occur during the gestation period. Production of a variety of abnormalities also shows a large change per unit dose. As would be expected on the basis of the kinds of abnormalities produced some are found to be lethal after birth. Although these effects on the developing embryo or fetus are reasonably well documented they relate only to total dose.

It is important to assess dose rate dependence for both lethal effects and abnormalities induced in the fetus, and we have initiated such work at ORNL and at the University of Tennessee-AEC Laboratory within the past year. Some effort has been made to establish the minimum dose required for production of specific abnormalities. Some of you, as biometricians, are well aware of the size of the populations required to establish minimum doses for most biological effects. It is of utmost importance to establish the effectiveness of radiation on fetal and juvenile animals for production of late somatic effects. The few data on human *in utero* radiation resulting from retrospective epidemiological studies in several countries are not consistent with each other in concluding an abnormally high radiosensitivity of the fetus for induction of leukemia and other types of cancer. In addition all prospective studies have been negative. We have initiated studies in mice at ORNL and dogs at the University of California at Davis to evaluate experimentally the suggestions derived from the human studies.

2.3. *Quality of radiation and its interrelationship to dose and dose rate.* There are many ways to look at the relative effectiveness of various kinds of radiation. In biophysical terms the most meaningful way is to classify the various ionizing radiations on the basis of the density of ionization or energy loss along the particle tracks as they pass through matter. Often the effectiveness per unit dose is described as a function of the *linear energy transfer* (LET) in tissue. Most of the assessment of relative biological effectiveness (RBE) has involved X-rays or gamma rays as compared with neutrons which produce primarily energetic protons as they are slowed down in tissue-like materials. Most of the data from the fundamental cellular studies as well as whole animal studies indicate that high LET radiations such as fast neutrons are five to ten times more effective per unit dose than low LET gamma and X-radiation. The best explanation to date for this effect is that most cells are incapable of repairing damage produced by the high LET radiations. The best evidence in this regard stems from dose-rate studies which show a dramatic reduction in effectiveness per unit dose with decreasing dose rate for low LET radiations, but little or no dose rate dependence for high LET radiations. In biophysical terms this suggests that several independent physical events are required for production of most somatic effects. This is tantamount to suggesting that a true threshold dose, however small, must exist for low doses of radiation received at very low dose rates. All somatic effects studied to date, whether immediate or delayed,

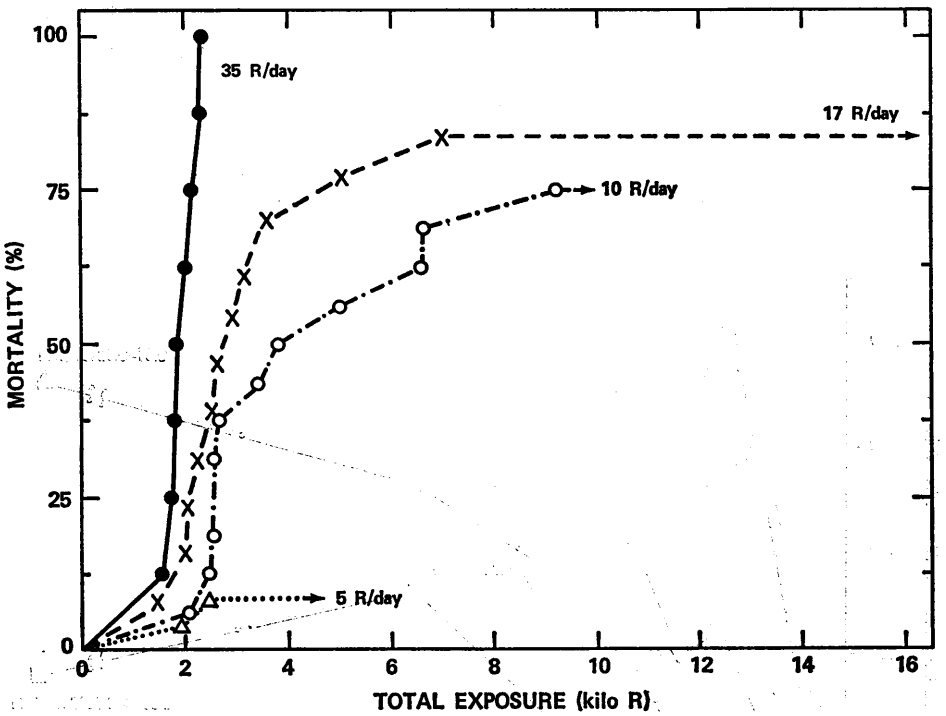

FIGURE 3

Mortality in beagle dogs exposed continuously to either 5, 10, 17, or 35 R/day in a cobalt-60 gamma ray field. The arrows indicate the total exposure reached at the time of this report.

show this interesting dose rate dependence for low LET radiations and much reduced or no dependence on dose rate for high LET radiations.

2.4. *Delayed effects and dose rate dependence.* Most discussions of radiation effects attempt to separate conceptually early and late somatic effects. A number of studies performed as part of the DBM program suggest a continuance of responses as a function of the dose rate at which the radiation is received. A classic example of this is the rather extensive dose rate study on dogs performed at Argonne National Laboratory (Figure 3). It is clear that survival time, as a result of continuous exposure until death, shows a continuous increase as the dose rate is reduced. At least a factor of 20 difference was found between the LD_{50} at the highest dose rate, 300 R/day, to the lowest so far used, 5 R/day. Although the survival times are remarkably different, the cause of death reflects primarily damage to the bone marrow, which ranges from septicemia, to anemia, to leukemia.

The most massive collection of data on dose rate effects on late somatic effects on animals come from mouse studies at the ORNL Argonne National Labo-

ratory and Brookhaven National Laboratory. Although data have been collected for a number of late effects including graying or depigmentation of hair, production of lens opacities resembling cataracts, and other disorders such as kidney damage, we will be concerned here with the overall life span shortening and production of cancer. These studies have shown these two effects to be intimately related because a major cause of life span shortening occurs as the result of the overall production of neoplasms. Figure 4 shows the overall life

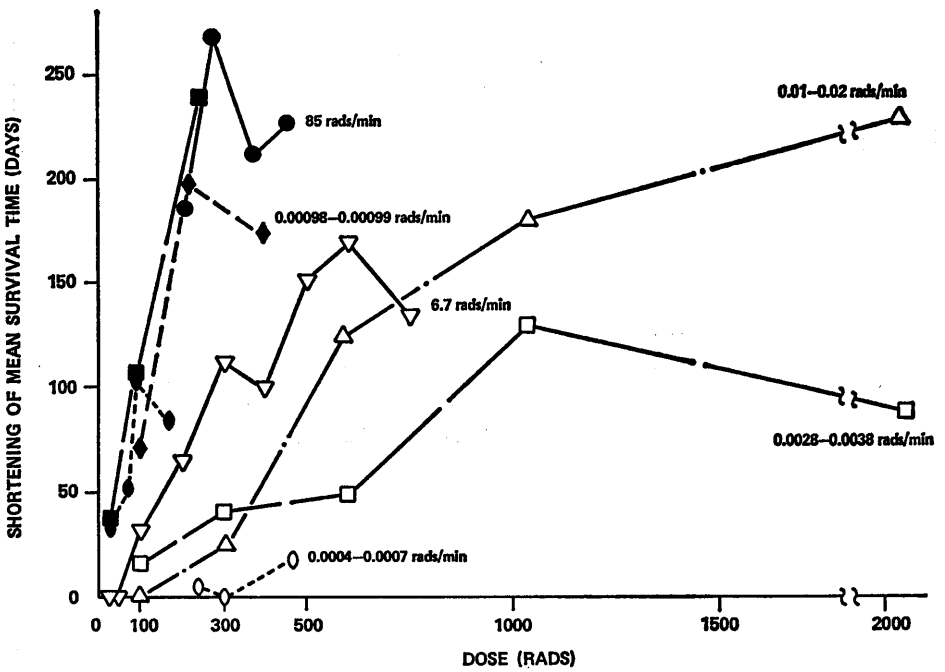

FIGURE 4

Life shortening in females as influenced by dose and dose rate of gamma rays and neutrons. Open symbols represent gamma rays, shaded symbols neutrons.

