ANL-7811

DR.1851

ANL-7811

CONF-701215-

194
7-9

CONFERENCE ON THE ESTIMATION OF LOW-LEVEL RADIATION EFFECTS IN HUMAN POPULATIONS

December 1970

U of C-AUA-USAEC

ARGONNE NATIONAL LABORATORY, ARGONNE, ILLINOIS

DISCLAIMER

The facilities of Argonne National Laboratory are owned by the United States Government. Under the terms of a contract (W-31-109-Eng-38) between the U. S. Atomic Energy Commission, Argonne Universities Association and The University of Chicago, the University employs the staff and operates the Laboratory in accordance with policies and programs formulated, approved and reviewed by the Association.

MEMBERS OF ARGONNE UNIVERSITIES ASSOCIATION

The University of Arizona	Kansas State University	The Ohio State University
Carnegie-Mellon University	The University of Kansas	Ohio University
Case Western Reserve University	Loyola University	The Pennsylvania State University
The University of Chicago	Marquette University	Purdue University
University of Cincinnati	Michigan State University	Saint Louis University
Illinois Institute of Technology	The University of Michigan	Southern Illinois University
University of Illinois	University of Minnesota	The University of Texas at Austin
Indiana University	University of Missouri	Washington University
Iowa State University	Northwestern University	Wayne State University
The University of Iowa	University of Notre Dame	The University of Wisconsin

Printed in the United States of America
Available from
National Technical Information Service
U S Department of Commerce
5285 Port Royal Road
Springfield, Virginia 22151
Price: Printed Copy $3.00, Microfiche $0.95

ANL-7811
Biology and Medicine

ARGONNE NATIONAL LABORATORY
9700 South Cass Avenue
Argonne, Illinois 60439

CONFERENCE ON THE ESTIMATION OF LOW-LEVEL RADIATION EFFECTS IN HUMAN POPULATIONS

Argonne National Laboratory
December 7, 8, and 9, 1970

Conveners:

George A. Sacher, *Argonne National Laboratory*
John B. Storer, *Oak Ridge National Laboratory*

Editor.

George A. Sacher

May 1971

FOREWORD

The sometimes acrimonious public discussions in 1969 and 1970 about the adequacy of existing ICRP, NCRP and FRC guidelines on exposure of human populations led to an awareness among radiobiologists of the need for a searching reexamination of the present situation in the radiobiology of low-level exposure The two conveners of the present Conference first discussed the desirability of such a conference in April, 1970, and proposed it at the May, 1970, meeting of the Executive Committee of the North American Late Effects Group The committee members were cognizant of the seriousness of the position, and voted to endorse the proposal They also recommended to the Radiation Research Society that a plenary symposium on the formulation of exposure guidelines be held at the May, 1971 meeting of the Society in Boston It can be noted parenthetically that the Society accepted the recommendation

Dr W K Sinclair, Director of the Division of Biological and Medical Research, Argonne National Laboratory, agreed to be sponsor and host for the Conference The travel expenses of most of the participants were paid by their own institutions The Division of Biology and Medicine, U S Atomic Energy Commission, made a grant, administered by the American Institute of Biological Sciences, to support the travel of some participants from universities who had no other source of travel funds

The contributions from the following institutions were based on research supported in whole or in part by the U S Atomic Energy Commission Argonne National Laboratory, Battelle-Northwest Laboratory, Brookhaven National Laboratory, University of California, Lawrence Radiation Laboratory, University of California, Davis, University of California, San Francisco, University of Chicago, Columbia University, New York University Medical Center, Oak Ridge National Laboratory, University of Rochester, University of Utah, and University of Wisconsin

The plan was to convene a small round-table conference of about two dozen active participants and a few observers from interested agencies The initial invitations were accepted almost unanimously, and then the need to achieve satisfactory balance and representation led to additions to the list, until the Conference convened with a roster of 44 participants and 10 observers It was still possible to adhere to the original symmetrical plan, which gave all participants an equal role in the discussions, but only at the price of uncomfortably short time allowances for the presentations The good will and dialectical skill of the speakers overcame this difficulty, and there was a stimulating discussion of a wide range of topics and viewpoints

