BY THE COMPTROLLER GENERAL

Report To The Congress

OF THE UNITED STATES

LM114088

Problems In Assessing The Cancer Risks Of Low-Level Ionizing Radiation Exposure

Volume 1 of 2 Volumes

After decades of research, important questions remain unanswered about the cancer risks of low-level ionizing radiation exposure. With the increasing use of materials and processes that produce ionizing radiation, it has become more important to resolve these questions. Medical diagnosis and therapy, mining, certain building materials, fallout from nuclear weapons tests, and the nuclear power cycle are among the many sources of ionizing radiation.

The uncertainties in this area pose particular problems for Federal agencies in deciding how best to spend limited research dollars. GAO believes that continued Federal research is necessary, and offers recommendations to strengthen this effort.

To be processed as 1 volume with combined pagination

UNITED STATES GENERAL ACCOUNTING OFFICE

214032

EMD-81-1
JANUARY 2, 1981

Total PAGES 733

Request for copies of GAO reports should be sent to:

U.S. General Accounting Office
Document Handling and Information
Services Facility
P.O. Box 6015
Gaithersburg, Md. 20760

Telephone (202) 275-6241

The first five copies of individual reports are free of charge. Additional copies of bound audit reports are $3.25 each. Additional copies of unbound report (i.e., letter reports) and most other publications are $1.00 each. There will be a 25% discount on all orders for 100 or more copies mailed to a single address. Sales orders must be prepaid on a cash, check, or money order basis. Check should be made out to the "Superintendent of Documents".

COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-196841

To the President of the Senate and the CW000001
Speaker of the House of Representatives

Public concern about the health effects of low-level ionizing radiation exposure has been heightened in recent years by the results of several controversial studies. This report presents our analysis of the scientific issues involved in determining the cancer risks from low-level radiation exposure, and it assesses the current status of knowledge about these risks. The report also evaluates the types of research that may lead to a deeper understanding of how ionizing radiation causes cancer.

Copies of this report are being sent to the Director, Office of Management and Budget; the Secretary of Energy; the Secretary of Health and Human Services; the Secretary of Defense; the Chairman, Nuclear Regulatory Commission; the Administrator, Environmental Protection Agency; the Administrator of Veterans Affairs; the Chairman, Interagency Radiation Research Committee; and the Chairman, Radiation Policy Council.

Elmer B. Staats
Comptroller General
of the United States

DLG05730
DLG05573

SEN06603
HSE01500

DLG04662
AGC00024
AGC00912
AGC00067

COMPTROLLER GENERAL'S REPORT TO THE CONGRESS

PROBLEMS IN ASSESSING THE CANCER RISKS OF LOW-LEVEL IONIZING RADIATION EXPOSURE

D I G E S T

BACKGROUND

Since 1902, when cancer was first attributed to overexposure to x-rays, the U.S. Government has spent close to $2 billion (approximately $80 million per year in recent years) on research on the health effects of ionizing radiation. At least 80,000 scientific papers on the subject have been published worldwide.

While much has been learned about the carcinogenic effects of high doses of radiation exposure, scientists are still uncertain about how ionizing radiation causes cancer, and how to predict the effects of exposure to low doses.

With the increasing use of materials and processes that produce ionizing radiation, it has become increasingly important to answer these questions. Medical diagnosis and therapy, mining, certain building materials, fallout from nuclear weapons tests, and the nuclear power cycle are among the many sources of ionizing radiation.

Despite the uncertainty about low-level radiation risks, Federal and international regulatory and advisory bodies must set standards for radiation exposure, and individuals need information to be able to make informed judgments for themselves. (See pp. 1-4.)

GAO undertook this study to determine:

--what definite conclusions, if any, can be drawn from current scientific knowledge about the cancer risks of low-level ionizing radiation exposure; and

--what conclusions can be drawn about the best direction for current and future Federal research. (See pp. 4-7.)

EMD-81-1

Tear Sheet. Upon removal, the report cover date should be noted hereon.

THE EFFECTS OF RADIATION

A large, acute dose of ionizing radiation can kill a person within a few days. Smaller doses of radiation received by a group of people can cause that group to have more cancers than would otherwise be expected. However, it is not possible to tell which cancers resulted from radiation and which resulted from other causes. (See pp. 19-20.)

Epidemiological Studies

A major approach to assessing the risks of exposure to ionizing radiation has been through epidemiology--statistical analyses of the cancer incidence among large groups of people who have had some special exposure to radiation.

These analyses have found increased cancer incidence among groups exposed to occupational and medical radiation and to radiation from atom bombs. The largest of these groups includes 80,000 of the survivors of the atom bomb explosions at Hiroshima and Nagasaki. Generally, the exposures studied have involved high doses of radiation received at high dose rates.

Epidemiologists have used estimates of the numbers of cancers induced by these high-level exposures to predict the numbers that may be induced by lower exposures. These predictions can vary widely depending on which of several mathematical equations is used. The choice of equation is a subject of considerable scientific controversy. (See pp. 34-41.)

An alternative is to try to study groups whose exposure has involved low doses of radiation. However, there are inherent statistical limitations and practical difficulties that make it unlikely that such studies can determine the risks from low-level radiation. For instance, it is estimated that a study group of 100 million women would be needed to obtain precise data on the excess breast cancer risk of women exposed to one rad of x-rays.

It may be possible from studying a few low-exposure groups to rule out the possibility that cancer risks are much larger than currently predicted. However, these studies need careful review to assure that they are of sufficient scientific merit to justify the cost of a long-term follow-up study.

In response to public concern and congressional mandate, Federal agencies have several new low-exposure studies under way, and are considering the suitability of others. (See pp. 41-51 and 63-67.)

In fiscal year 1978, $77.3 million in Federal research was funded for ionizing radiation. Of that amount, Federal agencies spent $20.4 million on epidemiological studies. (See p. 59.)

Animal Studies

Animal studies are used to support and supplement the findings from human epidemiological studies. They can compare the effects of different levels and types of radiation exposure, and assemble exposure data that is not available from human studies (e.g., plutonium exposure). However, animal studies (like epidemiology and other types of research) cannot provide accurate measurements of low-level radiation effects.

Maintaining large numbers of animals over their life-spans is very expensive, and the results (particularly from laboratory mice) are often difficult to apply to human beings. Nevertheless, carefully designed animal studies meet a unique need: since we cannot irradiate human beings, these studies provide an experimental means to study radiation effects in an intact body. (See pp. 67-68.)

During fiscal year 1978, Federal agencies spent $29.9 million on animal research. (See p. 59.)

Studies on Fundamental Mechanisms

Molecular and cellular studies and other basic research are used to investigate the mechanisms by which radiation causes cancer. Cellular studies offer a relatively fast and inexpensive means of measuring radiation effects directly. However, they share with other research methods the difficulty of measuring low-dose effects. Also, radiation effects in a laboratory dish may be very different from effects in a complex body. Selected animal experiments on the body's response to radiation exposure support molecular and cellular studies.

Although molecular and cellular studies cannot be expected to answer all the questions about radiation and cancer, they are likely to provide important insights into the underlying mechanisms. A better understanding of these fundamental processes is necessary to allow risk estimates of low-level radiation exposure to be developed with greater confidence. (See pp. 24-33 and 68-70.)

For fiscal year 1978, $10.1 million of the Federal radiation research effort went into cellular and molecular research. (See p. 59.)

CONCLUSIONS

--There is as yet no way to determine precisely the cancer risks of low-level ionizing radiation exposure, and it is unlikely that this question will be resolved soon.

--There is a continuing need for federally sponsored research in this area. GAO also believes that Federal research efforts can be strengthened.

--GAO agrees with the objectives of current congressional and Executive Branch initiatives to coordinate Federal research efforts in this area. A Federal interagency research review group could establish research priorities to help ensure that promising ideas are funded, that unnecessary duplication of effort is avoided, and that limited Federal research funds are spent effectively.

--Recently an Interagency Radiation Research Committee was formed by a memorandum issued by the President. However, because this is such an important area, GAO believes that a Federal interagency research review group should be created by legislation. In particular, GAO believes this interagency group should include official representatives of the public.

--GAO believes that molecular and cellular studies, supported by selected animal experiments, are likely to provide important insights into the mechanisms by which radiation causes cancer. GAO's work indicates that mechanisms research, particularly on molecular and cellular effects, warrants increased emphasis and priority.

--GAO also agrees with the majority of scientists it met with that a proper balance of high-quality research is needed including epidemiology and animal studies (particularly those using dogs and primates). However, in view of the high costs, long duration, and possible limited scientific usefulness of results from some epidemiological and animal studies, GAO believes that the Federal agencies should be extremely selective in funding projects in these categories. The agencies should ensure that the studies are of sufficient scientific merit to warrant their costs. It should be borne in mind that funding studies that are unlikely to yield useful results will limit the money available for other, more promising research.

--GAO also believes there should be an intensive effort to synthesize the results of radiation research. This might be done by developing quantitative theories of radiation carcinogenesis and critically testing their predictions with cellular and animal experiments. (See pp. 77-80.)

RECOMMENDATIONS

GAO recommends that the Congress:

--Enact legislation giving statutory authority to an interagency committee to coordinate Federal research on the health effects of ionizing radiation exposure.

GAO recommends that the Interagency Radiation Research Committee, whether established by legislation as GAO recommends or continued under Presidential memorandum, should:

--Ensure, in research on ionizing radiation exposure, that increased priority and emphasis are given to studying the mechanisms of cancer induction through cellular and molecular studies and other fundamental research.

--Ensure that the cognizant Federal agencies continue to conduct epidemiological studies of groups that offer large numbers of people and a range of radiation exposure doses.

--Because of limited funding, ensure that epidemiological studies involving primarily low levels of ionizing radiation exposure are of sufficient scientific merit to justify the costs of long-term follow-up efforts.

--Ensure that the cognizant Federal agencies continue to conduct a limited number of high-quality animal experiments, particularly with dogs and primates.

--Consider carefully and initiate actions to implement recommendations in the June 1979 report of the Federal Interagency Task Force. (See pp. 81-83.)

GAO also recommends that the Secretary of Health and Human Services discontinue distribution of a publication of the National Institute for Occupational Safety and Health that GAO found to contain certain erroneous and potentially misleading information. (See chapter 19 of the Technical Report, volume 2.)

AGENCY COMMENTS

Five Federal agencies commented on GAO's draft report. Many of their reviewers agreed that molecular and cellular studies warrant increased emphasis. However, they were concerned that GAO was:

--overestimating the ability of cellular research to help resolve uncertainties about cancer risks of low-level ionizing radiation exposure, and

--not adequately addressing the need for animal research in this area.

GAO is not recommending that epidemiological and animal research be done away with. On the contrary, GAO agrees that a balanced program of high-quality research is needed.

GAO does believe that the Federal Government should be more selective in the types of epidemiological research projects that it funds. This is not GAO's opinion alone, but is supported by the reports of the Interagency Task Force on the Health Effects of Ionizing Radiation and the National Academy of Sciences Committee on Department of Energy Research on Health Effects of Ionizing Radiation.

GAO also agrees that some animal research is very important and needs to be continued. GAO believes, however, that the Federal Government should be more selective in which animal studies are funded.

Three of the Federal agencies opposed GAO's recommendation that the Congress enact legislation giving statutory authority to an interagency committee to coordinate the Federal radiation research program. They stated that the existing Interagency Radiation Research Committee, created by Presidential memorandum in February 1980, fulfills the need.

Because of the intrinsic importance of this area of research and the degree of public interest in resolving the uncertainties about the risks of radiation exposure, GAO believes that Congress should enact legislation giving statutory authority to an interagency radiation research committee. This would give the committee more status, better communication with the Congress, and independent funding. (See pp. 84-85.)

CONTENTS

VOLUME I
SUMMARY REPORT

SECTION 1
INTRODUCTION

CONTENTS

This Summary Report contains brief discussions of the key findings, conclusions, and recommendations in our complete Technical Report, volume 2 of "Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure" (EMD-81-1).

Studying the effects of exposure to ionizing radiation involves extremely complex and technical issues. Of necessity, a detailed report of such a study must also be technical to a certain extent. For this reason, we have prepared this Summary Report primarily for non-technical readers. The detailed supporting data for our conclusions and recommendations are contained in the Technical Report.

This report consists of two volumes.

- Volume 1 contains the Digest and Summary Report.
- Volume 2 contains a copy of the Digest, plus the Technical Report and appendices.

BACKGROUND

Ionizing radiation consists of rays and particles that can knock electrons free from atoms. The first known forms of ionizing radiation (x-rays and the radiation from radium) were discovered and put into use in the late 1890's. Concern about the carcinogenic effects of ionizing radiation began in 1902, when cancer was first attributed to overexposure to x-rays.

Since that time, many experiences have confirmed that ionizing radiation can increase the incidence of cancer. Groups of people who have been exposed to radiation occupationally or medically or from atomic explosions have been studied, and this effect has been observed.

Radiation effects have been analyzed for more than 70 years, through both human studies and experimental research. As a result, a larger body of research data has been assembled on radiation effects than on the effects of other carcinogens, such as chemicals, which only recently are being intensively studied.

Nevertheless, important questions remain unanswered about the effects of ionizing radiation on people. Scientists are still trying to understand exactly how ionizing radiation causes cancer, and to determine how many cancers are caused by a given amount of radiation.