span shortening per unit dose for gamma rays that have been administered at various dose rates ranging from 85 rads/min to 0.0004 rads/min. It is clear that the effectiveness of gamma rays is systematically reduced as the dose rate is reduced. The shaded symbols show for contrast the results of neutron irradiations, over a similar range of dose rates, indicating more effectiveness per unit dose and independence of dose rate as previously mentioned.

Similarly when radiation induction of specific types of cancer are measured as a function of dose and dose rate, there is a remarkable reduction of the incidence per unit dose with reduction in dose rate, as shown in the next figure (Figure 5). These data are derived from the Oak Ridge study, and a similar

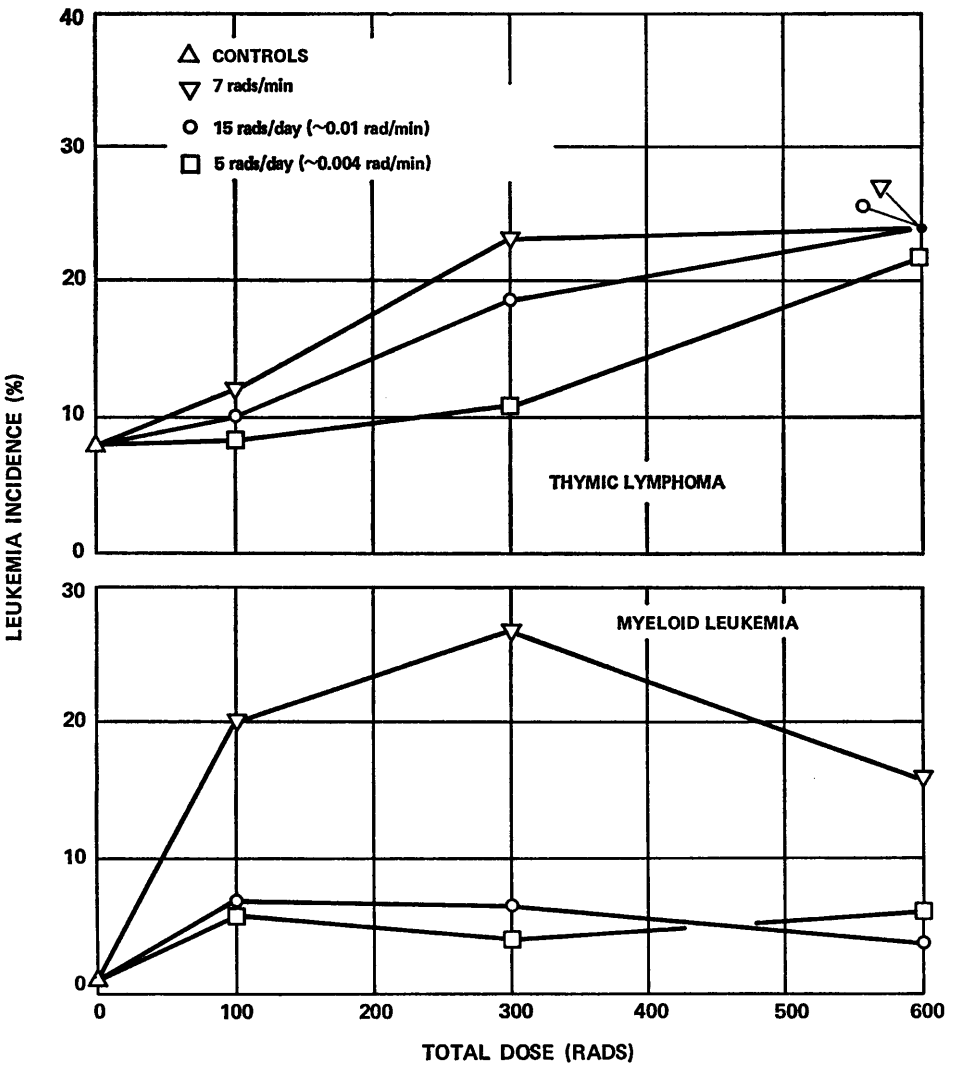

FIGURE 5

Leukemia incidence in relation to dose and dose rate of gamma radiation.

study at Argonne National Laboratory has provided confirmation of the dose rate effect for a number of mouse strains.

Although these studies give evidence for an overall reduction of radiation induced cancer incidence with decreasing dose rate for those radiations of most concern, none of the experiments have attempted to resolve the question of effects of minute doses received at the dose rates most likely to be involved in present or future developments in the nuclear energy program.

However, with the help of our biometrics staff in the National Laboratories mouse experiments are underway to evaluate life span shortening and specific tumor incidence at a total dose, as low as ten rads and at several dose rates for both low and high LET radiations. These studies are designed to detect tumor incidences in irradiated populations as compared with unirradiated populations which are significant at the five per cent level. These experiments may well serve as models for what can be practically done for other potentially hazardous agents being added to man's environment.

3. Human exposures

Studies in experimental animals are of great value in shedding light upon many aspects of radiobiology, but in order to apply the findings to humans there is a great need for direct information on human beings. As I have mentioned this is difficult to obtain and there are always certain drawbacks because of the nature of the sources, but when interpreted in light of results from experimental animals the data can be very useful.

Human experience with radiation exposures is found mainly in the following groups: (1) radium and thorium recipients; (2) uranium miners; (3) Nagasaki and Hiroshima survivors; (4) accidental exposures; (5) therapeutic exposures.

3.1. *Radium and thorium recipients.* Radium is a naturally occurring radioactive alkaline earth element which, when taken into the body, deposits primarily in newly forming bone. During radioactive decay, radium and its decay products emit alpha and beta particles and gamma rays and irradiate the contiguous cells which cover the bone and overlying tissue.

The unfortunate poisoning of human beings provided the opportunity to study the biological effects of radium, including bone cancer development, in a relatively large sample of humans. Radium serves both as a reference point between man and experimental animals for studying relative toxicology and as a reference point for calculating maximum permissible burdens for other radionuclides normally picked up by bone.