It was considered desirable to produce a concise report of the proceedings of the Conference, and the following procedure was adopted Each participant brought to the meeting a brief position paper in which he assessed the present status of the problem of low-level effects from the standpoint of his own discipline and research interests, and proposed potentially productive directions of research These statements were also the framework of his oral participation One or two rapporteurs were appointed for each session and instructed to bring in brief accounts of the sessions, with emphasis on recording the trend of the free discussion The position statements and rapporteur accounts make up the first and second sections of this report

The session chairmen were empowered to appoint ad hoc committees to report on specific topics that arose during the discussions One such report was requested, and it appears at the end of the first section Several conferees distributed preprints of full-length papers, or supplementary extended position statements These contributions are cited at the end of the first section

There was a meeting of the entire group, participants and observers, as a committee of the whole on the final morning of the Conference This is reported briefly in the third section of the report, which also contains an overview and critique of the Conference as a whole, prepared at the request of the conferees

For convenience in reference, the position papers and rapporteurs' accounts are printed on tinted paper.

We acknowledge with gratitude the assistance of Mrs Dorothy Carlson and Mrs Miriam Holden, of the Argonne conference secretariat, for efficient arrangements, Mrs Margaret Fieldhouse, of Argonne's Technical Publications Division, for editorial assistance, Mr Edward J Bauser, Executive Director, Joint Congressional Committee on Atomic Energy, for copies of JCAE publications and bibliographic assistance

George A Sacher
John B Storer
May, 1971

TABLE OF CONTENTS

CONFERENCE PARTICIPANTS

ABRAHAMSON, Seymour
The University of Wisconsin
Department of Zoology
1117 West Johnson Street
Madison, Wisconsin 53706

ADLER, Howard I.
Oak Ridge National Laboratory
Oak Ridge, Tennessee

AINSWORTH, E. John
Argonne National Laboratory

ALBERT, Roy E.
New York University Medical Center
Environmental Medicine Dept.
550 First Avenue
New York, New York 10016

BATEMAN, John L.
Brookhaven National Laboratory
Medical Department
Upton, New York 11973

BEEBE, Gilbert W.
National Academy of Sciences
National Research Council
Medical Sciences—Follow-up Agency
2101 Constitution Avenue, N. W.
Washington, D. C. 20418

BROERSE, J. J.
Radiobiological Institute, TNO
151 Lange Kleiweg
Rijswijk, ZH, The Netherlands

BRUES, Austin M.
Argonne National Laboratory

BUSTAD, Leo K.
University of California
Radiobiology Laboratory
Davis, California 95616

CALDECOTT, Richard S.
University of Minnesota
Department of Biology
123 Snyder Hall
St. Paul, Minnesota

CROW, James F.
The University of Wisconsin
Genetics Building
Madison, Wisconsin 53706

DARDEN, E. B.
Oak Ridge National Laboratory
Biology Division
Post Office Box Y
Oak Ridge, Tennessee 37830

DUFFIELD, Robert B.
Argonne National Laboratory

EDINGTON, Charles W.
U.S. Atomic Energy Commission
Division of Biology and Medicine
Washington, D. C.