With the growing use of materials and processes that produce ionizing radiation, it has become increasingly important to answer these questions. Federal and international regulatory and advisory bodies must set standards for radiation exposure, and individuals also need information so they can make informed judgments. Since the mid-1920's, national and international organizations have reduced their recommended permissible exposure levels manyfold. (Chapter 3 in the Technical Report presents a detailed history of radiation protection standards.)

Risk estimates have been based on an assumed "linear relationship" between radiation dose and effect. The linear relationship, expressed as a mathematical equation or "model", predicts that the amount of carcinogenic harm caused by radiation will double if the radiation dose doubles. The linear model is generally considered to be conservative, on the assumption that it would overestimate the effects of low levels of sparsely-ionizing radiation (x-rays and gamma rays). Present U.S. radiation protection guidelines are based on the linear model.

In July 1980, the National Academy of Sciences (NAS) Committee on the Biological Effects of Ionizing Radiation (the BEIR Committee) released its report on the risks of radiation exposure. The BEIR Committee uses a linear-quadratic model, which predicts less risk from low level exposure, for sparsely-ionizing radiation. There was considerable controversy among Committee members over the adoption of the new model.

The uncertainties about the cancer risks of radiation, especially at low levels, have been difficult to resolve for many reasons. Consider the following factors:

- Everyone is exposed to some ionizing radiation. It is impossible to avoid cosmic rays and other naturally occurring sources of radiation that permeate the environment.

- People of different age or sex respond to radiation differently.

- A cancer produced by radiation cannot be distinguished from one that did not have radiation as a cause. Research has indicated that many other substances and activities, such as smoking, can cause cancer.

- Scientists cannot yet characterize what cancer fundamentally is, much less describe precisely what role radiation plays.

Considering all this uncertainty, it is not surprising that scientific and political issues have become intertwined in the public debate on radiation protection regulation.

The scientific questions are: How does radiation cause cancer? How many cancers are caused by a given amount of radiation? Who is likely to get cancer if exposed to radiation, and when? The political questions are: If the risks from radiation are known, how much risk is acceptable? If the precise risk is not known, how much uncertainty is society willing to tolerate? Who is compensated when radiation produces cancer, and who pays? All these questions are related, but they belong to different areas of expertise, and they require different criteria for judgment.

PURPOSE OF THE STUDY

GAO undertook this study to consider the scientific questions about the cancer risks of low-level ionizing radiation exposure apart from the political ones. Our basic objectives were to determine:

- what definite conclusions, if any, about low-level effects can be drawn from current scientific knowledge; and

- what conclusions can be drawn about the best direction for current and future research.

We did not attempt to evaluate the adequacy of existing radiation protection standards.

As to our first objective, there do not appear to be very many definite conclusions that can be drawn about the cancer risks of low-level ionizing radiation exposure.

Most of what we do know comes from epidemiological studies involving groups of people who have been exposed to radiation either medically, occupationally, or from atomic bombs. Data from these studies have been the basis for most of the national and international radiation protection regulations and guidelines currently in effect.

While these studies have provided much useful data, they generally have involved high levels of radiation exposure, and it is uncertain how these results relate to what happens at lower exposure levels.

Further beclouding the issue is the fact that several recent analyses that could have helped clarify the situation have resulted in considerable controversy. In this report, we analyze the data from two studies involving low levels of radiation exposure--one study examines cancer deaths among workers at the Hanford nuclear facility in Richland, Washington, and the other examines leukemia deaths among Utah children who may have been exposed to fallout from nuclear weapons tests in Nevada. Both studies have encountered criticism in the scientific community because of the way they were structured and analyzed.

Another example of the controversy is the dispute within the BEIR Committee over the best method of estimating the cancer risk from low-level ionizing radiation. This dispute caused NAS to withdraw the original report after it had been released publicly in May 1979. NAS restructured the subcommittee on somatic effects, and the new report was issued more than one year later.

Our second objective was to determine what conclusions could be drawn about the best direction for current and future research on the health effects of ionizing radiation. There are essentially two objectives of the research program. The immediate goal is to develop a data base for estimating the risk of low-level radiation exposure. Risk estimates are based primarily on large-scale epidemiological studies, initiated many years ago, of people exposed to relatively high levels of radiation, and on animal research. These studies are expensive, and they have received a substantial portion of the Federal research dollars. Newer studies of lower levels of exposure are mainly aimed at refining the risk estimates developed from the older studies. However, there are inherent problems that seriously limit the knowledge that can be gained from analyzing low-dose effects.

The long-term goal of the radiation research program is to understand the mechanisms and processes of how radiation causes cancer. A promising source of data is the work being carried out on molecular and cellular effects. Selective animal experiments are also important to determine the interactions of surrounding tissue and the body's defenses. These research data can be used to develop and test quantitative theories of the mechanisms and processes of radiation damage and cell repair. Ultimately, if these fundamental processes are better understood, estimates of the risks of low-level exposure can be developed with greater confidence.

We believe it is essential to continue Federal funding for both the immediate and long-term research goals. However, we also believe that the basic mechanisms research, and particularly molecular and cellular studies, warrant increased emphasis and priority.

We believe that it is necessary to continue the epidemiological studies and animal research projects that provide useful data for risk estimates. Because of the expense and long-term nature of epidemiological and large-scale animal studies, and the limited results that are likely from low-dose studies, we believe that the cognizant Federal agencies must be very careful in selecting which new studies to fund.

SCOPE AND METHODOLOGY OF STUDY

At least 80,000 articles have been published internationally on the health effects of ionizing radiation. About 40,000 of these were funded by the U.S. Government through various agencies. Federal spending on ionizing radiation research since 1898 totals close to $2 billion, approximately $80 million per year in recent years.

We conducted a literature search to identify articles that raise critical issues, and interviewed researchers for their insights into problem areas. (One summary document that proved to be of limited use was published by the National Institute for Occupational Safety and Health. See chapter 19 in the Technical Report.)

We also held a series of meetings with many people having expertise or specific interest in the subject of low-level ionizing radiation exposure. These people represented a broad spectrum of viewpoints on the subject. For example, several questioned the accuracy of the linear model on which current radiation protection standards are based. Some prefer the linear-quadratic model, which generally leads to lower risk estimates, for sparsely-ionizing radiation. Others cite recent studies that indicated higher cancer risks than those expected. (These latter studies have been seriously criticized on methodological grounds.)

We determined from these discussions and from our own literature review that the problems of analyzing cancer and exposure data would be a major focus of our work. We examined in detail several published analyses. We also carried out our own analyses of the data used in these and several other studies.

We reviewed the current status of ionizing radiation research. This involved visiting experimental facilities as well as consulting with researchers active in the various fields. On the basis of our work, we evaluated the direction and emphasis of the research programs funded by Federal agencies.

Performing this work required the assistance of technical consultants in many areas. (A list of these consultants is in appendix I to the Technical Report.) We used the services of several statisticians, as well as experts in other fields such as genetics, pathology, immunology, and radiobiology. In each case, we planned and evaluated this work, and we are responsible for the conclusions drawn from the results.

We also met with an independent panel of experts, representing various disciplines and points-of-view, who had reviewed the initial draft of the report. We convened this meeting to ensure that important points had not been overlooked or given undue emphasis in our report. The fact that we gave the panel's comments careful consideration does not necessarily mean that the members endorse our conclusions and recommendations. (The panel members also are listed in appendix I to the Technical Report.)

As a further effort to assure the accuracy and balance of the report, we made a wider than usual distribution of the draft report for formal review and comment. We provided copies to the Department of Defense, the Department of Energy, several agencies of the Department of Health and Human Services (formerly Health, Education and Welfare), the Environmental Protection Agency, the Nuclear Regulatory Commission, the Veterans Administration, and the Office of Management and Budget. The Environmental Protection Agency and the Office of Management and Budget did not submit comments. We also provided copies of the draft to six researchers whose work we analyzed and several private organizations having interest in the subject. All the comments that we received were given careful consideration as we prepared the final report.

The comments came in varying formats, some more useful than others. For example, the comments from two Federal agencies consisted of compilations of responses from several agency staff members and researchers. Not all of these comments were relevant, and a few were too extreme in their positions. In addition, the reviewers within an agency did not always totally agree with each other.

Overall, however, the comments we received were cogent and we believe have helped us improve the report's balance and objectivity. The comments on the radiation research program are discussed at the end of the Summary Report. Other comments that we disagreed with or which we felt were particularly important are addressed at the end of the appropriate chapters of the Technical Report. We normally reprint the Federal agency comments in our final reports. Due to the size and complexity of this report, however, the comments were too voluminous and the reprinting costs prohibitive. Copies of the full texts of Federal agency comments may be requested from:

U.S. General Accounting Office
Energy and Minerals Division
441 G St., N.W.
Washington, D.C. 20548

We do want to point out that the agency comments may not be particularly useful for the reader. They are referenced to the chapter and page numbers in our draft report and do not correspond to the numbering in the final report.

ORGANIZATION OF THE REPORT

This Summary Report is divided into five sections. The Technical Report is similarly organized and covers in much greater detail the issues discussed here.

This section introduces the issues and offers a brief primer on the radiation facts and concepts needed to understand the technical problems.

Section 2 deals with the fundamental biological aspects of exposure to ionizing radiation. Our discussion begins with radiation damage in atoms and molecules and ends with the organization and activity of the body's immune system. We describe much of what is currently known--and not known--about the effects of radiation on the basic units of life, the cells. Although there are large gaps of knowledge in this field, we believe that understanding radiation effects at this biological level is essential for determining the relationship between radiation and cancer.

Section 3 discusses the difficulties of analyzing radiation effects among large groups of people. We examined the data on several groups who had been exposed to radiation. We studied the radiation doses they received, their incidence of cancer, etc. Generally, these people were exposed to high levels of ionizing radiation, and we wanted to see if the data could be validly extrapolated to determine how dangerous low-level ionizing radiation is.

Several mathematical models, in addition to the two already discussed, have been proposed to use the high-dose data to try to predict what would happen at lower doses. Although all these models make widely varying predictions, we found that--for each of four groups of people--more than one model described the data adequately. We concluded that it is doubtful that further research along these lines will permit precise predictions of effects from low doses of ionizing radiation, although such research may reduce some of the uncertainty of the predictions.

We examine these analytical difficulties in detail in the context of two studies of low-level radiation exposure: the Hanford nuclear workers and the Utah children living downwind from the nuclear weapons tests during the 1950's. We also inspect the possibility of conducting a study of multiple myeloma patients to determine whether the disease is correlated with low-level radiation exposure. In another analysis we point out that loss of life expectancy, as well as cancer incidence, from radiation exposure is an important public policy consideration. Finally, we consider how cancer incidence in a large population might be affected by the presence of small groups who are especially sensitive to radiation.

Section 4 examines Federal research efforts aimed at resolving the uncertainties about low-level effects. Most of the Federal radiation research budget is controlled by the Department of Energy, and most is aimed at large-scale epidemiological studies and animal research.

Section 5 provides in full our conclusions and recommendations on the Federal radiation research program. It also summarizes Federal agency comments on the radiation research program and our evaluation of them.

A BRIEF PRIMER

Radiation

The atom, a basic unit of all matter, consists of a nucleus, made up of protons and neutrons, surrounded by orbiting electrons. (See figures 1 and 2.) The electrons are bound to the atom by the electric attraction between their negative charge and the positive charge of the atom's nucleus.

Ionizing radiation consists of rays and atomic particles with enough energy to knock electrons free from (or ionize) atoms. The rays (x-rays and gamma rays) are types of electromagnetic radiation. The most common atomic particles are alpha particles (helium nuclei which contain 2 protons and 2 neutrons), beta particles (electrons), and neutrons.

Radiation ionizes atoms by transferring energy and momentum to the electrons. The amount of energy that the radiation loses as it travels through a material depends on many factors, including the density of the material and either the energy of an electromagnetic wave or the mass, velocity, and charge of an atomic particle.

The amount of energy lost by radiation per unit length of its path is the linear energy transfer (LET).

High-LET radiation, such as alpha particles and protons, gives up a lot of energy in a short distance and does not penetrate very far. Because high energy alpha particles will not penetrate the outer layer of skin, their main hazard to humans is from internal exposure, if

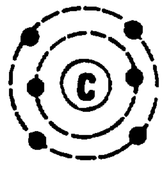


FIGURE 1

CARBON ATOM
Carbon atoms have six protons and usually six neutons in their nuclei. A neutral carbon atom has six electrons.

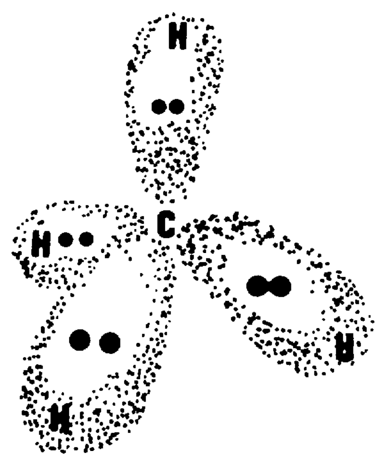


FIGURE 2

METHANE MOLECULE
A methane molecule consists of one carbon atom and four hydrogen atoms linked together. Each chemical bond in methane consists of two electrons shared between the carbon and a hydrogen atom.

alpha-emitting material is inhaled or ingested. Low-LET radiation, such as beta particles, x-rays, and gamma rays, is more penetrating. Beta particles pass through a few millimeters of tissue, while a high energy x-ray can pass completely through a person and release only a small part of its energy.