For the past twenty years a joint study of more than 400 persons bearing considerable body burdens of radium 226 has been in progress at AEC's Argonne Cancer Research Hospital and the AEC's Argonne National Laboratory. Most of these persons painted radium dials on luminous watches during 1920 to 1930; others received radium chloride by injection or orally as a medicament between 1920 and 1933. From 400 to 500 cases, mainly former dial painters, have been studied extensively at the Massachusetts Institute of Technology to determine the long-term effects of radium and mesothorium in human subjects. The MIT radium studies are being consolidated with those at Argonne Cancer Research Hospital-Argonne National Laboratory as part of a newly established Human Radiobiology project under the direction of Argonne National Laboratory. The names and location of more than 1,000 radium contaminated people are known. Of these, 70 per cent are still living. About 85 per cent of the living and 20 per cent of the deceased subjects have been studied. This long-term study has shown

that persons with a considerable body burden of radium have characteristic defects and destructive changes in skeletal structure; skeletal tumors and other rare tumors of the tissues lining the mastoid bone, paranasal sinuses, and oral cavity may also exist.

3.2. *Uranium miners.* The problem of pulmonary malignancy in uranium miners and other hard rock miners has been long recognized. Researchers at St. Mary's Hospital, Grand Junction, Colorado, have developed cytological examinations of miners' sputum to a level which indicates considerable promise as a readily obtainable screening and prognostic procedure. Assisting the St. Mary's group is a group of consultants in pathology who are attempting to establish uniform diagnostic test criteria which hopefully will have usefulness for general medical application.

Three facts make the development of an early test for cancerous lung lesions especially compelling: (a) as chronic irritation affects the lungs, the previously healthy cell lining undergoes degeneration to an identifiable "pre-cancerous" condition; (b) recovery of the abnormal cells has been observed (in sputum samples) where these individuals were removed from further exposure to lung irritants; and (c) with continued exposure to lung irritants these abnormal pre-cancerous cells show changes which are irretrievably headed into malignancy. Thus, timely preventative medicine based on early diagnosis is critical.

At Colorado State University at Fort Collins, human subjects are exposed to mine aerosols both in a controlled test tunnel and in general work areas in an operating uranium mine. Physical characteristics of the exposure aerosols are measured on samples collected currently with the exposures. Deposition patterns of radon decay products in the human respiratory tract are analyzed in a mobile whole body counting laboratory. Depositions in resultant doses are studied with respect to various mine atmospheres and personal control measures. Samples of urine, feces, blood and hair are collected from working miners and analyzed for long lived radon decay products in an attempt to discover bioassay procedures for correlation with measured exposures.

3.3. *Accidental exposures.* Radiation accidents have been very rare, however, for purposes of evaluating and accumulating information on radiation accidents, AEC has had a program for collecting data whenever possible. The sources include accidents and operations for recovery of fissionable materials, radioactive fallout (Marshallese), exposures from industrial radiography sources, exposures from particle accelerator beams, electronic tube exposures, accidental administration of large amounts of radiotherapy to patients through miscalculations or mislabelling, and accidental misplacement of laboratory gamma ray sources. Data have been collected at the Oak Ridge Associated Universities from several accidents. Careful cataloging of the various experiences will allow the AEC in the future to pursue follow-up studies for the remote effects and bring together the combined experience of the physicians who have managed victims with total body irradiation or combinations of total body irradiation and local destructive radiation lesions of the extremities.

On March 1, 1954, a nuclear weapons test detonation at the Pacific Proving

Ground produced fallout which was unexpectedly carried by winds over the inhabited Rongelap Atoll and adjacent islands. During the past five years abnormalities of the thyroid glands have been detected in a number of the Marshallese people of Rongelap Island who were accidentally exposed in 1954. These abnormalities, believed to be late effects of radioiodines deposited in the thyroid at the time of fallout, were detected during routine annual medical surveys of these people by the AEC's Brookhaven National Laboratory and the Trust Territory of the Pacific Islands. The thyroid abnormalities consisted of 18 cases with benign nodules, two others with marked hypothyroidism, and one case of cancer of the gland. Most of the abnormalities have occurred in children exposed to radiation at less than ten years of age. It is estimated that the thyroid glands of the children receive a dose of between 700 to 1400 R of radiation from internally deposited radionuclides plus 175 R of penetrating gamma radiation from outside the body. It is not known whether the one case of thyroid cancer, observed in a 40 year old woman, was related to radiation exposure. The population of the atoll, regularly examined by a medical team from BNL, has a clearly higher than normal incidence of thyroid abnormalities that has been related to the presence of radioactive iodine in fresh fallout.

The early effects of fallout exposure on the Marshallese has been well documented. The 64 people on Rongelap received 175 rads of gamma radiation which proved to be sublethal but caused early nausea and vomiting. Significant depression of formed blood elements lasted over a period of several months. Exposure of the skin resulted in burns and loss of hair. In addition, absorption into the body of radioisotopes of iodine from contaminated food and water with deposition in the thyroid gland proved to be the most serious internal exposure. Recovery of formed blood elements to near normal and healing of skin lesions with regrowth of hair occurred by the end of the first year. No acute or chronic effects of exposure to other internally absorbed radioisotopes has been noted.

3.4. *Therapeutic exposures.* Clinical and laboratory data from human total body irradiation exposures in the United States have been obtained and coded, and are being analyzed by electronic computer methods. The Oak Ridge Associated Universities material on patients obtained from their radiotherapeutic programs since 1957 and from additional human data (including over 3,000 case histories obtained from other hospital centers with similar treatments) have been gathered for a study to determine what dose ranges in man cause loss of appetite, nausea, vomiting, diarrhea, fatigue, weight loss, fever, skin reddening, loss of hair, and blood cell changes in number and type including anemia, chromosome damage, decreased resistance to infection, decreased antibody synthesis, premature aging and development of cancer.

Dose response relationships derived from these data were reported to the Space Radiation Study Panel of the National Research Council of the National Academy of Sciences. These data also appear in a four volume compendium published by the National Aeronautics and Space Administration entitled "Compendium of Human Responses to the Aerospace Environment."

On November 26, 1946, President Truman approved a proposal by the then Secretary of the Navy, Mr. James Forrestal, which instructed the National Academy of Sciences-National Research Council to undertake a long range, continuing study of the biological and medical effects of the atomic bomb on man. It was decided that the AEC should provide the funds; and since that time the AEC has funded for, and has provided, programmatic supervision of this research program which has come to be known as the Atomic Bomb Casualty Commission (ABCC). The first contract with the National Academy of Sciences was executed on April 17, 1948, with renewals at intervals. Since its inception in 1947 through June of 1969 more than 468 scientific papers have been published on various aspects of the ABCC research program and referred by medical journals throughout the world.

The ABCC observations are applicable to the long term effects in man for all types of ionizing radiation. The basic population sample in the ABCC is comprised of approximately 50,000 Japanese selected on a basis of their history and records of exposure and 50,000 equally selected matched control Japanese. Observations on this population which justify definitive statements or conclusions at this time are:

(1) Cataract of a rather specific type involving the posterior subcapsular tissue of the lens developed in about 100 people after exposure. It tends to regress with time, and may be successfully treated by surgery.

(2) The incidence of leukemia in the exposed groups began to rise in 1948 and reached a peak in 1952–53 some 20 to 50 times that in the control population; the incidence subsequently has decreased but remains with variations at a level slightly higher than that expected for the population. In general those persons receiving the higher doses developed the condition sooner, but there was nothing clinically unusual about the disease itself. It is very important to learn whether the incidence of leukemia will increase more rapidly than expected as the population ages, as leukemia is primarily a disease of the aged; or whether it will increase at all.