ELKIND, M. M.
Brookhaven National Laboratory
Department of Biology
Upton, New York 11973

FRIEDELL, Hymer L.
Case Western Reserve University
University Hospitals
Department of Radiology
2065 Adelbert Road
Cleveland, Ohio 44106

FRY, R. J. Michael
Argonne National Laboratory

GOLDMAN, Marvin
University of California
Radiobiology Laboratory
Davis, California 95616

GRAHN, Douglas
Argonne National Laboratory

GRIEM, Melvin L.
The University of Chicago Clinics
Department of Radiology
959 East 59th Street
Chicago, Illinois 60637

HARVEY, Elmer B.
International Atomic Energy Agency
Research and Isotopes Department
11-13 Kaerntnerring
A-1011 Vienna, Austria

HEMPELMANN, Louis H.
Strong Memorial Hospital
260 Crittenden Boulevard
Rochester, New York 14620

HOLDER, Lawrence E.
Western Environmental Radiation Laboratory
Post Office Box 15027
Las Vegas, Nevada 89114

HOLLANDER, Carel F.
Experimental Gerontology Unit, TNO
151 Lange Kleiweg
Rijswijk, ZH, The Netherlands

MAYS, Charles W.
University of Utah
Radiobiology Department
Salt Lake City, Utah 84112

MEWISSEN, Dieudonne J.
The University of Chicago
Department of Radiology
950 East 59th Street
Chicago, Illinois 60637

MICHAELSON, Sol M.
University of Rochester
Department of Radiation Biology
and Biophysics
400 Elmwood Avenue
Rochester, New York 14620

MILLER, S. A.
Argonne National Laboratory

MILLS, William A.
Environmental Protection Agency
Research Division
Office of Research & Monitoring
5600 Fishers Lane
Rockville, Maryland 20852
[Formerly with DHEW-PHS Bureau
of Radiological Health]

PALMITER, Claire C.
Environmental Protection Agency
Division of Criteria and Standards
Office of Radiation Programs
5600 Fishers Lane
Rockville, Maryland 20852
[Formerly with Federal Radiation
Council]

PARK, James F.
Battelle-Northwest Laboratory
Biology Department
Post Office Box 999
Richland, Washington 99352

REISKIN, Allan B.
University of Connecticut Health Center
McCook Division
2 Holcomb Street
Hartford, Connecticut 06001

ROSENBLATT, Leon S.
University of California
Radiobiology Laboratory
Davis, California
Mailing Address: 1831 Delaware Street
Berkeley, California 94703

ROSSI, Harald H.
Columbia University
College of Physicians and Surgeons
630 West 168th Street
New York, New York 10032

ROWLAND, Robert E.
Argonne National Laboratory

RUST, John H.
The University of Chicago
Departments of Radiology & Pharmacology
950 East 58th Street
Chicago, Illinois 60637

SACHER, George A.
Argonne National Laboratory

SAENGER, Eugene L.
University of Cincinnati
College of Medicine
Department of Radiology
Radioisotope Laboratory-General Hospital
Cincinnati, Ohio 45229

SARTWELL, Philip E.
Johns Hopkins School of Hygiene & Public Health
Department of Epidemiology
615 North Wolfe Street
Baltimore, Maryland 21205

SELTSER, Raymond
Johns Hopkins School of Hygiene & Public Health
Department of Epidemiology
615 North Wolfe Street
Baltimore, Maryland 21205

SILINI, Giovanni
C.N.E.N.
Laboratorio di Radiobiologia Animale
Via Anguillarese
S. Maria di Galeria (Roma), Italy 00060

SINCLAIR, Warren K.
Argonne National Laboratory

STAPLETON, George E.
U.S. Atomic Energy Commission
Division of Biology & Medicine
Washington, D. C. 20545

STORER, John B.
Oak Ridge National Laboratory
Biology Division
Post Office Box Y
Oak Ridge, Tennessee 37830

TAMPLIN, Arthur R.
University of California
Lawrence Radiation Laboratory
Livermore, California

TAYLOR, Lauriston S.
National Academy of Sciences
2101 Constitution Avenue, N. W.
Washington, D. C. 20418

VOILLEQUE, Paul G.
U.S. Atomic Energy Commission
Idaho Operations Office
Post Office Box 2108
Idaho Falls, Idaho 83401

WALBURG, H. E., Jr.
Oak Ridge National Laboratory
Biology Division
Post Office Box Y
Oak Ridge, Tennessee 37830