Radiation Measurements and Units

The amount of radiation energy absorbed by a body (per gram of tissue) is measured in units called rads. Equal numbers of rads of different types of radiation do not produce equal effects. The relative biological effectiveness (RBE) measures this relationship between different types of radiation. X-rays and gamma rays, which are used as reference radiations, are usually assigned an RBE of 1. Radiation of higher LET has a higher RBE. The RBE also depends on the total dose, the dose rate, the effect measured, and many other factors. For convenience, fixed values called Quality Factors (Q) have often been assumed for RBE. Standard values are 10 for neutrons and 20 for alpha particles.

Another unit--the rem--is also used, expecially in assessing population exposures involving more than one type of radiation. The dose-equivalent in rems is the absorbed dose in rads multiplied by the Quality Factor. For low-LET radiation (gamma rays and x-rays), the rad and rem are roughly the same. For high-LET, they vary considerably.

Sources of Radiation

Table 1 estimates the total U.S. population exposure to ionizing radiation in 1978. Half of the ionizing radiation people are exposed to comes from natural background sources, either from cosmic rays or from radionuclides (unstable atoms) in the earth, the atmosphere, and within the body. There are radioactive elements present to some degree in almost all materials. Mining, building, and certain other activities contribute to human exposure by uncovering radioactive material and moving it near people.

Medical diagnosis and therapy (primarily x-rays) account for 45 percent of the total U.S. exposure to ionizing radiation. Most of the remaining 5 percent is from the fallout from nuclear weapons tests. Nuclear energy currently accounts for slightly more than one-tenth of one percent.

The extent of an individual's exposure to both natural and man-made ionizing radiation depends greatly on where and how the person lives and works. In a seventy year lifespan, the average American receives about 10-15 rads of ionizing radiation. Individual doses, however, can range from 5 rads to hundreds of rads.

Low-Level Ionizing Radiation Exposure

Low-level radiation exposure is a relative term. There is no consensus on a precise definition. Whether a particular dose or dose-rate of radiation is considered "low" may depend on the person making the judgment, the

Table 1 An Estimate of Total 1978 U.S. Population Exposure

Source	Population Exposure (Thousands of person-rems* per year)	Percent	Average Individual Annual Exposure (Millirems)**
Natural Background	20,000	50	100
Medical Radiation	18,000	45	90
Nuclear Weapons Fallout	1,000-1,600	3.2	5-8
Technologically Enhanced (Mining, Building, etc.)	1,000	2.4	5
Nuclear Energy	56	0.14	0.28
Consumer Products	6	0.015	0.03
Nuclear Weapons Development, Testing, and Production	0.165	0.0004	0.00008
Total (Approximate)	40,000		

*The product of the average individual dose in a population times the number of individuals in the population. Based here on the 1970 U.S. population of 200 million.
**A millirem is one-thousandth of a rem.

Source: "Report of the Work Group on Exposure Reduction," Interagency Task Force on the Health Effects of Ionizing Radiation, HEW, June 1979, p. 21.

source and type of radiation, the parts of the body irradiated, and other factors.

In general, we have used the term "low-level" as referring either to yearly whole-body doses up to 5 rads, or to cumulative doses up to 50 rads from low-LET radiation.

SECTION 2
RADIATION AND BIOLOGY

INTRODUCTION

A large, acute dose of ionizing radiation can kill a person within a few days. Smaller doses of radiation received by a group of people can cause that group to have more cancer cases than would otherwise be expected. Excluding genetic effects, an increased cancer incidence among some groups is the primary harmful effect that has been correlated with radiation exposure. However, it is not possible to tell which of the cancers were caused by radiation and which arose from other causes.

One approach to assessing the cancer risks of radiation exposure is through statistical analyses of large-scale human and animal studies, discussed in sections 3 and 4. The other major approach attempts to understand the fundamental mechanisms and processes of how radiation causes cancer. The primary source of mechanisms data is from molecular and cellular research.

Cancer is a disease characterized by the uninhibited growth of a group of cells. Research on how radiation affects cells proceeds at three levels. The first level considers how radiation affects the atoms and molecules within the cell. The second level looks at the outward behavior of the cell, and how changes here are related to the internal biochemical changes. Finally, since the body is a complex system of many cells with diverse functions, the last level of investigation involves the interactions among cells, both normal and cancerous ones, and the role of the body's systemic defenses.

From this point of view, radiation research cannot be considered an isolated topic. All of the questions just described are intimately related to most areas of biology and medicine. Any advance made in the radiation field contributes to the general field, and vice versa. Although a great deal is known in these areas, many important questions remain.

In this section, we

-- describe the structure of cells and the chemical effects of radiation on molecules;

-- describe some results of fundamental research;

-- indicate how that research might eventually provide a more thorough understanding of radiation and its effects on people; and

-- suggest some important areas for future research.

STRUCTURE OF CELLS

The simplest organisms consist of a single cell, while the most complex ones have millions of cells which carry out specialized functions. (See figure 3.) Each cell functions through myriad chemical and physical processes. Not only must the cell perform its own vital body function, it must also pass on to its daughter cells the capability of performing that same function. This transmitting of instructions to daughter cells primarily

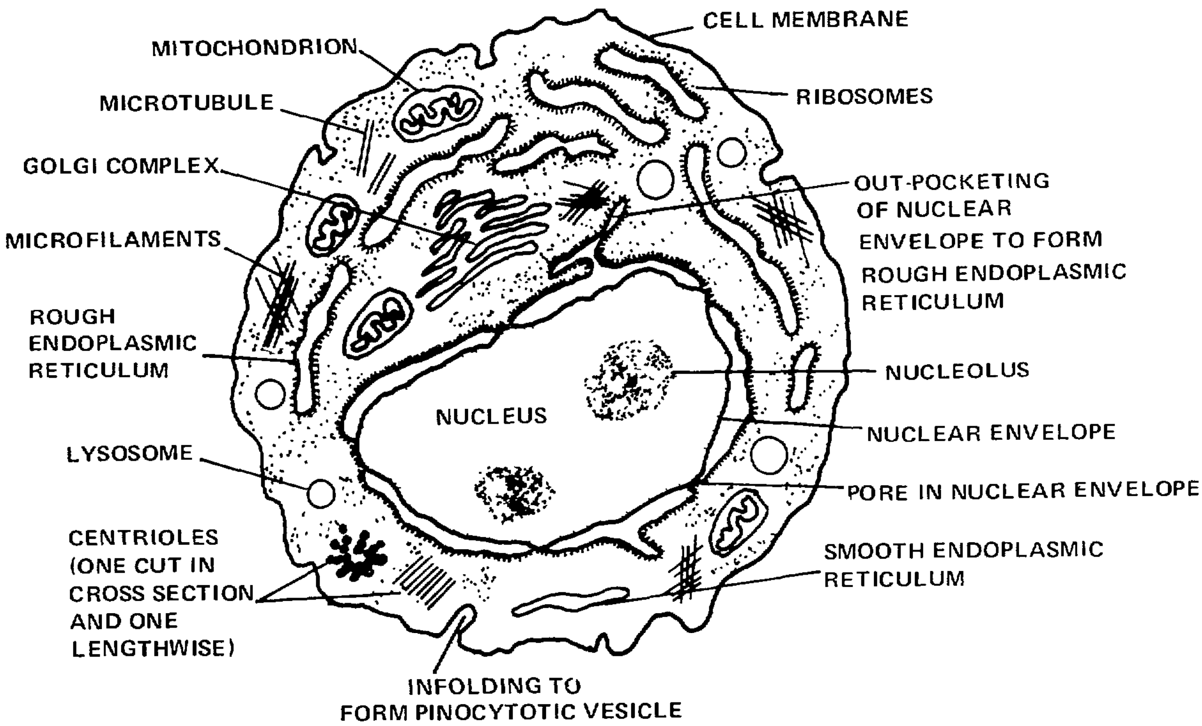


FIGURE 3

EUCARYOTIC CELL contains a true nucleus and an assortment of organelles. This type of cell is characteristic of all multicellular organisms.

is done through the cell's information molecule called DNA (deoxyribonucleic acid).

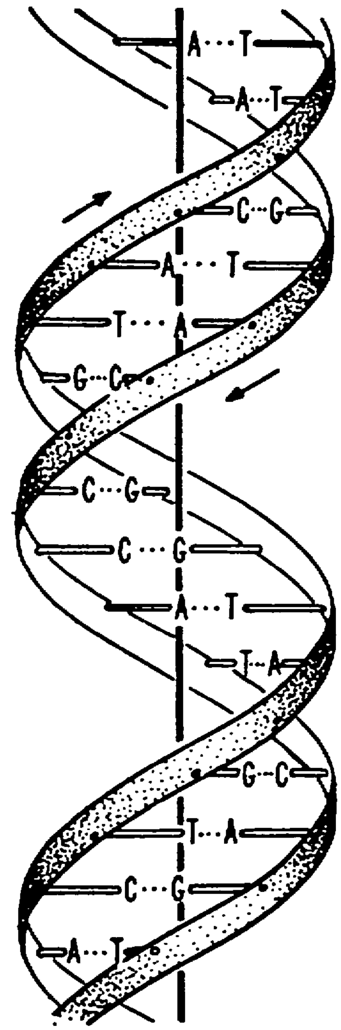
The DNA is built with four basic units called nucleotides. The order of the nucleotides spells out the information contained by the DNA. The DNA is double-stranded; that is, it consists of two facing strands made up of nucleotides. Nucleotides that face each other are always paired in the same way. Thus, one strand of the DNA is a model for building the other strand. This arrangement is essential for cellular reproduction, and for repair of DNA damage. The two strands are twisted into a double helix. (See figures 4 and 5.) The DNA is further coiled and clumped so that 5 feet of it (one ten millionth of an inch wide) is contained in each human cell.

In human cells, the DNA is organized into 46 paired chromosomes (23 from each parent). The chromosomes are further divided into genes, each of which specifies the structure of a particular product. A cell's products determine its structures and functions.

DNA controls the biological machinery of a cell through complex, only partly understood mechanisms. Damage done to the DNA--whether by radiation, chemicals, or other physical processes--can have profound effects on the cell. The cell might be unable to reproduce itself; or it might survive and transmit faulty instructions to its daughter cells, thereby producing cells with mutations.

A schematic illustration of the double helix. The two sugar-phosphate backbones twist about on the outside with the flat hydrogen-bonded base pairs forming the core. Seen this way, the structure resembles a spiral staircase with the base pairs forming the steps.

FIGURE 5



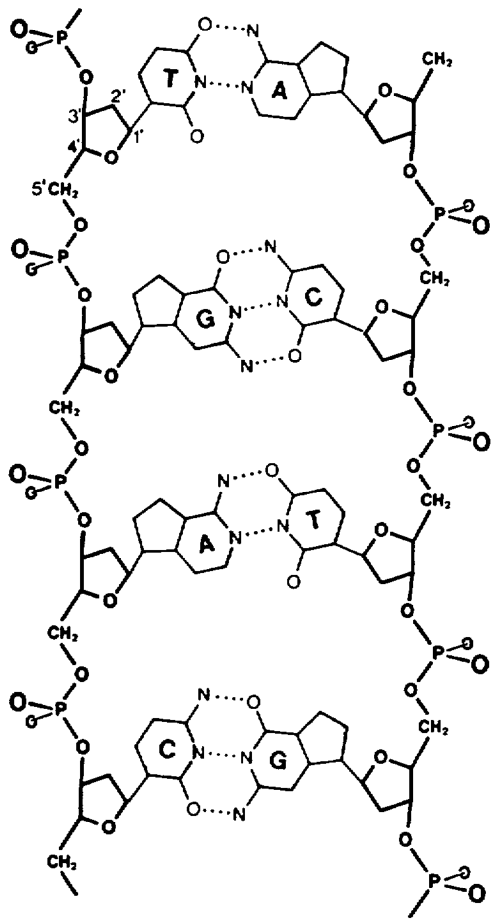


FIGURE 4

DNA is a two-chain structure. The two backbones of the molecule, built from phosphate groups alternating with deoxyribose molecules, are antiparallel: the chains are oriented in opposite directions. Base pairs connect the backbone chains like rungs of a ladder. Dots represent hydrogen bonds.

CHEMICAL EFFECTS OF IONIZING RADIATION

Atoms are the building blocks of ordinary matter, and it is through its effects on atoms that radiation affects cells and, finally, whole organisms. Cellular behavior is governed by the chemical interactions among atoms.

When radiation ionizes an atom, the atom is almost certain to react chemically with other atoms and molecules around it. If these chemical reactions damage or interfere with a crucial cellular process or component, this will be reflected in the cell's behavior.

It is believed that ionizing radiation mainly affects cells by damaging their DNA (chromosomes). Radiation can do this directly or indirectly. Direct damage occurs when radiation knocks electrons free from DNA molecules. It is the movement of electrons that makes chemical bonds which hold atoms together in molecules.

Cells are more than 75 percent water. When radiation ionizes a water (H_2O) molecule, a series of chemical reactions usually takes place which results in the formation of other molecules called free radicals. The hydroxyl free radical (OH) in particular is extremely reactive. Hydroxyl ions, produced from water molecules attached to the DNA, are the major sources of indirect radiation damage. It is not certain how much damage to DNA is done directly and how much indirectly.