(3) Cancer of the thyroid gland has shown an increased incidence, particularly in those surviving the higher exposures. Since the natural incidence of this disease is low it is necessary to continue to observe the population in order to accumulate enough cases for statistical validity. Persons receiving lower doses probably will develop the disease sometime in the not too distant future, if they are going to.

(4) A major research effort (1956), followed up by a resurvey (1966), concluded that there were no radiation-induced genetic effects observed in the children born of one or both exposed parents. Since that time more sensitive tests for mutations have been developed which may be employed in the ABCC population if the cooperation of the Japanese can be obtained.

(5) By virtue of a ten-year study at the Oak Ridge National Laboratory the radiation emission fields of both weapons were reconstructed and the combined neutron and gamma-ray exposures were calculated for nearly every survivor

with an accuracy of plus or minus 10 to 15 per cent. Previously the biological effects had to be related to the distance of the person from ground zero. The calculations have been verified independently by Japanese scientists. Reliable dose/effect relations can now be established for the radiation effects being studied. The greater precision of the dose/effect relationships, particularly of the low dose exposures, ought to be useful in examining questions on the linearity or nonlinearity of responses of man to irradiation.

(6) The incidence of leukemia in children born of exposed parents is not different from that of children of unexposed parents. Also, the parents of children who do develop leukemia are equally divided as to having been exposed and not exposed, corrections having been made for the lesser number of parents in the exposed group.

4. Internal emitter program

Studies which deal primarily with experiments related to radiotoxicity of internally deposited radionuclides and their metabolic behavior date back to the Manhattan Project of the early 1940's. Because of its central importance o the development of a national nuclear energy program biological experiments related to the potential toxicity of plutonium can be traced back virtually to its discovery in February 1941. Animal experiments using CF-1 mice to determine the toxicity of injected plutonium were performed at the Metallurgical Laboratory at the University of Chicago in 1944 by Brues, Lisco and Finkel. By 1947 these researchers published several articles in the open literature calling attention to the carcinogenic properties of plutonium when administered in relatively large quantities to experimental animals [10], [11].

I should diverge at this point for a moment to say that the field of radiation protection had been established formally on both the national and international levels in the period 1928 to 1929. Of further interest is the realization that this year we are observing the 76th anniversary of the discovery of X-rays by Roentgen which was followed a year later by Becquerel's discovery of radioactivity.

On the first of December, 1952, the first dog was injected at the University of Utah for the purpose of comparing long term biological effects of a single intravenous injection of radium 226 and plutonium 239 in adult Beagles. Because of prior experience with radium toxicity in man (Dr. Martland reported the first radium recipient fatality in 1925) [12] it was clear that strontium 90, ^{239}Pu and other bone seeking radionuclides could become of interest to the nuclear energy industry. To determine the extent of the potential hazard, several long term investigations were initiated to make use of the human radium data by designing the studies around the following relation:

$$\frac{^{239}\text{Pu Effects on Man}}{^{226}\text{Ra Effects on Man}} \simeq \frac{^{239}\text{Pu Effects on Beagles}}{^{226}\text{Ra Effects on Beagles}}$$

Thus the toxicity of ^{239}Pu can be predicted from the information on the ^{226}Ra patients and the animal experiments using ^{239}Pu and ^{226}Ra.

Of course, several factors contribute uncertainty to this design. For example, the surface to volume ratios of bone in the Beagle and Man, the fact that the radium subjects received radium by oral ingestion over a period of months and the uncertainty of the importance of radium 228 and thorium 228 which some radium subjects also received. Because of the latter consideration, ^{228}Ra and ^{228}Th were added to the original experimental design. In 1954, ^{90}Sr was added to the design because of increased interest in radioactive fallout.

The radioactivities administered as a single intravenous injection to groups of 12 or more 17-month old beagles, were:

^{90}Sr — 0.57–100 microcuries per kilogram
^{239}Pu — 0.0006–2.8 microcuries per kilogram
^{228}Th — 0.0017–2.8 microcuries per kilogram
^{226}Ra — 0.0057–10 microcuries per kilogram
^{228}Ra — 0.19 to 10 microcuries per kilogram

Table I shows the tumor response for the ^{226}Ra series. The incidence of osteosarcomas (bone tumors) decreases with injection level-cumulative radiation dose. Also of interest is the increase in time from injection to death (latent period) as a function of decrease in radiation dose. This general pattern has been observed in all the experimental groups to date.

Because of the importance of ^{90}Sr as a potential hazard to man from world-wide nuclear fallout, a major research project was established at the University of California, Davis campus. This effort is complementary to the Utah studies but differs in that ^{226}Ra and ^{90}Sr are given as multiple intakes to simulate continuous intake from nuclear fallout (^{90}Sr) or occupational exposure (^{226}Ra). To achieve uniform labelling of the skeleton with ^{90}Sr, dams were placed on a

TABLE I

OSTEOSARCOMAS IN UTAH BEAGLES (1 MARCH 1969) ^{226}Ra
All injected dogs at levels 5, 4, and 2 have died.

Injection level	Injected $\mu Ci/kg$	Deaths		Osteosarcoma dog averages	
		Total	Osteosarcomas	Years from inj. to death	Rads one year before death
5	10.4	10	9	3.04	10900
4	3.21	13	12	4.36	4530
3	1.07	12	11	6.28	1940
2	0.339	13	5	10.28	837
1.7	0.166	9	1	11.25	458
1	0.0621	12			
0.5	0.0220				
0.2	0.0074				
0	0.0000	12			

diet containing from 0.007 to 3.33 microcuries ^{90}Sr per gram of dietary calcium; their progeny were kept on the same dose level until young adulthood (18 months of age). The dietary calcium was kept at a one per cent level to maintain a constant specific activity.

To date, the lowest level in this experiment which has caused radiation deaths amounts to doses of about 2,000 millirads per day, or about 730,000 millirad per year. For comparison the FRC Radiation Protection Guide assigns a population dose limit of 0.17 rem per year or about one-half millirem per day on the average.

Other Beagles were given eight semi-monthly intravenous injections of ^{226}Ra beginning at 14½ months of age to simulate the brief repeated exposures of the radium dial painters. The amounts injected from 0.024 to 10 microcuries ^{226}Ra per kilogram of body weight, will allow comparison with the Utah series. The injection and feeding regimens were completed in 1970 and late effects will not be known for some years.

Another study on the effects of ^{90}Sr in a large species has been in progress at the former Hanford Laboratories (now the Pacific Northwest Laboratories of the Battelle Memorial Institute) since 1958. About 900 miniature pigs, similar in size to man, with a relatively long life span have been used in this study of the parental and two generations of progeny. Starting at nine months of age, levels of 1, 5, 25, 125, 625, and 3,100 microcuries of ^{90}Sr were fed *each day* to females. The offspring were maintained at levels of 1, 5, 25 and 125 microcuries per day.