WHITMORE, Gordon F.
University of Toronto
Department of Medical Biophysics
500 Sherbourne Street
Toronto 5, Ontario, Canada

WILLHOIT, Donald G.
University of North Carolina
Environmental Sciences Dept.
131 School of Public Health
Chapel Hill, North Carolina 27514

WOLFF, Arthur H.
Environmental Protection Agency
Office of Radiation Programs
5600 Fishers Lane
Rockville, Maryland 20852
[Formerly with DHEW-PHS Environmental Health Service]

WOLFF, Sheldon
University of California Medical Center
Third & Parknassus
San Francisco, California 94122

YANDERS, A. F.
University of Missouri
College of Arts and Sciences
210 Jesse Hall
Columbia, Mo. 65201

YUHAS, John M.
Oak Ridge National Laboratory
Biology Division
Post Office Box Y
Oak Ridge, Tennessee 37830

CONFERENCE PROGRAM

Session 1 (Monday morning, December 7, 1970)
Chairman, L. K. BUSTAD
Mammalian Radiobiology

Session 2 (Monday afternoon, December 7, 1970)
Chairman, G. F. WHITMORE
Mammalian Radiobiology (continued)
Genetics and Cellular Radiobiology

Session 3 (Tuesday morning, December 8, 1970)
Chairman, R. E. ALBERT
Human Epidemiology

Session 4 (Tuesday afternoon, December 8, 1970)
Chairman, W. K. SINCLAIR
Physics and Models
Exposure Guidelines: The Process

Session 5 (Wednesday morning, December 9, 1970)
Chairman, G. A. SACHER
Meeting as a Committee of the Whole

POSITION PAPERS

Mammalian Radiobiology

SYSTEMIC AND PHYSICAL FACTORS

POSITION STATEMENT ON SYSTEMIC AND PHYSICAL FACTORS

Pietro Metalli and Giovanni Silini

C N E N Laboratorio di Radiobiologia Animale

The dose corresponding to a "low level" of irradiation is a relative quantity whose definition requires practical considerations Radiation protection standards were at all times the results of empirical approaches to various problems posed by the current qualitative and quantitative knowledge of radiobiological effects Rather paradoxically, therefore, a low level of radiation is that which is thought to induce a low rate of effects, according to our knowledge and experience

The available information on the effects of small radiation doses in animal populations, including man, is extremely limited Of all possible effects, those which have actually been found are similar in nature to the long-term lesions observed after higher exposures Their frequency is assumed to decrease with decreasing doses down to very small values, practically undetectable over the background of spontaneous cases

Predictions on the incidence of low level effects in man are founded on the extrapolation to low doses (and low dose-rates) of a few sets of data observed at relatively high doses (and dose-rates) The validity of the extrapolation procedures is limited by a number of assumptions concerning especially the shape of the dose effect relationship [1] Therefore the degree of confidence attached to these predictions cannot be properly assessed, but seems largely a matter of opinion, often reflected by the "conservative" position of the international bodies in recommending dose limits for human exposure [2]

It would be impossible to base our future action regarding these problems on an attitude which is different from the present pragmatic line The effects which must be considered with the greatest concern for human protection are those for which a clear cut threshold has not been shown in the dose-effect curves At present they appear to be the impairment of fertility, some kinds of developmental lesions, the damage to the genome and the induction of malignancies [3]

Estimates of these effects on human populations may and should be refined, but the level of effect which is of actual interest for radiation protection should be the guide-line to further experimentation A better definition of these levels for all kinds of damage would be of great help to radiobiological research

It is conceivable, in any case, that further advancements in this field will come primarily from the careful study of exposed humans in all cases where this is practicable The epidemiological studies of such population groups, however, will only provide some key reference points for the human species at relatively high doses