There are other molecules (called scavengers) in a cell which can inhibit the action of free radicals. These radical scavengers deactivate free radicals, and so reduce the amount of damage to DNA.

DNA DAMAGE AND REPAIR

Some molecules can repair damage done to DNA by simply transferring electrons or other atoms to replace those that radiation has knocked off. Damage caused by low-LET radiation is more easily repaired in this way than that caused by high-LET radiation.

There is evidence that cells have mechanisms that can repair more extensive damage to the DNA. Cell enzymes are able to cut out a damaged section of a DNA strand, insert a new section, and splice the strand back together.

The efficiency of these repair mechanisms differs among cells and the type and dose of radiation. These mechanisms might be particularly important at low levels of radiation exposure.

The best understood mechanisms--though there is still much not known--are those that repair a type of DNA damage known as thymine dimers, produced by non-ionizing, ultraviolet light. Thymine dimers are produced when two adjacent nucleotides containing thymine have extra bonds between them. The extra bonds can garble the message contained on the DNA. There are at least three different processes by which the damaged section of DNA can be returned to its original state.

The damage caused to DNA by ionizing radiation falls into several broad categories. In single strand breaks, only one of the two nucleotide strands of a DNA molecule is broken. There is much evidence that single strand breaks can be repaired. If both strands of DNA are broken near each other, the whole DNA molecule breaks apart. The extent to which DNA double strand breaks are repaired is unclear.

Three other types of DNA damage can occur. Injury to the inner, information-containing parts of DNA nucleotides produces base damage. Cross-linking of the complementary DNA strands can occur, and DNA can also be bonded to other molecules. It is not well known how repair processes affect these last three types of damage.

Repair can be either error-free or error-prone. Error-free repair, such as two of the mechanisms which repair dimers, reduces the risk from radiation. Error-prone repair--that does not return the DNA precisely to its original state--could tend to aggravate the harm done by radiation.

DNA repair is more difficult after high-LET radiation than after low-LET radiation, presumably due to the greater density of damage and the higher proportion of double strand breaks from high-LET radiation.

EXPERIMENTS WITH CULTURED MAMMALIAN CELLS

Cells from mammals can be isolated and grown in laboratories, where they can be directly studied. Under appropriate conditions, single cells can divide to produce a colony of daughter cells identical to the parent cell. In this way, mammalian cells can be treated as if they were one-celled organisms, and their responses to radiation can be measured by the number or special characteristics of the colonies they form.

Compared to experimenting with whole animals, using cultured cells has many advantages. Measuring radiation effects on cultured cells is relatively fast and cheap. In addition, detailed analysis can be made, because a cell is a relatively simple, isolated system, and experimental conditions and the type of cells used are easily varied. However, in common with other areas of study, it is difficult to obtain accurate results at low doses. Also, the relationship between radiation effects on cultured cells and the effects in bodies has not been completely established.

Three types of reactions (or responses) of cells to radiation are studied:

1. Inactivation is lack of ability to form a visible colony.

2. A mutation is an inheritable alteration in the sequence or structure of the DNA in a cell. A mutation often produces a change in the character of a colony that distinguishes it from a normal colony. There is some indication that ionizing radiation, unlike many chemical mutagens, may predominantly induce larger (chromosomal) mutations rather than point mutations (small changes within genes).

3. Transformation involves changes in the growth characteristics of colonies. In particular, the cells tend to pile up into chaotic clumps. (See figures 6 and 7.) It is believed that a transformed cell may have properties similar to

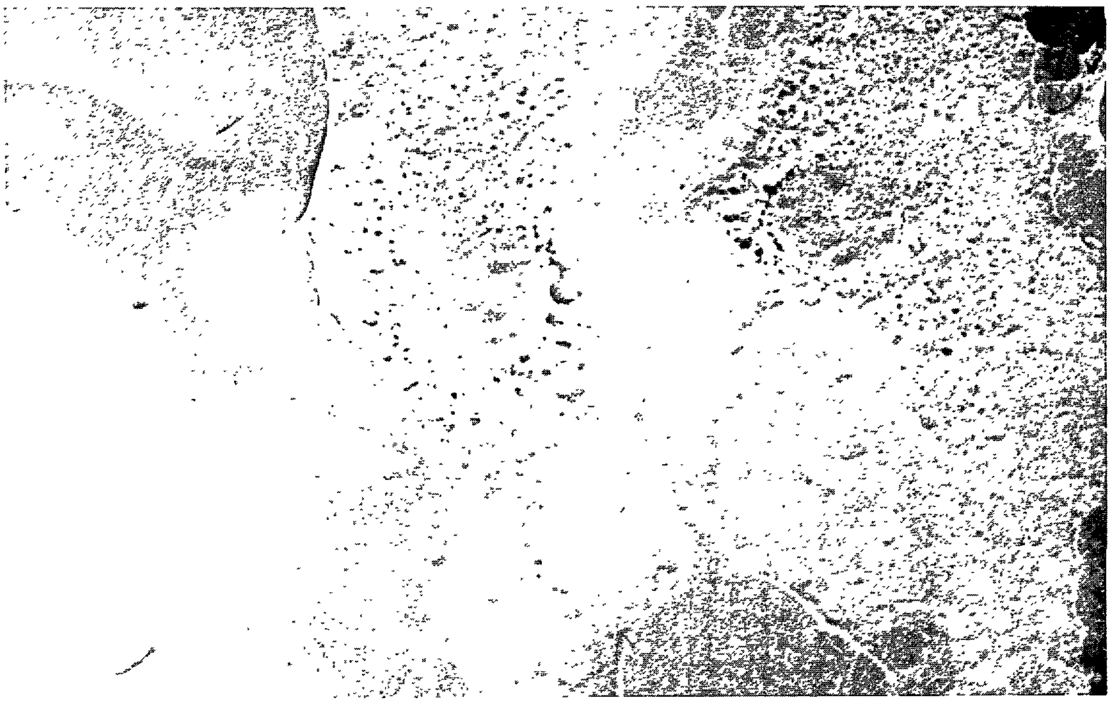


FIGURE 6. UNTRANSFORMED CELLS (MOUSE FIBROBLASTS) AS VIEWED WITH THE SCANNING ELECTRON MICROSCOPE. (Courtesy of E. L.Lloyd)

FIGURE 7. TRANSFORMED MOUSE FIBROBLASTS AS VIEWED WITH THE SCANNING ELECTRON MICROSCOPE. (Courtesy of E.L.Lloyd)

a cancerous cell. Transformation might involve a type of mutation.

Inactivation experiments are the most numerous and most accurate. Transformation experiments are at an earlier stage of development than mutation studies, and there are many uncertainties to be resolved.

Although a great deal of experimental data have been gathered in these areas, the basic mechanisms are not understood. (For example, it is puzzling that experiments show a very much higher frequency of transformation-induction than of mutation-induction.) There are, consequently, few unifying principles by which to tell what the data mean.

Nevertheless, some broad conclusions can be drawn. High-LET radiation is, in general, more effective in producing an inactivation, mutation, or transformation than low-LET radiation. A high dose-rate of low-LET radiation also is generally more effective at producing these reactions than the same total dose at a low dose-rate. Cells can tolerate a great deal of damage to the DNA; much of this damage is either correctly repaired or irrelevant to the cell's continued growth and division. However, repair mechanisms may either raise or lower the frequency of transformations. The response of cells to radiation can be drastically altered by changes in experimental conditions, such as the medium in which the cells grow, the density of cells, the time during the cells' life cycle when they are irradiated, and the amount of time that elapses before the cells are allowed to begin growing after irradiation.

There are many technical questions that make it difficult to interpret results and apply them to human beings. Experiments may have unknown and, therefore, uncontrolled variables. Different cells have different responses to radiation. Specifically, cells from established cell lines, which are developed for their infinite growth potential, behave differently from cells that have been freshly separated from an animal. It is not clear which type of cell is more representative of various cells in a live animal.

The most commonly-used cells for transformation experiments have been mouse and hamster cells. Human cells have been much more difficult to transform. It is not known whether this is due to poor experimental procedures or to a fundamental difference between human and animal cells. Furthermore, the relationship of transformed cells to cancer cells has not been completely established.

A substantial amount of data has been developed on the effects of ionizing radiation on cells. What is badly needed now is a means of synthesizing and interpreting that data. This might be possible by developing quantitative theories; i.e., expressing a hypothesis of radiation mechanisms in a mathematical formulation whose predictions can be tested against experimental data. Many theories of radiation inactivation, mutation, and transformation have been proposed. Some of these are contradictory, and experiments designed to test their assumptions and predictions are needed.

Experimental results and understanding of the underlying mechanisms are not yet adequate to allow an unequivocal extrapolation of dose-response curves (the mathematical description of how many inactivations, mutations, or transformations are caused by a given amount of radiation). Similar limitations apply in human epidemiological and animal studies. However, cell research can manipulate experimental conditions, so that the disagreements among mathematical models can be tested. This is not the case with human research: people cannot be irradiated to test models of radiation effects.

Studies of radiation effects on cultured mammalian cells can provide data of great statistical and experimental accuracy. Areas of future research concerning inactivation, mutation, or transformation include:

- Studies of radiation-sensitive mutant cells, such as cells from people with the genetic disease, ataxia telangiectasia.
- Development of quantitative theories of radiation actions.
- Experiments to test and distinguish among proposed models.
- Experiments to further explore possible cellular repair processes and their relationship to radiation effects.
- Studies to determine the relationship among different types of cultured cells, and between cultured cells and cells in an animal.
- Experiments to further explore how radiation interacts with other chemical and physical agents and with viruses to affect cells.

- Experiments to determine the relationships between changes in the genetic material and cell behavior.
- Further investigation into the molecular basis of all these phenomena.

THE IMMUNE SYSTEM

Even if all mechanisms in an individual cell were to be understood, there are still many other phenomena which must be investigated before the complete connection between radiation and cancer is known. The human body is a complex system. The interactions of cells are what determine the body's behavior, not the action of one particular cell in isolation.

The body has many levels of defense against radiation-induced cancer. First, there are the internal repair mechanisms in each cell, discussed earlier. Then, there is some evidence that normal cells can sometimes suppress the growth of malignant ones. Finally, there are the body's systemic defenses, particularly the immune system.

The immune system consists primarily of blood cells called leukocytes (literally, white cells) that travel around the body, in and out of the blood stream, actively seeking out invading microorganisms and other substances dangerous to the body. They identify, kill, neutralize, and dispose of foreign materials, helping return injured tissue to normal function. There are many different types of leukocytes to fulfill these various functions.

The immune system is very sensitive to ionizing radiation. The primary effect is on the lymphocytes (a type of white blood cells) and on the stem cells of the bone marrow and thymus. A large acute dose of radiation can kill virtually all of the leukocytes in the blood stream. Without the leukocytes, the body is unable to control the usually innocuous bacteria that inhabit the intestines, and a person may die of internal poisoning.

With repeated, low-level doses of radiation, stem cells can regenerate sufficiently and no immediate harm occurs. However, the accumulation of small injuries to the stem cells increases the chance of a malignant change occurring in one stem cell. When a cell arises which is unresponsive to the usual regulatory signals, continues to divide, and floods the body with its progeny, it is called leukemia. It is usually the first cancer to appear in excess after a large group of people receive unusual doses of external radiation. Another cancer of the white blood cells is multiple myeloma. The cancerous cells of multiple myeloma remain in the bone marrow where they cause destructive lesions of the bone.

There is some evidence that the immune system can destroy cancer cells, but it is not conclusive. It also appears that cancer cells are sometimes able to fight back against the immune system and render it ineffectual.

Some important areas for research on the immune system are: the molecular basis for immunological responses; the unexplained sensitivity of lymphocytes to radiation; and the interaction between cancer cells and the immune system.

SECTION 3
RADIATION AND HUMAN POPULATIONS

INTRODUCTION

Exposure to ionizing radiation increases an individual's probability of getting cancer. Still unresolved is the question of how many cancers are caused by a given amount of radiation. This relationship between radiation dose and cancer incidence is called the dose-response function or curve.

The present understanding of how radiation causes cancer is insufficient to predict exactly the effects of low-level radiation. Furthermore, with present techniques, there is no way to distinguish between the cells of human cancers induced by radiation and the cells of cancers induced by other causes. Thus, tissue examination cannot establish radiation as the only possible cause of a particular case of cancer. For these reasons, other methods--primarily epidemiological studies of people who have been exposed to radiation--have been used in attempts to determine the approximate risks from radiation.

There are fundamental problems that complicate any epidemiological study of radiation exposure, particularly those involving low-level exposures. In this section we discuss these problems in the context of several studies. This work formed much of the basis of our conclusion in section 4 that epidemiological studies should not be expected to provide reliable conclusions about the precise relationship between low-level radiation exposure and cancer.

Problems of Epidemiological Analyses

Analyzing radiation effects through epidemiological studies is complicated by several factors.

1. Statistical nature of problem.

Epidemiologists compare the incidence of cancer in groups with different levels of radiation exposure. One of the reasons it is difficult to interpret cancer incidence data is the presence of random fluctuations; i.e., fluctuations that cannot be accounted for with present knowledge.

Coin flipping provides an example of random fluctuations. When a coin is flipped once, there is a 50 percent chance that it will turn up heads. However, in a series of many "experiments", each experiment consisting of flipping the coin 10 times, there will be a variety of results. Most often there will be 5 heads and 5 tails. But each of the possible results, from no heads to 10 heads, can occur.