Deaths followed in about three months at the highest level (3,100 microcuries per day) and about nine months at the 625 microcuries per day level. Lymphoid metaplasia has been observed in some progeny of the 1, 5, 25 and 125 microcurie per day exposure groups but not in the control groups. Myeloid metaplasia was observed in virtually every parental or offspring exposure group and myeloid neoplasia was found in the 25, 125 and 625 microcurie per day groups. Time to death was inversely related to radiation dose.

Neoplasia of the hematopoietic system has been observed in these and in the Davis studies, both of which involve continuous intake and uniform labelling of the skeletal tissues. In contrast, the major biological effect seen in the Utah studies has been osteosarcoma (bone tumor) formation. This is a good example of the importance of the specific kind of exposure on the kind of biological insult which is produced.

These are only several examples of some of the "older" research programs in the internal emitter field. Space does not permit an exhaustive review.

5. Inhalation carcinogenesis

Airborne radioactivity was implicated as a pulmonary carcinogen early in this century although it had been known for several centuries that pitchblende miners developed fatal pulmonary diseases. The earliest evidence for the pul-

monary carcinogenicity of ^{239}Pu in mice was reported by Temple and co-workers in 1959. Because of the importance of the inhalation route of exposure in the nuclear energy industry a sizeable research program has developed.

The AEC research program on inhalation carcinogenesis is mainly related to the following areas:

(1) Development of theoretical and empirical models to describe deposition, retention, translocation and radiation dose rate patterns of inhaled radionuclides within the lung and other tissues of interest.

(2) Investigation of early and late effects of several species of plutonium, other transuranic elements, selected fission products, and other selected materials (for example, rare earth elements) following inhalation of various physical and chemical forms of these nuclides.

(3) Studies of inhaled constituents of uranium mine environments in experimental animals; this program is correlated with the uranium miners by comparative studies of sputum cytology and chemical analyses of lung samples from miners and experimental animals and by comparative measurement of constituents of mine air and animal exposure chambers.

(4) Studies of the cytokinetics of lung cells, macrophage function and transport of radioparticulates and the effects of pharmacologic agents on phagocytosis and clearance mechanisms.

(5) Development of feasible therapeutic means of reducing lung burdens of radioactive materials following deposition.

Over the years our collective experience has indicated that inhalation as a route of exposure to radioactive (and stable) materials in industry must be assigned a high probability. Large projected increases in nuclear power production with attendant increases in nuclear fuel manufacture and processing indicate the need and justification for the program outlined above. Another consideration, despite the very low probabilities of release, is that of high specific activity radioparticulates from nuclear propulsion reactors and thermoelectric generators Systems for Nuclear Auxiliary Power (SNAP) designed for numerous uses. Paralleling these developments will be greatly expanded production of uranium ore, the majority of which will come from mines rather than from open pit sources.

Many reasons exist as to why it is important to conduct this program. Aside from the obvious relation to personnel protection within the nuclear energy industry, much of the information obtained from the program is applicable to the more general problem of environmental pollution from nonradioactive materials. As regards radiation protection, there is a very cogent reason for studying the effect of inhaled radioactive materials. Radiation protection standards and criteria for bone seeking radionuclides, as promulgated by organizations such as the National Council for Radiation Protection and Measurements (NCRP) and the International Commission on Radiation Protection (ICRP), actually are based on a dual system: The observations based upon the human radium recipients and calculated "allowable" exposure esti-

mates, maximum permissible dose (MPD), which can be related to multiples of the radiation dose rate arising from natural background.

Earlier I noted that AEC's central program for the bone-seeking radionuclides is built around a large-scale retrospective epidemiological study of radium toxicity involving several thousand people who were exposed through employment (mostly radium dial painters) or medical treatment. These studies serve as a base line of intercomparison for comparative experiments in which the toxicity and relative hazard of other bone seeking radionuclides are assessed. No such standard based upon human data exists for the lung or for soft tissues in general.

I can only mention several of the many interesting research efforts which are part of this large program in inhalation carcinogenesis. One area of current interest is the third area I previously mentioned, studies of inhaled constituents of uranium mine environments and experimental animals.

The radiobiology of radon and its progeny has been studied in rodents for some years at the University of Rochester Atomic Energy Project. More recently, studies of radon and its progeny have been undertaken in dogs. Four dose levels are being studied in 30 dogs, covering the range of 250 to 3800 working level months (WLM). Average concentrations of radon in its decay products are: radon, 0.6 uCi/liter; radium A, 0.45 uCi/liter; radium B, 0.3 uCi/liter; and radium C-C′, 0.18 uCi/liter. Exposures are 20 hours per day for the required number of days, at the rate of five days per week, until the desired exposures are reached. The radon decay products are carried on normal room dust in this experiment. This work is being conducted in conjunction with the National Institute of Environmental and Health Sciences of the U.S. Public Health Service.

Related studies, some also jointly funded with the USPHS, are under way at the Pacific Northwest Laboratory of the Battelle Memorial Institute. This program is also designed to investigate possible causative or contributing factors in the observed increased incidence of lung cancer among uranium miners. One portion of the experiment involves a study of the long term biological separation of long lived alpha emitters in the uranium decay chain. In another study samples of lung tissue from deceased miners are analyzed for numerous nuclides by neutron activation analysis.

The elements scandium and antimony, typically high in concentration among individuals with mining experience, were found to be low in nonminer lung samples. Similar studies are being conducted at the Argonne National Laboratory.

In addition, hamsters have been exposed at the Pacific Northwest Laboratory to various combinations of uranium ore dust together with radon and its progeny or to radon and progeny alone. The observed metaplastic changes were more severe in the hamsters exposed to both agents and no tumors were observed. Supporting experiments with beagles are also beginning at the Pacific Northwest Laboratory of the Battelle Memorial Institute and will include exposure

TABLE II

EXPERIMENTAL DESIGN (PNL-BMI)
Controls were sham-exposed under conditions identical to those used for the experimental groups.

Exposure Groups	No. Hamsters	No. Dogs
1. Controls	100	9
2. 30 WL Rn daughters	100	
3. 600 WL Rn daughters	100	
4. 600 WL Rn daughters with U-ore dust	100	20
5. Cigarette smoke	—	20
6. Cigarette smoke + 600 WL Rn daughters and U-ore dust	—	20
7. Diesel engine exhaust	100	—
8. Diesel engine exhause + 600 WL Rn daughters with U-ore dust	100	

to radon and its progeny plus combinations of uranium ore, diesel exhaust fumes, and tobacco smoke. The experimental design is shown in Table II.

This program was established to study the effects, in experimental animals under controlled conditions, of four potentially carcinogenic air contaminants to which uranium miners are exposed, that is, radon and its daughters, cigarette smoke, uranium ore dust, and diesel exhaust fumes. It is believed that results from these studies will provide the basis for definitive research to properly assess the interrelationships of the several hazardous materials in mine atmospheres working concomitantly to cause damage to the respiratory epithelium, emphysema, fibrosis, and precancerous or cancerous changes in the lungs.

In another phase of this work simultaneous measurements of human respiratory deposition and the concentration, particle size, and charge of aerosols are being made to define the significant factors relating occupational exposure to hazard. In the relationship of aerosol properties, respiratory deposition and excretion are measured in actual work atmospheres. Field studies have been initiated in a uranium mine and in a uranium fabrication plant.