All other problems concerning the test of assumptions and extrapolations must still be approached on animal models, since no theoretical speculation will ever solve experimental problems such as the linearity of dose-response relationships at very low doses The search for such models and a better definition of the experimental practice must presently be pursued The magnitude of these efforts requires extensive collaboration

References

1 International Commission on Radiological Protection, ICRP Publ 8, Evaluation of Risks from Radiation Pergamon Press, London, 1966

2 International Commission on Radiological Protection, ICRP Publ 9, Radiation Protection (September 17, 1965) Pergamon Press, London, 1966

3 International Commission on Radiological Protection, ICRP Publ 14, Radiosensitivity and Spatial Distribution of Dose Pergamon Press, London, 1966

POSITION STATEMENT ON SYSTEMIC AND PHYSICAL FACTORS

J. B. Storer

Oak Ridge National Laboratory

My remarks are made in the context of a scientific discussion in which we are concerned with the best estimates of radiation effects. They do not necessarily apply to the setting of radiation protection standards where a whole series of conservative constraints must be applied.

Data from human populations for certain radiation effects (principally cancer induction) are reasonably good in the high dose and high dose rate range. Prospects are good that the data will become even better as follow-up studies are continued. Even so, there are disagreements as to which cancers can be radiation induced and the incidence to be expected at these high doses. The disagreements are due in part to inadequate estimates of dose to various tissue sites.

There is little or no prospect of obtaining useful data on human beings exposed to low total doses at low dose rates. To estimate effects at these low doses and low rates it will be necessary to continue to extrapolate from the effects observed at high doses. The principal value of empirical studies in experimental animals is to provide a basis for these extrapolations.

Are results from experimental animals such as mice relevant? The answer probably depends on the nature of the lesion leading to late sequelae. If the principal injury is to the information system of the cells, then presumably experimental studies are relevant. One would expect differences in some details of radiation responses, but the general principles should be similar. If the prime injury is not to the information system, then animal studies may be less relevant, but in this case the entire problem is enormously simplified in that radiation becomes just another toxic agent with the usual threshold for response and sigmoid dose-response curve.

Among the general principles that have emerged from experimental studies of somatic effects are the following:

1. Protracted exposure is generally less effective than a brief exposure to the same total dose.
2. Dose-response curves vary considerably with genotype, sex, and biological endpoint. Strict linearity is not often seen.
3. Interaction of radiation with other environmental variables can profoundly affect the shape of the dose-response curve.

Experimental studies particularly needed include further work with variations in dose rate, carefully executed studies in radiation pathology to determine which diseases can be radiation induced and the nature of the dose-response curve for each disease, and additional effort to understand the basic nature of the radiation-induced injury.

RELEVANCE OF ANIMAL EXPERIMENTATION TO ESTIMATING SOMATIC EFFECTS OF LOW-LEVEL RADIATION IN HUMAN POPULATIONS

H. E. Walburg, Jr.

Oak Ridge National Laboratory

Recognizing that radiation standards for somatic effects have been set by extrapolation of high dose effects in humans, and accepting the probability that low-dose radiation effects in humans will never be directly measured, it is essential to question how animal experiments can be properly utilized to predict such low-dose radiation effects in humans. It has been popular in the past to hypothesize that radiation induces a general decrement in cell, tissue and organ function which leads to earlier development of the same lethal diseases seen in unirradiated animals, the so-called "accelerated aging phenomenon." This general effect, it was thought, leads to the life-shortening effects of radiation, which may be similar in man and experimental animals, whatever the cause of death. There is no evidence to support this hypothesis, however, and the data may better fit another hypothesis, e.g., that life-shortening effects of radiation are due to induction of some specific diseases but not others. If this is true then the general relevance of animal model systems disappears and relevance is found only in models of the specific diseases which are observed both in man and the experimental animal under consideration. Unfortunately, many of

the radiation-induced diseases of the mouse, one of the most common animal models used in radiobiology, have no human analogs, either quantitatively or sometimes even qualitatively, e g , thymic lymphoma, Harderian gland adenocarcinoma, ovarian tumor Since the life-shortening effects of radiation in the mouse are probably due to such irrelevant diseases, life-shortening as an end point would seem to be equally irrelevant to human radiation biology