The varying number of heads obtained in "identical" experiments are random fluctuations. These fluctuations occur because the experiments are not really identical; the coin is not being flipped exactly the same way each time. Although all of the factors that influence the flip of the coins are not known, statisticians can calculate the probability that a particular number of heads or tails will result.

Knowledge about all the contributing factors is similarly limited in any analysis of cancer incidence in an irradiated population. Therefore, the analyst can only try to determine the probability that an increase in cancer incidence is due to radiation and is not a random fluctuation. Such a determination can never be absolute. The uncertainty of conclusions becomes greater as the number of cancer cases becomes smaller. This means that to measure the small effect expected from low levels of radiation, a huge number of people must be studied.

Statisticians usually consider an increase in cancer incidence to be "statistically significant" if there is less than a 5 percent probability that it is a random fluctuation.

2. <u>Inadequacy of available data</u>.

There are relatively few human groups whose exposure to radiation can be fruitfully analyzed to determine ionizing radiation effects. The most useful of these groups are those in which exposures ranged from small to relatively large doses of radiation. None of these groups is large enough to give a definitive dose-response curve at low levels of radiation. By far the largest such group is the survivors of the atom bomb attacks at Hiroshima and Nagasaki. Other groups have been exposed at work or during medical treatment.

3. <u>Other difficulties in analysis</u>.

In assessing human data, it is often difficult to accurately reconstruct individual doses of radiation from available records. Even if the overall dose can be determined, this may not be sufficient to determine the relevant dose. For example, radiation exposure to the foot is unlikely to cause or contribute to cancer of the mouth. Furthermore, it is sometimes not known which types of cells are the originators of particular kinds of cancer. This increases the difficulty of determining the relevant dose for dose-response functions.

With currently available epidemiological data, statistically significant increases in cancer incidence often are not found until years after the radiation exposure. This minimal latency period is longer for some cancers than for others. There is also a wide variation in the times tumors appear in individuals who have suffered similar exposure. These variations make it even more difficult to know which group of cancers might be attributable to a specific radiation exposure.

It is hard to find a proper comparison group for any epidemiological study, but in studies of radiation carcinogenesis it is especially difficult. Apparently identical cancers can be caused by radiation, chemicals, and perhaps other factors. Differences in exposure to background radiation among individuals may be as large as the total low-level exposure to occupational or medical radiation in some groups. Exposure to medical radiation also varies widely. Chemicals can promote or inhibit the effects which radiation causes by itself. Both radiation and chemicals can affect the strength of the body's defense mechanisms, as can other factors.

4. Size of the effect.

Notwithstanding these difficulties, human epidemiological studies have provided important estimates of the effects of radiation exposure, particularly at high doses. The predictions of low-level effects are much less certain. For example, a common estimate is that, if 10,000 people all received 1 extra rad of low-LET radiation, there would be 1 extra cancer death. Since 1,670 "spontaneous" cancers are expected over the lifetime of these people, analysts cannot detect the one radiation-induced cancer. Even if the radiation effect is underestimated by a factor of 50, analysts would have difficulty distinguishing the radiation effect from random fluctuations. To obtain precise data about the effects of 1 rad of low-LET radiation could require a population of 100 million people. (We discuss this problem in more detail in section 4.)

5. Study design and methodology.

Analyzing epidemiological data can produce misleading results if careful consideration is not given to the methodology and statistical tests to be used. In order to ensure objectivity in statistical analysis, the researcher should ideally plan the method of analysis before seeing the data. This includes selecting hypotheses to be tested, creating categories such as dose ranges that divide the total study population into smaller groups, and selecting appropriate statistical tests. If the data were observed before the method of analysis was selected, the researcher might be inclined to attribute undue significance to peculiarities that can always be found, even in purely random data.

The statistical methodology of many epidemiological studies have been criticized by other scientists. These criticisms frequently are directed at the selection of the study group or the controls. Some studies have been criticized because the researcher used simple analyses, such as proportional mortality, rather than more sophisticated techniques, such as person-years at risk. Other studies have been criticized because they did not control for factors that complicate the analysis. For instance, a study that includes radiation-induced lung cancer should analyze smoking data for the study group and controls.

In general, therefore, statisticians are reluctant to draw or to accept strong conclusions from one data set. In particular, new and surprising results are, and should be, viewed with skepticism until verified through other studies.

TESTS OF DOSE-RESPONSE CURVES

The most extensive epidemiological data on the effects of ionizing radiation exposure involve people who have been exposed to relatively high doses (up to 100's of rads). Data on the effects of chronic exposure to smaller doses have been more difficult to obtain and more difficult to interpret. Therefore, analysts have tried to estimate the risks of low-level radiation by determining how the effects of low doses are related to those of higher doses.

Several hypotheses have been proposed to describe this relationship. As noted earlier, the linear model predicts that, if radiation exposure doubles, then the number of cancers caused by radiation doubles. The quadratic model predicts a fourfold increase in radiation-caused cancer if radiation exposure doubles; on the other hand, the square-root model predicts a 40 percent increase. The linear-quadratic model predicts that there is a linear response at low doses and a quadratic response at higher doses. Based upon the data from high doses, these models predict widely varying effects from low doses of radiation.

GAO carried out tests to determine how well each of several different dose-response models describe or "fit" four well-known human data sets: (1) leukemia in patients who were treated with x-rays for the disease ankylosing spondylitis, (2) lung cancer in uranium miners, (3) bone cancer in radium dial painters, and (4) leukemia in atom bomb survivors at Hiroshima and Nagasaki. Although there are more than 50 potential human populations (see appendix II to the Technical Report) and each of the four data sets has acknowledged limitations, we chose them because they have provided the basis for current estimates of risk from radiation exposure.

The results of our tests show that:

- Each data set could be fit acceptably by more than one model.

- In general, statistical tests on radiation epidemiological data can show that some dose-response models are wrong. They cannot show which one is right.

- It is unlikely that the best shapes to the dose-response curves in man can be resolved by statistical analysis alone. What is needed is a better understanding of the fundamental mechanisms by which cancers are induced by radiation.

CANCER INCIDENCE IN HANFORD WORKERS

Detailed records on occupational radiation exposure have been maintained since 1943 on approximately 30,000 employees of the Hanford nuclear facility in Richland, Washington. Between 1975 and 1978, several researchers analyzed the exposure data and death records of these workers and drew widely differing conclusions about the radiation effects.

Critique of Mancuso, Stewart, and Kneale

We examined two published analyses by Drs. Thomas Mancuso, Alice Stewart, and George Kneale on cancer mortality among the 30,000 Hanford workers. The results of these analyses have been highly controversial.

In their first analysis (1977), Mancuso et al. compared the cancer mortality of irradiated and unirradiated Hanford workers. They divided workers into dose groups and ranked the groups by cancer incidence, and they calculated the average radiation dose of victims of various causes of death.

The results of this analysis showed a higher proportion of irradiated workers among the cancer deaths (66 percent) than among the non-cancer deaths (61.1

percent). Their estimate that radiation caused 26 excess cancer death implies that Federal and international regulatory bodies have been seriously underestimating the effects of low radiation levels. In fact, the estimate suggests that the Hanford workers' risk of dying from radiation-induced cancer is on the order of 10 times greater than expected under conventional risk estimates. Most of the deaths attributed to radiation were from lung cancer, multiple myeloma, and pancreatic cancer.

For reasons discussed below, we do not believe the 1977 Mancuso et al. analysis is sound. Some of the problems remain in their 1978 analysis which drew conclusions closer to conventional estimates.

There are several features of the Hanford data that, if not properly taken into account, can distort or obscure any conclusions reached.

For example, the "healthy worker" phenomenon has an important influence. Individuals who work steadily for one employer have significantly better health and greater life expectancy than the general population. However, the healthy worker phenomenon is not uniform over all causes of death. In particular, long-term workers seem to be just as susceptible as the general population to most kinds of cancer. This means that because long-term workers are living longer and not dying from other causes, a larger proportion of their deaths are from cancer than the proportion among the general population. Most of the irradiated Hanford workers were long-term employees; most of the unirradiated group represent workers employed for less than two years. Mancuso et al. included short-term workers in their initial analysis; they have excluded short-term workers in their 1978 and subsequent re-analyses.

Another influencing factor is the amount of radiation received by the workers. By 1973, about 4,000 Hanford workers had died from all causes. Of these, only 180 were exposed to more than 5 rads of radiation. This means that most of the workers may have received more than twice as much radiation from normal background and medical sources as they did occupationally.

A relatively few higher dose cases can unduly influence some analyses. Of the 180 workers receiving over 5 rads, only 52 received more than 20 rads of radiation exposure. Eleven of the 52 workers died from cancer. Eleven cancer deaths is not an unusually large number, but there is a peculiar distribution of types of cancer. There were three cases each of multiple myeloma, pancreatic cancer, and lung cancer. Multiple myeloma and pancreatic cancer typically account for 2 percent and 5 percent, respectively, of all cancer deaths. Because these numbers are so small, it is difficult to evaluate their significance. If it is assumed that these results are not a fluctuation, probably 2 or 3 of the multiple myeloma deaths and 2 or 3 of the pancreatic cancer deaths are due to a carcinogen.

A particularly important cause of lung cancer is smoking. The lung cancer death data in the Hanford study closely parallel the mortality data from emphysema, a disease that has not been correlated with radiation exposure. This suggests that the incidence of lung cancer reflects smoking habits rather than radiation effects.

However, neither of the published Mancuso et al. analyses provided smoking data.

There are other troubling aspects of the Hanford data. Overall, the number of cancer deaths is close to what is expected among long-term (at least 2 years) Hanford workers. Also, there was a deficit of deaths among Hanford workers from other cancers, including leukemia--one of the main types of cancer that has been correlated with low-LET radiation exposure. The data on other diseases, such as metabolic disorders and cirrhosis of the liver, can be interpreted to show correlations with radiation. This suggests that there are strong correlations between accumulated radiation exposure and lifestyle, and between such exposure and physical condition.

The Hanford workers were exposed to many different materials. There is no way in the Mancuso et al. analysis to rule out the possibility that chemicals or other carcinogens at Hanford caused all excess cancer that may have been observed.

Analysis of Hanford Data

In performing our own analysis of the Hanford data, we tried to avoid as many as possible of the influencing factors discussed above. We used a data tape supplied by Dr. Mancuso, which contained annual measured external radiation doses, a measure of internal radiation exposure, and death data.

Since there has been considerable controversy over the results of Mancuso et al., and since we critiqued their analysis before beginning our own, we cannot claim to have made a completely objective analysis according to the usual statistical requirements. However, by comparing overly simple analyses with one based on a model we believe to be better suited to the problem, we show how the original analyses tend to overestimate radiation effects.

Calculations with this latter model indicate that radiation has not had a statistically significant effect on cancer deaths among Hanford workers. This conclusion is consistent with the results of Mancuso et al.'s most recent (October 1979) calculations. These calculations, as yet unpublished, were done using a model similar to ours. A recently published analysis of Battelle's Hanford data by Ethel Gilbert and Sidney Marks also failed to find any statistically significant radiation effect.

Inclusion of the data on surviving workers further weakens evidence of a radiation effect. There is a so-far unexplained tendency for surviving workers to have a higher average dose-per-year than those who died.

Our estimate that one cancer death among the Hanford workers may have been induced by radiation is compatible with conventional risk estimates for this population. However, our estimate is highly uncertain, even with the use of a more sophisticated model. If the small effect on cancer deaths overall is assumed to be due merely to chance, there may be an effect on deaths from "highly-sensitive" cancers (such as multiple myeloma and pancreatic cancer). Whether this is a real effect cannot be resolved by analyzing the present Hanford data.

Somewhat more reliable conclusions about radiation effects may be possible, as additional data on Hanford worker deaths accumulate in the next decade.

Appendix XVI to the Technical Report contains comments by Drs. Mancuso, Stewart, and Kneale, along with our response. We believe that their comments do not present any substantive rebuttle to our conclusions.

SURVEY OF MULTIPLE MYELOMA PATIENTS

Even though the Hanford data do not establish a correlation between radiation and multiple myeloma, there was an unusual incidence of the disease among the Hanford workers, especially those with a cumulative dose of 20-35 rads of radiation. A 1975 study of U.S. radiologists has also raised the possibility that multiple myeloma may be induced by low-level radiation exposure. Both results are puzzling because the possible multiple myeloma effect is not matched by an effect on leukemia, more commonly associated with radiation exposure.

This prompted us to investigate the exposure history of a small group of multiple myeloma patients in Massachusetts and New Hampshire. We wanted to see whether these patients shared common histories, particularly in regard to medical radiation. (This type of study is called "case-control".) The results might suggest whether a larger study could develop useful information.

We interviewed 89 multiple myeloma patients and a comparison group of 120 men and 108 women. Our survey was a rough, preliminary one that was not expected to yield definite conclusions, and does not meet most of the standards required for a scientific study.

Both x-ray therapy and occupational exposure seemed to show up more frequently among the multiple myeloma patients than among the comparison group. However, some of the cases listed as having occupational exposure probably received occupational doses of less than one rad, which would not be relevant to the 20-35 rad dose range. The exposure histories were too fragmentary to draw any conclusions.

Our survey shows that the main problem in conducting a study of multiple myeloma patients will be to identify a source of accurate exposure data. If more accurate data on radiation exposure can be assembled, a larger study may be able to clarify the Hanford multiple myeloma results.