The dosimetry of selected tissues in radium workers as applied to lung carcinoma in uranium workers is under investigation at the Massachusetts Institute of Technology. The unusually high incidence of carcinomas in the sinus cavities of radium recipients suggest the importance of obtaining the quantitative estimate of the dose rate to overlaying epithelial tissues of the sinus cavities from the presence of radium and its progeny in and around the cavity. It is hoped that results of this dosimetry study will be applicable to the problem of lung carcinomas in uranium miners.

An investigation being conducted at St. Mary's Hospital at Grand Junction, Colorado is designed to study sputum cytology from uranium miners with and without past smoking history. Out-growths of this project will be the development of uranium miner tumor registry and an atlas describing sputum cytology. In an attempt to integrate these observations with experimental data, lung washings from dogs containing plutonium or radon progeny are obtained prior

to dog sacrifice at the Pacific Northwest Laboratory of the Battelle Memorial Institute and compared with samples obtained from uranium miners and from confirmed cases of pulmonary neoplasia.

The fate of inhaled lead 210 in human subjects is being investigated at the University of Rochester Atomic Energy Project. This study is related not only to the uranium mining problem as regards long-lived radon progeny such as ^{210}Pb, but also to the general problem of lead contamination in the environment.

6. Radioisotopes movement in the environment

Another aspect of the AEC's concern about environmental health may be illustrated by examples of food chain studies. While the transfer routes of energy and materials through a food chain form a highly complex web, many times it is possible to follow the passage of nutrients using radioactive tags or tracers. We are concerned with five basic questions: (1) What organisms and populations are involved in a particular food chain? (2) What are the pathways of energy and materials in food chains? (3) What are the dynamics of food chains? (4) What concentration of elements (including radioisotopes) occur in food chains? and (5) Can useful predictive mathematical models be made of food chains? Considering these last two items, concentration and models, studies using radioisotopes in food chains may provide suitable models for predicting the fate of pollutants such as pesticides in the environment.

We have sponsored such studies in several areas of the country. For example, researchers at the Ohio State University in 1964 [13] treated four acres of a natural marsh with chlorine 36 ring labeled dichloro-diphenyl-trichloroethane (DDT). The labeled DDT was traced throughout the marsh ecosystem over a four year period. The main concern of the project was with food chain aspects of DDT accumulation. The total quantity of DDT usually was determined from environmental samples of whole organisms though some tissues and organs were assayed. I might mention two findings. The DDT was applied on granules which disintegrated in the water, but little DDT was ever present there at any time because the insecticide was rapidly removed from the water by plankton and other organisms. Secondly, the highest tissue residues of DDT usually was found in the highest tropic levels.

The data from this study has been used by scientists at Battelle's Pacific Northwest Laboratories to construct a computer simulation model to represent the dynamics of DDT in this marsh. I will quote from their report [14]. "An exponentially decreasing input function (representing release of DDT from the granular formulation in which it was applied) determines concentration in water, from which one- or two-compartment models represent the concentration in various forms of flora and fauna. The overall results generally suggest that simple models, of the kind used to study radionuclide transfer through food chains, will provide reasonably good representations of the behavior of DDT in food chains."

The Ohio State Group and a group from SUNY is now studying the dispersion of ^{36}Cl labeled DDT in a meadow area.

Now, I will review briefly some other food chain studies we support as additional examples of our program.

Figures 6 and 7 show models of cycling of cesium 137 in a tulip poplar forest. During a year, the forest produced an average of 1,550 kilocalories of foliage per square meter. Insect leaf feeders in the forest canopy consumed over five per cent of this production, while concentrating radiocesium to levels nearly 50 per cent that of foliage.

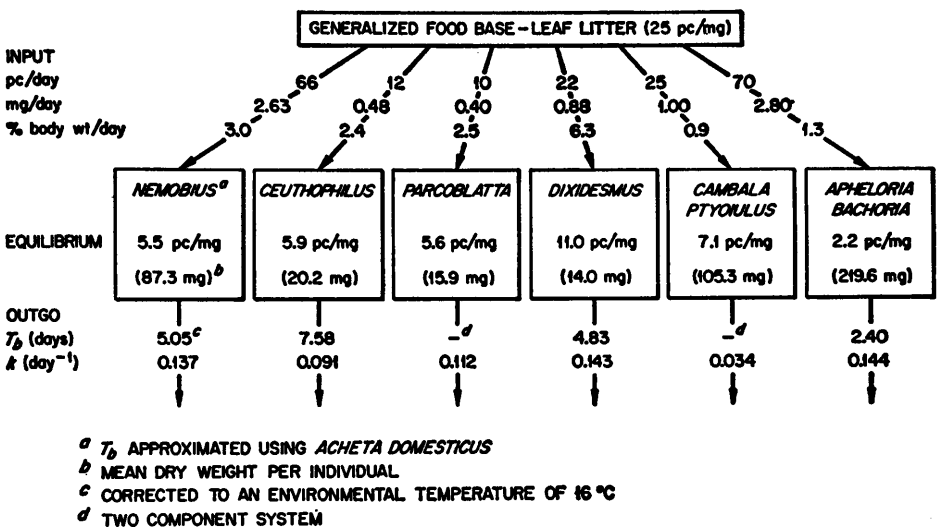

FIGURE 6

Cesium 137 Cycling in Forest Insects. Charted is the radioactive cesium transfer and leaf litter consumption by forest floor insects and millipedes as determined by Oak Ridge National Laboratory studies in food chain dynamics. *Upper arrows* indicate the flow of radiocesium and organic matter from leaf litter to arthropods (crickets *Nemobius* and *Ceuthophilus*, wood roach *Parcoblatta*, and millipedes *Dixidesmus*, *Cambala*, *Ptyoiulus*, *Apheloria*, and *Bachoria*). *Lower arrows* indicate biological turnover of radioactive cesium (*Outgo*) by metabolic processes. From biological half-lives (T_b), the daily loss of radiocesium is calculated. Since the equilibrium concentrations of radiocesium (shown in boxes) remain unchanged, daily *Input* must equal the *Outgo*. *Input* is calculated from elimination coefficient (k) times the *Equilibrium*. Calculated *Input* is shown for radiocesium (picocuries per day) and dry matter (milligrams and per cent body weight per day). Information obtained by this radioactive tracer technique demonstrated a relatively small food requirement for these forest floor animals as well as relatively low cesium 137 body burdens compared to radioactivity levels in their food supply.

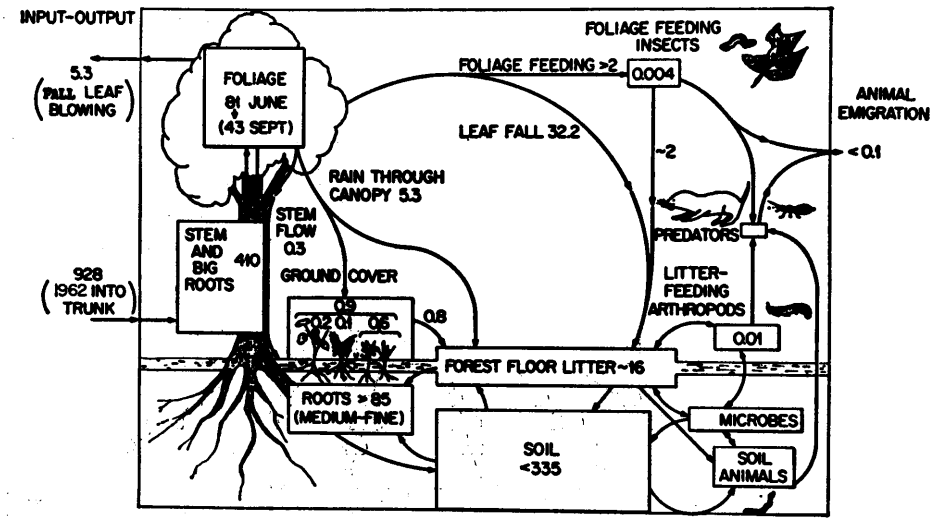

FIGURE 7

Cesium 137 Forest Cycling. Drawing shows the radiocesium cycle in a tagged tulip poplar forest ecosystem (*Liriodendron tulipifera*) at Oak Ridge National Laboratory. This forest (20 × 25 m. or 65 × 82 ft.) was originally tagged several years ago with cesium 137, a long-lived radionuclide. Continuous inventory has followed the seasonal and annual distribution of radiocesium between components of the forest ecosystem. Numbers in boxes are microcuries (1/1,000,000 of a curie) per square meter of ground surface area in summer. Arrows indicate the pathways of radiocesium transfer between compartments. Numbers by the arrows are estimates of total transfer during the growing season.

These examples should not give you the impression that we are concerned only with terrestrial ecosystems. Our support of food chain studies in marine and freshwater systems is equally as large. Let me give you some examples from those areas.

The rates and mechanisms of the chemical and mixing process in the oceans are being studied for us at several sites by University staff and researchers from some of our National Laboratories. At the Pacific Northwest Laboratory these processes are being investigated by use of material chemical elements and radioactive tracers in the ocean. In addition the staff there has used neutron activation to measure the distribution of mercury. Incidentally, they have found significantly higher levels of mercury in Pacific Ocean samples than in those from the Atlantic Ocean. Normal oceanic chemical and biological processes cannot account for the high mercury values. There is some indication that in estuaries, mercury levels are diluted by the entering river.

Several other studies we support deal with marine food chains per se. The immensity of the problem is illustrated by the fact that in the sea about a million

species of organisms exist which can be affected by pollutants, including radioactivity. These organisms also cover a wide spectrum of mobility and range of habitat. At the Scripps Institution of Oceanography some progress is being made in amplifying the usually oversimplified idea of the marine food web (Figure 8).

As I indicated earlier, we are interested in the concentration of various elements in food chains. As a final example of our work in this area I will offer a study of cesium 137 concentrations in freshwater, a study conducted at the

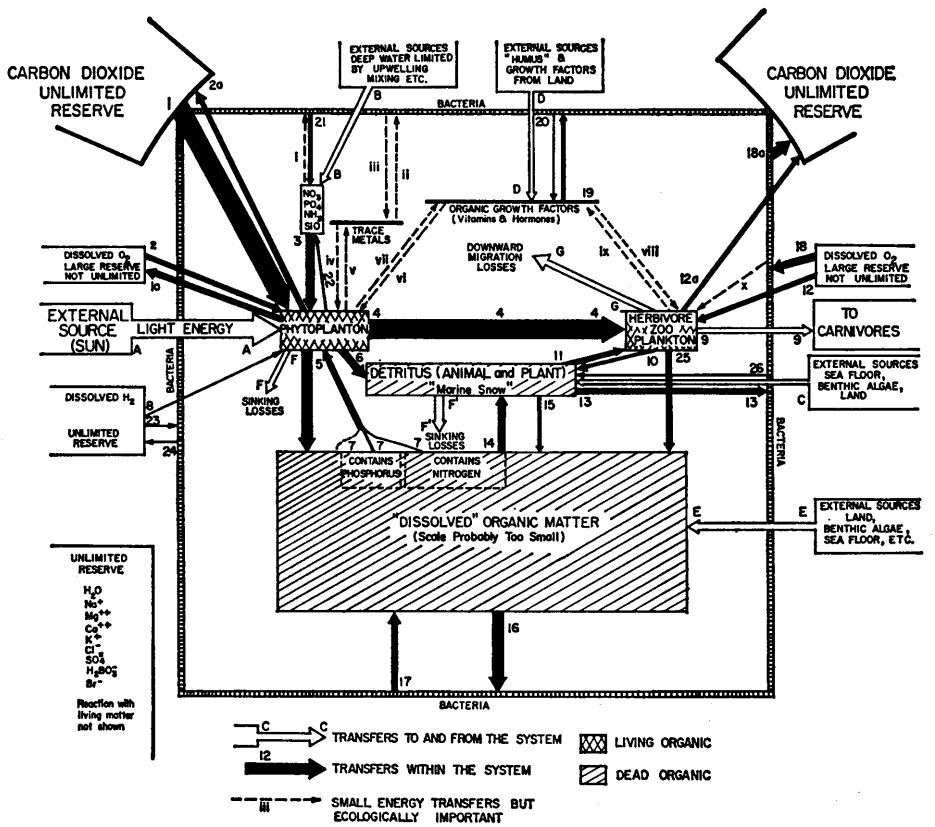

FIGURE 8

Conceptual Relationships in Marine Food Web. Box model illustrating the major components of the sea's biological reservoir, some of the physical and chemical factors which affect them, and the principal routes of material or energy transfer between the components. This Institute of Marine Resources, University of California, diagram is simplified in that it emphasizes the originating part of the marine life cycle and is restricted largely to organisms and processes within the euphotic portion (zone of light penetration) of a water column.

Oak Ridge National Laboratory. Algae were grown in water tagged with cesium 137. Then one group of snails was fed the algae which remained in the tagged water which did not contain algae. The concentration factor for algae was 2,300. For the snails the concentration factor for algae was only 98, and for snails in water alone, the concentration factor was 28. Cesium thus does not invariably concentrate at each successive level of a food chain.

There are many other examples I could give you, and more models and systems analyses in all stages of development. I will not prolong this review. However, before leaving the topic of environmental health I should point out that we are studying the effects of radionuclides in the environment as well as their fate. This program can perhaps be appreciated by the range of environmental studies, involving, for example radiation effects on rodents and rodent relatives, deer, birds, sheep, insects, reptiles, and amphibians, and a host of lower forms, and several plant species. These studies involve not only effects on individuals in nature, but on populations and ecosystems. We have studied the results of exposure to and recovery of ecosystems from ionizing radiation. Among those areas which have been studied are:

(1) Ecosystems directly damaged by nuclear device testing: (a) Trinity Site, Alamagordo, New Mexico, first nuclear test; (b) Binkini and Eniwetok Atolls, (and, indirectly, Rongelap Atoll) in the Marshall Islands; and (c) Nevada Test Site, Nevada, Sedan crater and other areas.

(2) Ecosystems subjected to relatively massive exposures of ionizing radiation from gamma ray sources (cobalt 60 or cesium 137) given in both chronic (continuous or long term) and acute (prompt, or short-term) doses: (a) Brookhaven Ecology Forest, Long Island, Oak-Pine Forest; (b) Yucca Flat, Nevada, desert plant and animal enclosures; (c) Terrestrial Ecology Project, Puerto Rico Nuclear Center, a tropical rain forest; and (d) a short grass prairie near Colorado State University.