CHILDHOOD LEUKEMIA MORTALITY IN UTAH

Another highly publicized series of exposures involved fallout from nuclear weapons tests conducted by the Federal Government in Nevada between 1951 and 1958. There has been continuing public concern about the possible health hazards associated with these tests. Congressional committees and an interagency task force appointed by the President have been studying the issue and considering alternatives for compensating people who may have developed radiation-related illnesses as a result of the nuclear tests.

In February 1979, a team of researchers headed by Dr. Joseph Lyon published a study which found a statistically significant excess of leukemia deaths among children who may have been exposed to fallout in the State of Utah and two subgroups--southern Utah and Utah males. The study found a smaller increase in the childhood leukemia death rate in northern Utah, where fallout exposure was assumed to be low. (However, these more populous northern counties actually contributed 33 of the total estimated excess of 52 leukemia deaths.) Figure 8 shows the fallout path from one nuclear weapons test.

Lyon et al. did not maintain that fallout caused the excess leukemia deaths among Utah children, but this possibility is suggested by the presentation of their analysis.

Whether the excess leukemia deaths represent a true effect of fallout is unclear. Lyon et al. mention that there were low leukemia death rates among the pre-test and post-test control children in southern Utah. (This trend is consistent with the national leukemia mortality rates among white children in the 1950's, which were substantially lower in rural areas than in urban areas. Southern Utah is predominantly rural while northern Utah has several large cities.) As a result of the low death rates in the comparison periods, the more than two-fold increase in the leukemia death rates of the high-exposure children in southern Utah just brought their rates to slightly above the national statistics.

We noted that the death rates in the comparison groups were proportionately much lower in the 10-14 age group, among whom Lyon and his colleagues detected the strongest leukemia effect. Our analysis, which modifies the data for these 10-14 year old controls, yields a somewhat lower but still significant estimated excess of

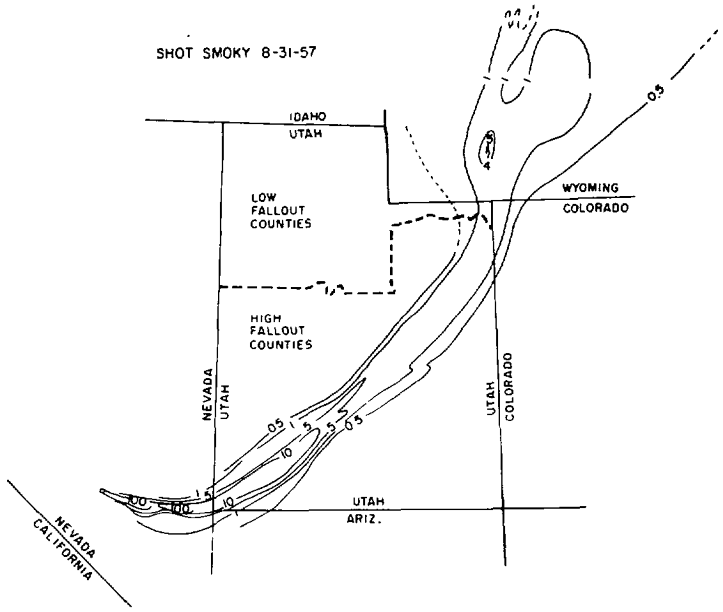


FIGURE 8 Fallout-Exposure Map (44 Kiloton Test, "Shot Smoky," August 31, 1957).

The contour lines indicate residual surface intensities in milli-Roentgens per hour at 12 hours after a test.

leukemia deaths in southern Utah and a much lower estimated excess in northern Utah.

Other trends in national childhood leukemia mortality rates, in addition to rural-urban differences, have been observed by researchers. Leukemia death rates, which had been growing quickly, for white children appear to have peaked, but at different times for particular age groups: for infants, in 1943; for 1 to 4 year olds, in 1953; and for 5 to 14 year olds, in the early 1960's. These trends in the leukemia mortality rates are important in assessing the Lyon et al. analysis because expected leukemia deaths among the high-exposure children were derived by merging the death data of other children in the control periods before and after the nuclear fallout years.

One of the Lyon et al. graphs shows the decline in childhood leukemia mortality as beginning in about 1968. Our analysis, based on this assumption, suggests that combining the two control periods would underestimate the expected leukemia deaths by about 10 percent. Even when the expected deaths are adjusted upward by 10 percent, the estimated excess leukemia deaths, using GAO's modified data, remain close to statistically significant in southern Utah, with 14.5 among 32 observed leukemia deaths. However, the estimated excess deaths become a negligible 4.2 among 152 observed in northern Utah, and we found no statistically significant excess for the State of Utah or among Utah males.

A major problem in analyzing the childhood leukemia data is that no accurate data have been available on how much fallout was received by Utah residents. The Lyon et al. paper points out that some tests were monitored inadequately, and some tests were not monitored at all. These problems may have introduced a factor of 2 into the uncertainty of external dose estimates for exposed populations. Before 1957, there are no reported measurements of the isotopic composition of fallout and its possible entrance into the human food chain.

In September 1980, the Secretary of Health and Human Services (HHS) announced that five Federal agencies will fund $4 million of research related to the potential health effects of fallout from the Nevada nuclear weapons testing program. The Department of Energy (DOE) and the Department of Defense (DOD) plan to spend $2 million to develop more reliable estimates of internal and external radiation doses from the fallout. HHS plans to spend about $1 million for studies of thyroid abnormalities and adult leukemias.

The DOE project, which is based on preliminary work by a team of University of Utah researchers, plans to derive approximate fallout levels for each community by measuring the radiation levels of bricks in buildings. In the DOD project, doses from internal radiation will be estimated from the body burdens of radionuclides. Firmer conclusions about the magnitude of the effect of fallout exposure, if any, may be possible if more accurate estimates of fallout doses can be developed. However, even with improved dosimetry, it is unlikely that reliable dose-response data can be derived with the possible exception of thyroid cancer. The thyroid gland concentrates radioiodine, which can enter the body in milk from cows grazing in radiation-contaminated pastures. It may be possible that doses can be measured fairly accurately by analyzing the thyroid tissue.

ESTIMATING LATENCY

It is not only important to know how many cancers will be caused by radiation, but also when these cancers are likely to appear. In the cases that have been studied, there is some period--ranging from 2 to 20 years--between the radiation exposure and the time a group begins to have a statistically significant excess of cancer. This time is called the minimal latency period. The length of the latency period may depend on many factors: type of radiation, type of cancer, the dose and dose-rate, and the sex, age, lifestyle, and other characteristics of the individuals in the group that was exposed.

The latency period associated with a type of cancer has important public policy implications. Assuming equal incidence and fatality rates, a cancer with a two-year latency period after radiation exposure is more harmful than one with a much longer latency period. For public policy, it is just as important to consider the loss of life expectancy caused by radiation as it is to consider the number of excess cancers.

We examined two of the different models used to predict when radiation-caused cancers are likely to appear. The absolute risk model predicts that, after the latency period is over, a radiation-caused cancer is equally likely to occur in any following year and, therefore, simply adds to the natural incidence. The relative risk model predicts that the occurrences of radiation-caused cancer follow the same pattern as the natural cancer rate, which usually rises sharply with age (i.e., the radiation risk is proportional to natural incidence).

The choice of model affects the number of predicted cancers. For example, many more cancer deaths are predicted from background radiation under the 1972 BEIR Committee's relative risk model than under its absolute risk model. However, when the predicted age at death of the victims is taken into account, the drop in life expectancy is about as large under the apparently optimistic absolute risk model as under the relative risk model.

We tested both of these models to see how well they fit cancer incidence data of the Japanese atom bomb survivors. The results show that the data are not adequate to choose between the two models. The additional atom bomb survivor data, which will be available in the near future, are not likely to provide any more definite conclusions.

SUSCEPTIBLE GROUPS IN THE POPULATION

The preceding analyses have discussed how radiation affects large groups of people. However, there is evidence that sensitivity to ionizing radiation may vary significantly among individuals depending on the stage of the life-cycle at which the exposure occurs. For example, children exposed to ionizing radiation are apparently more susceptible to radiation-induced cancer. In addition, there may be individuals whose genetic heritage makes them highly susceptible to radiation-induced cancer.

Thus, it is possible that there are subgroups in the general population that are super-sensitive or highly-sensitive to radiation. (Correspondingly, there could be a highly-resistent subgroup.)

Estimates of deaths from low doses of radiation are derived from the number of deaths observed from exposure to higher doses, usually assuming a linear relationship between the high and the low doses. However, if there are unusually sensitive subgroups, low doses would cause these people to die in greater numbers than predicted by the linear model. The total population response could be underestimated, if all or most of the people in a sufficiently large subgroup get cancer from low doses.

It is also possible that these people would get cancer simply from background radiation. In that case, more total cancers and more loss of life expectancy might be attributed to unusual radiation exposures than are really warranted.

We believe groups suspected of being unusually sensitive to the induction of cancer by ionizing radiation warrant further study. An effective means of protecting segments of society may be to prevent radiation exposures at critical periods in the lifecycle.

Several susceptible groups whose cells are sensitive to ionizing radiation have already been identified. These people suffer from one of four inherited diseases: Ataxia Telangiectasia, Fanconi's Anemia, Bloom's Syndrome, and one form of Retinoblastoma. The few people with these diseases have inherited two copies of a defective gene. There is as yet no evidence that persons with these inherited diseases are abnormally sensitive to the induction of cancer by ionizing radiation. However, people with these diseases are more likely to get cancer in general. Their susceptibility to cancer may be linked to DNA repair deficiencies.

An elevated incidence of cancer has also been seen in a study of the relatives of people in one of the disease groups. It may be that people who carry only one copy of the critical gene of these diseases are more sensitive than average to radiation. There could be a considerable number of these people, perhaps as much as one or more percent of the population.

SECTION 4
THE FEDERAL RADIATION RESEARCH PROGRAM

INTRODUCTION

In this century the U.S. government has devoted close to $2 billion for research on the health effects of ionizing radiation, spending roughly $80 million annually in recent years. Because of its potential impact on human health, and the uncertainty about the effects of low levels of exposure, ionizing radiation will continue to be the subject of intensive Federal and private research.

In this section, we discuss the status and some proposed changes in the Federal research efforts. In order to assess those efforts, we

-- compiled a list of Federal research on the health effects of ionizing radiation for fiscal year (FY) 1978 and evaluated the prospects of that program;

-- reviewed the June 1979 report of the Interagency Task Force (formed in May 1978) on the health effects of ionizing radiation;

-- reviewed legislation that would create a Federal Conference on Research into Biological Effects of Ionizing Radiation, and

-- investigated the impact on researchers of a review being carried out by the National Academy of Sciences (NAS).

The major goal of the Federal radiation research program is to develop data for estimating the risks from ionizing radiation exposure. These risk estimates are the basis for Federal radiation protection guidelines for workers and for the general public. Most of the results are obtained from large-scale human epidemiological studies and animal experiments. Continued funding of carefully selected epidemiological and animal studies is important both to refine current risk estimates and to ensure that estimates do not greatly underestimate the true risk.

Much less emphasis has been given to the long-term goal of understanding the underlying mechanisms of how radiation causes cancer. Because statistical analyses cannot determine the risks of low-level radiation exposure, we believe reliable assessments of these risks can only eventually come from understanding these fundamental processes. For this reason, we believe molecular and cellular research should be stepped up. An intensive effort also should be made to synthesize these results by developing quantitative theories, which can be tested with data from animal and human studies.

We recognize that any evaluation of a research program involves a considerable degree of subjectivity. The choice of programs to be emphasized depends largely on a sense of direction, and it is uncertain which directions will yield big payoffs.

FEDERAL AGENCY FUNDING

In FY 1978 (October 1, 1977 to September 30, 1978), the Federal Government supported 500 research projects on the health effects of ionizing radiation. Those projects cost $77 million and were sponsored by six agencies:

Department of Energy (DOE)
Department of Health, Education, and Welfare (HEW)--now the Department of Health and Human Services (HHS)
Department of Defense (DOD)
Nuclear Regulatory Commission (NRC)
Environmental Protection Agency (EPA)
Veterans Administration (VA)

Table 2 shows the subject areas of the Federal research program. They include epidemiological studies, animal research, molecular and cellular research, studies of the environmental distribution of radioactive materials and the pathways by which they reach human beings (pathways studies), and other research (mainly, developing quantitative theories).

DOE funded 69 percent of the research on the health effects of ionizing radiation in FY 1978. It inherited this leading role from the Energy Research and Development Administration (ERDA), and prior to that the Atomic Energy Commission (AEC). In 1946, Congress empowered AEC to conduct the health effects research program as part of its broader responsibilities for developing nuclear power and nuclear weapons.