(3) Ecosystem subjected to relatively high radiation from radioactive wastes: Oak Ridge, White Oak Lake bed—a meadowland community established after draining of a lake which had been used as a settling pond for radioactive waste from ORNL facilities between 1945 and 1955.

(4) Ecosystem directly damaged by neutron irradiation from unshielded reactors: (a) Marietta, Georgia, southeastern pine forest adjacent to Lockheed Materials Testing Reactory; and (b) ORNL, southeastern pine forest community in vicinity of Oak Ridge Health Physics Research Reactor.

The one result common to the above studies and which may be called a "tentative hypothesis" is that recovery tends to follow "ecologically normal" and predictable successional trends; that is, patterns following damage from radiation are similar to those following fire, logging, or stripping of topsoil and other natural catastrophic events.

Finally, we have expanded our research in another area, research on thermal effluents as potential pollutants. We hope this enlarged program will lead to increasingly definitive predictive models dealing not only with thermal effects, but also thermal in addition to other water quality factors.

While I believe that knowledge now in hand is fully adequate to permit the establishment of practices and procedures in nuclear operations which assure safety of man and his environment, we have a considerable way to go in order to be able to predict quantitatively the effects if any of extremely low levels of exposure produced by the release of small quantities of radioactivity to the environment.

Since we are striving to describe effects produced by exposures which are a small fraction of natural exposures, we are faced with difficult and frequently vexing statistical problems in attempting to isolate effects produced by radiation from changes produced by much larger levels of natural radiation, other environmental stresses, and normal biological processes. Possible synergism between radiation exposure and other environmental agents add to the complexity. I believe that we will make greatest inroads into this problem by achieving, through both basic environmental and molecular and cellular level studies, a better understanding of the nature of radiation induced damage and the repair capability of damaged cell systems, populations and ecosystems.

We face difficult problems also in our efforts to predict the dose to man which results from radioactivity released to the environment. Nuclear reactors release such small quantities of radioactive material that it is difficult to measure them in the environment at any distance from the point of release. We have, however, available and under constant development sophisticated radiation detection methods which permit us to measure extremely low-levels of radioactivity and to construct and improve models for the movement of radionuclides in the environment and to man.

It appears likely that many of the techniques which we have developed and are now using for radiation and radioactivity will be very useful for studying the movements and effects of a variety of pollutants which are becoming an ever increasing source of concern.

It is frequently said that radiation and radioactivity is the most thoroughly studied environmental pollutant. I believe this is so and hope that I have succeeded in giving you some idea of the range of these studies and our approaches to outstanding problems.

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Discussion

Question: J. Neyman, Statistical Laboratory, University of California, Berkeley

Were there any systematic studies, experiments, conducted on the cocarcinogenic effect of radiation?

Reply: J. Totter

There have been some studies involving cocarcinogenesis. In particular, there has been a series of studies conducted at Oak Ridge National Laboratories on the combined effects of partially burned hydrocarbons, viruses, radiation, chromic oxide, and calcium chromate. These studies were supported by the National Cancer Institute. The results showed the very great difficulties involved in conducting meaningful experiments with so many variables when relatively low incidence rates are involved. Part of the data are to be found in the Atomic Energy Commission Symposium Series, Number 18, "Inhalation carcinogenesis," (1970).

Question: Thomas F. Budinger, Donner Laboratory, University of California, Berkeley

In reference to Professor Neyman's question on the availability of data on cocarcinogenesis, the retrospective analysis of Gibson and co-workers (*New England Journal of Medicine*, Vol. 279 (1968), p. 906) is relevant. That study showed an increase incidence in leukemia when *both* virus diseases and irradiation *in utero* occurred. Children who received radiation *in utero* but did not have

a childhood viral disease had the same incidence of leukemia as the population at large. Synergism between leukemia virus and extracts of city smog in the transformation of rat or hamster cell cultures was shown recently in Proceedings of the National Academy of Science by Freeman and co-workers (*Proc. Nat. Acad. Sci.*, Vol. 68 (1971), p. 445).

Question: John R. Goldsmith, Environmental Epidemiology, California Department of Public Health

Macht and Lawrence (*Amer. J. Roentgenology*, Vol. 73 (1955), p. 422) studying offspring of radiologists, and comparing these with offspring of other medical specialists have suggestive evidence of greater frequency of congenital defects in offspring of the more heavily exposed and also a greater frequency of male offspring among spontaneous abortuses. Has this data been taken into account in your statements, and are such populations being restudied with care to avoid response bias?

Have populations, such as veterans with intensive and frequent diagnostic radiation for diseases like duodenal ulcer been followed to try to detect late somatic and genetic effects?

Reply: J. Totter

My statements concerning effects in humans are chiefly based on Atomic Bomb Casualty Commission studies which probably provide the most extensive data available.

Question: Burton E. Vaughan, Ecosystems Department, Battelle Memorial Institute, Richland, Wn.

You stated, if I heard clearly, that doses to the Japanese population, in the ABCC study, were calculated to $\pm 15\%$ accuracy. You also stated that it was not necessary to estimate rough distance to ground-zero, for establishing dose. Would you clarify these statements: (1) How are the doses established? (2) Are accurate doses established for all 50,000 people, or some smaller number?

Reply: J. Totter

Estimates of doses to individual Japanese survivors in Hiroshima and Nagasaki have been refined considerably over a simple estimate calculated from their distance from the hypocenter. Survivors have been interviewed exhaustively to determine their precise location at the time of bombing and shielding factors determined as accurately as possible. Furthermore, the yields from the two explosions have been reestimated with much greater reliability than could be ascribed to the early estimates. Doses have been estimated for over 22,000 people who are believed to have received significant exposures. An additional 55,000 doses were estimated for persons in the zero to 9 rad range with a median of zero.

Question: R. J. Hickey, Institute for Environmental Studies, University of Pennsylvania, Philadelphia

Would you please comment on two topics?

(a) There are geographic regions, such as the Malabar Coast, where natural background radiation is very high. Could you provide information pertaining to health effects in such regions?

(b) In a publication by Van Cleave recently, on "Late Somatic Effects of Ionizing Radiation," there is a review discussion on what was called "negative life shortening effects of ionizing radiation." An example involves studies in the fifties by Egon Lorenz. Would you please comment on the concept and evidence regarding "negative life shortening effects?"

Reply: J. Totter

(a) Some studies have been made of the populations exposed to high background radiation in India, in France and in Brazil. In no case were there found to be effects above statistical variation which could be definitely ascribed to radiation. In the Indian studies some indications of effects were found in the group that was exposed to greater than 20 fold normal background, but the sample size is too small to give good statistics. I understand that this material will be presented at the 1971 Geneva Conference on Peaceful Uses of Atomic Energy.

(b) The "negative life shortening" effects of low doses of radiation which have been observed in several instances are thought sometimes to be seen because of great difficulty in providing an entirely suitable control group. Some investigators believe that low doses of radiation especially when continually administered may stimulate repair mechanisms which provide extra protection against "wear and tear" from other causes. So far as I am aware no one has made observations of this sort in humans.