DOE's program has emphasized epidemiological and animal research. DOE sponsored several major epidemiological studies in FY 1978 including $7.8 million through NAS to continue the lifespan study of Japanese atom bomb survivors, $2.6 million for Argonne National

Table 2 TYPES OF RESEARCH FUNDED BY FEDERAL AGENCIES IN FY 1978

		Epidemio-logical	Animal	Molecular and Cellular	Other	Pathways	Total	Percent
DOE	Proj	27	72	24	10	80	213	
	$	15,590	20,297	3,665	1,729	12,014	53,295	69%
HEW	Proj	59	47	86	1	5	198	
	$	2,730	4,120	5,200	21	166	12,237	16%
DOD	Proj	2	40	15	–	–	57	
	$	1,600	4,123	1,132			6,855	9%
NRC	Proj	5	8	–	–	10	23	
	$	348	1,264			1,522	3,134	4%
EPA	Proj	1	2		–	6	9	
	$	125	53	–		1,498	1,676	2%
VA	Proj	–	–	2	–	–	2	
	$			81			81	0.1%
Total	Proj	94	169	127	11	101	502	
	$	20,393	29,857	10,078	1,750	15,200	77,278	
	Percent	26%	39%	13%	2%	20%		

($ in 1,000's)

Laboratory to track 5,000 people industrially or medically exposed to radium 30 to 60 years ago (including the radium dial painters), and $1.1 million for research and logistical support to track the incidence of diseases, particularly thyroid abnormalities, among people in the Marshall Islands who were exposed to fallout from a 1954 hydrogen bomb test. To estimate risk from high-LET radiation produced by the nuclear fuel cycle, DOE has funded several large-scale animal experiments on the metabolism and toxicity of plutonium and other radionuclides within the body. Ten percent of DOE's funds went to molecular and cellular research and to develop quantitative theories.

In FY 1978, HEW funded 16 percent ($12.2 million) of the research on the health effects of ionizing radiation. Forty-two percent ($5.2 million) of HEW's funds went to molecular and cellular research, mainly through the National Cancer Institute in the National Institutes of Health (NIH). A portion of the HEW health effects program is funded through the Bureau of Radiological Health in the Food and Drug Administration. The Bureau regulates diagnostic and therapeutic medical equipment (the source of 45 percent of the total U.S. exposure to ionizing radiation).

DOD sponsored 9 percent ($6.9 million) of the research. Almost all of DOD's research is performed in-house by the Armed Forces Radiobiology Research Institute and the U.S. Air Force School of Aerospace Medicine. DOD spent $1.9 million in FY 1978 ($4.9 million in FY 1979 and $6.8 million in FY 1980) to identify all civilian and military participants at U.S. atmospheric nuclear weapons tests, to determine the radiation dose for each participant, and to assemble data about each test series.

NRC and EPA, together, supported 6 percent ($4.8 million) of the research. NRC regulates radiation emissions from nuclear powerplants, and EPA sets standards for total radiation emissions into the general environment. Half of NRC's and almost all of EPA's radiation research funds sponsored pathways studies.

VA sponsored only 2 projects ($81,000) on the health effects of ionizing radiation. Both VA and DOD are involved in claims made against the United States Government as a result of military and civilian exposures to radiation from nuclear weapons tests.

TYPES OF RADIATION RESEARCH

Table 2 reflects the emphasis on developing data for risk estimates. Combined, epidemiology and animal research, which are primarily aimed toward this goal, comprised 65 percent of the Federal radiation research program in FY 1978. Four large epidemiological projects alone accounted for 17 percent ($12.9 million) of the budget. Five of the animal studies received over $1 million each and, together, comprised about 8 percent of the total budget.

Studies directed at underlying mechanisms, such as molecular and cellular research, received much less support. Only 15 percent of the budget went to these studies, to projects to develop quantitative theories, and to other minor categories of health effects research.

The remaining 20 percent of the budget funded pathways studies. This category includes measuring radioactivity levels in the general environment and in the vicinity of radiation-emitting facilities. It also includes studying the amount of radioactive elements that enter the food chain through soil and water. This research is important for establishing emissions standards for the different stages of the nuclear fuel cycle and for identifying sources of significant radiation exposure. However, it is a different category of research than that directed at discovering the health effects of ionizing radiation, and we did not evaluate its potential results.

The evidence indicates that the Federal Government will give even greater emphasis to large-scale epidemiological studies. The Interagency Task Force made 10 research recommendations in its June 1979 report; nine sought to refine current risk estimates. In recent years Federal agencies have initiated several new studies of low-level exposure groups, and the Congress is considering the feasibility of others. Public Law (P.L.) 95-601, enacted in 1978, directs NRC and EPA (in consultation with HEW) to evaluate and report to the Congress on options for epidemiological research on the health effects of low-level ionizing radiation.

As we discuss in the following pages, there are serious problems that limit the usefulness of human epidemiological studies involving low doses of radiation. Studies of low-dose effects in animal populations also have limitations.

Epidemiology

It was through epidemiology that a correlation between cancer and ionizing radiation was established. Studies of groups who had experienced unusual radiation exposures found a significantly higher incidence of cancer than in similar groups who had not received such exposure. Epidemiological studies have yielded important information about the types of cancers that may be induced, the latency period, and the factors that may influence cancer induction. Government decisions about safe levels of exposure rely on risk estimates that are derived primarily from epidemiological studies.

Estimates of risk for low-doses and dose-rates of radiation have been extrapolated primarily from data from exposures to relatively high radiation doses (from 50 to hundreds of rems) and high dose rates (above 1 rem per minute). The relationship between these high-dose effects and the possible effects from low doses is uncertain.

There are fundamental problems in trying to determine the dose-response relationship from any study of low-level radiation exposure. The primary problem is that the lower the dose being studied, the larger the study population has to be.

According to a common estimate of radiation risk, if 10,000 people are exposed to one additional rad of low-LET radiation, then over the lifetime of the group, one additional cancer death would be expected. In the United States, the normal lifetime expectation of dying of cancer is 1,670 per 10,000 births. Statisticians would usually consider any number of cancer deaths between 1,600 and

1,740 to be a random fluctuation from the expected number. Thus, the study group needed to measure the effect of one rad must be substantially larger than 10,000.

An appendix to the report of the Interagency Task Forces' Work Group on Science addresses this problem of sample size. According to the appendix, obtaining precise estimates of the excess breast cancer risk of women exposed to 1 rad of x-rays would require a study group of 100 million women. Even if the breast dose were 10 rads, the required sample size would be 1 million women. The sample size for 1 rad exposures would be less than 100 million, but still huge, for those cancers that are less common than breast cancer.

An additional complication in studying low-level effects is the contribution of background and medical radiation. In a lifetime, a person in the United States is likely to receive about 13 rads from background radiation and from routine medical procedures. A person's measured occupational or accidental exposure may represent only a small fraction of his total dose.

Because of the large amount of work already done on radiation, further studies, in order to make useful scientific contributions, must be relatively precise. It is already known that radiation can cause cancer. What is needed now is an accurate quantitative description of that relationship. Even if the problems of sample size and of other radiation exposure could be solved, optimally an epidemiological study would still need:

-- accurate dosimetry for each individual in the study population;

-- a lifetime follow-up on each individual;

-- complete health and occupational records;

-- suitable comparison populations, and

-- a knowledge of the other influences each individual has been subject to (e.g. environment, smoking habits, genetic heritage).

The Interagency Task Force cited these requirements and noted that, "...for most irradiated populations, however, it is difficult if not impossible to satisfy all these criteria."

Because of these problems of sample size, other radiation exposures, etc., the Interagency Task Force recommends that the objective of large-scale epidemiological studies of groups exposed to low-level radiation should be to develop more accurate upper limits of risk. Although such studies would not be expected to yield precise estimates of radiation-induced cancers, they could show whether the observed cancer incidence is compatible with conventional risk estimates. The Interagency Task Force further states, "Before any study is undertaken, however, thorough investigation concerning feasibility and data accessibility is crucial."

We agree. As discussed here and in section 3, we do not believe that large-scale epidemiological studies of low-level exposures should be expected to provide reliable scientific data on the precise relationship between low-level ionizing radiation exposure and cancer. Studies with more realistic goals, such as seeking to develop more accurate upper risk limits, need careful review to assure that they are of sufficient scientific merit to justify the cost of a long-term follow-up study. Two studies of nuclear shipyard workers (discussed in chapter 20 of the Technical Report) illustrate some of the the problems of analyzing the effects of low radiation doses.

An NRC contractor has completed the review Congress required of options for low-dose epidemiological studies. The contractor concluded that, of the groups not already being studied, no candidate population is available for study that could yield reasonably accurate scientific information on the cancer risk from low-level ionizing radiation.

In some cases, there may be compelling social or legal reasons for conducting a study. An example is the recently announced $4 million research related to offsite fallout exposures from the Nevada nuclear weapons tests of the 1950's. The dosimetry studies may provide a sounder basis than is presently available for settling claims related to the Nevada test series. However, the moral and legal justification for such studies have to be weighed against the difficulties of determining radiation effects among groups receiving predominantly low doses of radiation. <u>It should be borne in mind that funding studies that are unlikely to yield useful results will limit the money available for other, more promising research.</u>

Because of the difficulties of measuring low-level effects directly, ongoing studies to refine risk estimates based on higher-dose exposures are warranted. In particular, we believe it is important to continue studies, such as those of the Japanese atom bomb survivors, the radium dial painters, and the uranium miners, that provide a range of graduated doses whose effects can be compared. Epidemiological studies that may offer clues to the mechanisms of radiation-induced cancer -- such as studies of people with genetic repair deficiencies -- also warrant continued support.

Animal Research

The data from animal experiments (primarily on rodents and dogs) are also used to support and supplement the risk estimates developed from human epidemiology. For determining the cancer risks of most types of exposures, both human and animal data are available. Animal experiments, however, provide the main source of data for several radionuclides, such as plutonium, that can be ingested or inhaled. (They also are essential for studying the genetic risks of ionizing radiation exposure.)

Animal experiments meet several important needs that human studies can not:

-- the radiation doses can be measured and manipulated in order to study the dose-response;

-- the size of the populations at each dose level chosen can be varied;

-- precisely known doses can be delivered;

-- control can be maintained over the animals' environment for their lifetimes;

-- experiments can be repeated independently by other researchers to test reproducibility;

-- the pathological workup can be extensive and comprehensive; and

-- the role of exposure to other substances can be studied by suitably designed experiments.

-- the efficacy and safety of agents designed to ameliorate or prevent radiation effects can be tested.

There are also several disadvantages to large-scale animal research. It is expensive, because the health of the animals must be followed throughout their lifespan. In order to determine low-level effects huge numbers of animals must be studied. Also, the results, particularly for rodents, are difficult to apply to human beings.

Nevertheless, animal research provides important data for refining risk estimates, especially for exposure to radionuclides. In particular, we believe the ongoing dog experiments to investigate the metabolism and toxicity of internal emitters should be continued to completion.

Fundamental Research on Mechanisms of Radiation Carcinogenesis

The long-term goal of the Federal radiation research program is a better understanding of the fundamental mechanisms and processes of cancer induction. This field spans a range of experiments, including chromosomal aberrations, DNA repair mechanisms, radiation effects on cells (cell death, mutation, and transformation), and animal experiments on the modifying effects of the body's tissue and systemic defenses. Based on our examination of mechanisms research, particularly molecular and cellular studies, we believe this fundamental research is likely to provide important insights into the relationships between low-level radiation exposure and cancer.

The molecular and cellular effects of radiation are studied on the premise that the observed changes are equivalent, in some degree, to the changes that take place in irradiated body cells. For example, cells that have been "transformed" (cells that clump and pile up instead of growing in a single layer) are equated with malignant or cancerous cells. Although this relationship has not been completely established, tumors have developed when transformed mouse and hamster cells have been injected into animals.

To the extent that transformed cells can be equated with malignant cells, transformation studies offer a way to investigate how radiation causes cancer and to measure the effect on cells of various types of ionizing radiation. Cellular studies, particularly transformation studies, are relatively new, however. There are many uncertainties that must be resolved about the relationship between cell effects seen in laboratory experiments and the actual effects of radiation on a living body. It has proved difficult to transform normal human cells, and the mouse and hamster cells used are fibroblasts, not the epitheleal cells in which most cancers arise. In common with other areas of research, it is difficult to obtain accurate results at low doses.

Despite these uncertainties, experiments with different types of cells and conditions of radiation exposure can be used to develop and critically test quantitative theories of the mechanisms of radiation action on living cells.

Small-scale animal experiments supplement molecular and cellular research by studying modifying factors (e.g., the presence of adjacent normal cells, and the action of the immune and endocrine systems), and factors that can promote the initial damage (e.g., the rate of cell division or exposure to promoting agents).

Obviously, molecular and cellular studies alone cannot provide answers to all the questions about the complicated processes of radiation-induced cancer. However, by contributing to the overall understanding of the relationship between cancer and low-level radiation exposure, molecular and cellular studies could lead to better risk estimates.

The costs of these studies are low compared to large-scale epidemiological studies and animal experiments, and the reward is likely to be substantial. We believe molecular and cellular studies, supported by small-scale animal studies focused on radiation mechanisms, warrant increased emphasis and priority in the Federal research budget. Efforts to develop and test quantitative theories of radiation carcinogenesis also need to be stepped up.

CURRENT EFFORTS TO IMPROVE THE FEDERAL RADIATION RESEARCH PROGRAM

Coordinating Federal Radiation Research Efforts

In the past two years, the Congress and the President have taken actions to broaden and redirect Federal research on the health effects of low-level ionizing radiation exposure. In November 1978, the Congress enacted two laws that increase the responsibility of other Federal agencies, beside DOE, for this research. P.L. 95-622 requires HEW to establish a comprehensive research program, and to review all Federal agency research programs in this area. P.L. 95-601 directs NRC and EPA, in consultation with HEW, to evaluate options for epidemiological research.

In May 1978, in response to the growing agency and congressional concerns, the President formed the Interagency Task Force on the Health Effects of Ionizing Radiation.

In its June 1979 report, the Interagency Task Force recommended that Federal research programs on ionizing radiation be coordinated by an interagency committee, chaired by the Director of NIH.

The Administration approved this recommendation, and on February 21, 1980 issued a memorandum to seven Federal agencies announcing that the Secretary of HEW had been instructed to establish an Interagency Radiation Research Committee. The committee is to coordinate research priorities to ensure that research is conducted and funded by the appropriate agencies under guidelines developed by the Committee. The Committee will be terminated after four years unless extended by Presidential Directive. (The President also issued Executive Order 12194 on February 21, 1980, creating the Radiation Policy Council. The Council would coordinate the formulation and implementation of Federal policy relating to radiation protection.)

During the final preparation of this report, our Office of General Counsel questioned the present funding of the Administration's Committee, as well as the Radiation Policy Council. In particular, there is concern about whether they comply with the funding constraints of section 608 of the Treasury, Postal Service and General Government Appropriation Act (P.L. 96-74). We plan to consider this matter further, and, if warranted, report on our findings.

On October 24, 1979, S.1938 was introduced in the U.S. Senate to create a Federal Conference on Research into Biological Effects of Ionizing Radiation and a Federal Council on Radiation Protection. The functions of these interagency bodies are similar to those of the Administration's Committee and Council--they would work to coordinate and improve the management of the Federal radiation research and protection responsibilities--and they would be authorized to operate until July 31, 1985. The primary differences are that the S.1938 Conference and Council would be statutory and each would include two official public members. S.1938 would also transfer EPA's authority to set Federal radiation protection guidelines to the Federal Council on Radiation Protection.

The possible risks of exposure to ionizing radiation have become an important policy issue with the growing use of radiation sources for energy and for medical purposes. Consequently, we believe that a Federal interagency research review group should be created by legislation. This would give it more status, better communication with the Congress, and independent funding.

We also strongly support having public participation in this interagency effort. Public members can offer a fresh perspective, independent of organizational ties. Participation by public members also can help allay concerns among the general public on whether the Federal Government is trying hard enough to solve these problems.

We believe it is important that research priorities be set so that promising ideas are funded, unnecessary duplication of effort is avoided, and the limited Federal research dollars are spent effectively. Research funds should be allocated on the basis of in-agency and outside peer review. However, a small percentage could be set aside for two special groups:

-- A limited number of Nobel Prize caliber scientists who should be funded for life. These researchers have so proven themselves that they should not have to waste their time hustling after research money. Many countries already do this. It is very similar to getting tenure at a university.

-- Highly outstanding young researchers who might have difficulty in winning any of the limited funds in the peer review process, but who may have new innovative research approaches.

The Interagency Task Force made a number of recommendations that we believe are important:

- The research review group ". . . should encourage expansion in the number of scientists and institutions performing the research, and assure that scientists of high quality are funded." We believe that it also is important to stress the participation of scientists with differing approaches to the problems of radiation exposure in order to ensure that researchers with unusual ideas have access to funding.

- NIH and other agencies could provide more of the fiscal support for the national laboratories. The national laboratories were established by AEC to plan and implement its research and development program, which included research on the health effects of ionizing radiation. Currently, DOE approves the national laboratories' research programs based on its own priorities. DOE's control of the national laboratories makes them much less useful for other Federal agencies and focuses their staffing and interests toward DOE's responsibilities.

- The research review group should also ". . . take care to ensure that a diversity of Federal agencies continue to fund research, particularly in high priority research areas."

The NAS Review for DOE

In response to intense congressional criticism of its radiation research program in January and February 1978, DOE's Office of Environment initiated an independent review of its 16 epidemiological projects by NAS. We believe this review resulted in considerable unnecessary expense and use of scientists' valuable time.

After some initial work, NAS recommended, and DOE agreed, that the review be expanded to include all 300 DOE radiation research projects. To gather information about each project, the NAS committee adapted the reporting form used by NIH (a form unfamiliar to most DOE scientists). Each principal researcher was to complete the form and to submit supporting documentation. This included biographical sketches, a comprehensive progress report (not to exceed 12 single-spaced pages), and journal articles that were based on the research.

We interviewed some researchers about the time and effort they devoted to these project summaries. Researchers stated that the purpose of the NAS review was not totally clear. They were concerned that the committee would use the summaries to make judgments on the funding of individual projects. As a result, some submissions, excluding journal articles, were 50 pages long. A typical project report for one laboratory was 35 pages long and required four weeks to prepare. A scientist at another DOE laboratory estimates that it took a full staff-year of effort to prepare his laboratory's project summaries. Most of this information was already available to the NAS committee through project proposals, annual project summaries, and the laboratories' annual reports submitted to DOE.

Two months after DOE requested this information, HEW asked NAS to review the total Federal radiation research program including the DOE program. (The HEW review is required by P.L. 95-622.) NAS agreed and has formed the Committee on Federal Research on Biological and Health Effects of Ionizing Radiation (the FREIR Committee). The NAS committee reviewing the DOE research program therefore reverted to the initial plan of limiting its review to 16 human health effects projects.

To meet its objectives, the FREIR Committee is reviewing a sample (about 20 percent) of the total Federal radiation research program. The principal researchers for these projects (for Federal funding agencies other than DOE) have been asked to submit the original research grant application, any application for renewed funding, and an appropriate recent publication of the research results. Thus, the comprehensive reports submitted to DOE by 284 principal researchers, which involved many staff-years of effort to compile, probably will be put to only minimal use.

SECTION 5
CONCLUSIONS AND RECOMMENDATIONS
ON FEDERAL RADIATION RESEARCH

INTRODUCTION

Our evaluation of the Federal radiation research program was based on the work summarized in sections 2 and 3. This work (covered in chapters 4 through 18 in the Technical Report) led to a number of detailed conclusions which contributed to our assessment of Federal research efforts. Although it has not been possible in this brief Summary Report to include all of these conclusions, our major conclusions have been discussed.

All of the recommendations in our report are directed toward improving the Federal radiation research program. For this reason, this section provides in full the conclusions we drew from our assessment of the Federal program, and our recommendations to the Congress and to members of the Interagency Radiation Research Committee.

CONCLUSIONS

- We believe there is a continuing need for federally sponsored research into the health effects of low-level ionizing radiation exposure. We also believe that Federal research efforts can be strengthened.

- We agree with the objectives of the current congressional and Executive Branch initiatives to coordinate Federal research efforts in this area. A

Federal interagency research review group could establish research priorities to help ensure that promising ideas are funded, that unnecessary duplication of effort is avoided, and that the limited Federal research dollars are spent effectively.

- Recently an Interagency Radiation Research Committee was formed pursuant to a memorandum issued by the President. However, because of the importance of the area, we believe that a Federal interagency research review group should be created by legislation. This would give it more status, better communication with the Congress, and independent funding. In particular, we believe this interagency group should include official representatives of the public.

- The NAS review of the DOE radiation research program illustrates the problems created by uncoordinated and hurried attempts by Federal agencies to respond to public and congressional criticisms.

- Human epidemiological studies cannot be expected to determine the relationship between low-level ionizing radiation exposure and cancer.

- A few epidemiological studies on low-level exposure groups may be warranted in an attempt to develop more accurate upper limits of risk from low-level radiation exposure. However, Federal agencies should carefully review each low-exposure study for its scientific merit.

- The primary reason for initiating some studies of low-level exposure groups is to meet perceived legal or social responsibilities, rather than to develop scientific data.

- We believe there is too much emphasis on epidemiological studies of low-level ionizing radiation exposure. Regardless of the reasons for conducting studies on low-level exposure, the inherent limitations on these types of studies make it highly unlikely that any reliable conclusions will be reached. <u>It should be borne in mind that funding studies that are unlikely to yield useful results will limit the money available for other, more promising research.</u>

- One important area of epidemiology which deserves continued support is refining estimates of risks from medium and high levels of ionizing radiation exposure. In particular, we believe it is important to continue the studies of the Japanese atom bomb survivors, the uranium miners, and the radium dial painters throughout their lifetimes. Continued support is warranted for similar studies that provide a range of doses whose effects can be compared, and for studies that may offer clues to the ways in which radiation causes cancer.

- Large-scale animal research on the cancer risks of low-level radiation exposure has several disadvantages. Experiments are expensive because the health of the animals must be followed throughout their lifespan. As in human epidemiology, huge numbers of animals must be studied to determine the effects of low-level exposure. Also, the results, particularly for rodents, are difficult to apply to humans. We believe that large-scale animal experiments should be carefully reviewed for their scientific merit.

- Despite the limitations, some large-scale animal research fulfills unique research needs. It is essential to continue through completion such experiments as those with beagle dogs that analyze the metabolism and toxicity of radionuclides within the body.

- A better understanding of the underlying mechanisms of cancer induction by radiation is necessary to allow scientists to develop risk estimates of low-level exposures with greater confidence.

- Molecular and cellular studies, supported by small-scale animal experiments, are likely to provide important insights into the relationship between low-level radiation exposure and cancer.

- For these reasons, mechanisms research, particularly on molecular and cellular effects, warrants increased emphasis in the Federal radiation research program.

- In order to synthesize the findings of radiation research, an intensive effort is needed to develop and critically test quantitative theories of radiation carcinogenesis through carefully designed experiments.

RECOMMENDATIONS

We recommend that the Congress:

--Enact legislation giving statutory authority to an interagency committee to coordinate Federal research on the health effects of ionizing radiation exposure.

The President recently established by memorandum an Interagency Radiation Research Committee. Because of the intrinsic importance of this area of research and the degree of public interest in resolving the uncertainties about the risks of radiation exposure, we believe that such a committee should have a legislative mandate. We believe it will be more effective with additional authority and independent funding. We also believe it is particularly important that the enacting legislation should:

a. provide for official participation on the committee by members of the public, and

b. provide for specific levels of review of human epidemiological studies, both within the sponsoring agency and by the committee, to assure they are of sufficient merit to justify the costs of long-term follow-up efforts.

Senate bill 1938, 96th Congress, would create such an interagency radiation research group. We have testified on S.1938 and provided formal written comments on it, and believe it can effectively accomplish the objectives of this recommendation.

We recommend that the Interagency Radiation Research Committee, whether established by legislation as we recommend or continued under Presidential memorandum, should:

--Ensure, in research on ionizing radiation exposure, that increased priority and emphasis are given to studying the mechanisms of how radiation causes cancer through molecular and cellular studies and other fundamental research.

--Ensure that the cognizant Federal agencies continue to conduct epidemiological studies of groups, such as the Japanese atom bomb survivors, the uranium miners, and the radium dial painters, that offer large numbers of people and a range of radiation exposure doses.

--Because of limited funding, ensure that epidemiological studies involving primarily low levels of ionizing radiation exposure are of sufficient scientific merit to justify the costs of long-term follow-up efforts.

--Ensure that the cognizant Federal agencies continue to conduct a limited number of high-quality animal experiments, including those analyzing the metabolism and toxicity of radionuclides in beagle dogs, and small-scale experiments to investigate radiation mechanisms.

--Consider carefully and initiate actions to implement recommendations in the June 1979 report of the Interagency Task Force, in particular

a. encourage expansion in the number of scientists and institutions performing the research, and assure that scientists of high quality are funded,

b. have NIH and other agencies provide more of the fiscal support for the national laboratories, thereby giving them more access to the laboratories, and

c. ensure that a diversity of Federal agencies continue to fund research, particularly in high priority research areas.

RESPONSE TO AGENCY COMMENTS

We received a number of detailed comments dealing with our discussion of radiation research. Many reviewers agreed that molecular and cellular studies warrant increased emphasis, but they were concerned that GAO was:

-- overestimating the ability of cellular research to help resolve uncertainties about cancer risks of low-level ionizing radiation exposure, and

-- not adequately addressing the need for animal research in this area.

In addition, three Federal agencies opposed our recommendation that Congress enact legislation giving statutory authority to an interagency committee to coordinate the Federal radiation research program.

As discussed in section 4, there are no guarantees of success in any research areas. We do believe that efforts to study the fundamental processes of radiation carcinogenesis should be intensified, particularly through molecular and cellular research. However, we recognize that this work alone cannot answer all the questions about the induction of cancer by radiation. We did not intend to imply that epidemiology and animal research can be dispensed with. On the contrary, we agree that a balanced program of high-quality research is needed, and we have identified examples of the types of epidemiology and animal research projects that we believe should be emphasized.

We do believe that the Federal Government should be more selective in the types of epidemiological research projects that it funds. This is not GAO's opinion alone, but is supported by the reports of the Interagency Task Force on the Health Effects of Ionizing Radiation, and the National Academy of Science's Committee on DOE Research on Health Effects of Ionizing Radiation. We also believe that the Federal Government should be more selective in which animal studies are funded.

Finally, we continue to believe that Congress should enact legislation giving statutory authority to an interagency committee to coordinate the Federal radiation research programs. This would give the committee more status, better communications with the Congress, and independent funding.

☆ U S GOVERNMENT PRINTING OFFICE 1980 720-023/4809

(001960)

AN EQUAL OPPORTUNITY EMPLOYER

UNITED STATES
GENERAL ACCOUNTING OFFICE
WASHINGTON, D.C. 20548

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE,$300

POSTAGE AND FEES PAID
U. S. GENERAL ACCOUNTING OFFICE

U.S MAIL

THIRD CLASS