In view of this problem of relevance, how can animal experiments prove useful? Certainly where valid models of radiation-induced human disease exist (e g , chronic granulocytic leukemia) the physical and environmental factors important to induction, such as dose-rate effects, RBE of high-LET radiations, and the influence of host factors can be evaluated Even in the absence of valid disease models, important information can be gleaned from animal experiments Data from these experiments can lead to "useful generalizations" as suggested by R H Mole Thus if observations on radiation induction of a certain disease in a wide variety of species permit a generalization which quantitatively fits all the data, it is reasonable to assume such an effect for human populations as well Second, data on the mechanism of radiation induction of animal diseases, even though they are not relevant to human disease, may still provide the key which will clarify the mechanism by which radiation induces human diseases

IMPLICATIONS OF DOSE RATE AND DOSE FRACTIONATION

D G Willhoit

University of North Carolina

Present State of Knowledge - Dose rate and dose fractionation have previously been recognized as factors which modify the effectiveness of a given radiation dose, but have been considered only as potential added safety factors, owing to a lack of precise quantitative dose-response data Leukemia, life shortening, and genetic mutations in mice have been demonstrated to be dependent on dose rate and dose fractionation Leukemia and life shortening in man have only been demonstrated following relatively high dose rate exposures For example, the exposures of radiologists consisted of numerous small dose fractions delivered at exposure rates in the neighborhood of 1 R/min Likewise, leukemia associated with fetal irradiation occurred following exposures of a few roentgens delivered in a brief time interval Following is a description of a model developed in this laboratory recently which bears directly on the dose rate phenomena

Dose Rate Effects - The dependence of cell survival on dose rate can be described by a three-component model The components are 1) single-target, single-hit, 2) multi-target, single-hit, and 3) repopulation due to division The unique feature of the model is the introduction of a time-dependent extrapolation number to account for the numer of "hits" which are repaired during exposure The model was fitted to experimental HeLa cell data, but qualitatively is consistent with other dose rate studies Conclusions based on the model are 1) increasing dose rates between 3 and 100 R/min result in a progressive increase in the relative importance of the multitarget inactivation component, 2) low dose rates <3 R/min) are due to single-target, single-hit inactivation, 3) the relative contribution of multitarget, single-hit inactivation to cell killing is greater at high doses than at low doses Similar qualitative results have been reported for chromosome abnormalities and genetic effects in mice Russell's data indicate that the threshold for multitarget mutations is between 0 8 and 9 R/min for spermatogonia, but for oocytes the dose rate dependence extended down to 0 009 R/min The single-target, single-hit component may be attributed to that fraction of the cell population which is in the G_2 and M phases of the cell cycle which are characterized by an extrapolation number of 1 0 The absence of division in the oocyte may account for the sex difference in the dose rate effect

Dose Fractionation - The interpretations of most fractionation studies have been in terms of comparisons with single-dose results or relative short overall fractionation periods Work in this laboratory has shown that for equal daily exposure rates, the survival times of mice exposed 30 min/day were shorter than those of mice exposed continuously This difference is readily interpreted in terms of the above dose rate model, that is, low rate irradiation acts primarily by single target interactions and high rate irradiation by both single and multiple target interactions

Future Courses of Action - The role of single and multiple events in the induction of specific disease entities should be investigated

LATE EFFECTS OF RADIATION

J M Yuhas

Oak Ridge National Laboratory

Radiation standard setting bodies assume that a given dose of radiation will induce the same incidence of late effects, whether it is given chronically, in a series of fractions, or as a single brief exposure While this is contrary to most experimental data, the assumption must be maintained since the data presently in hand are insufficient for calculating the relative "sparing" factors for chronic or fractionated delivery

This insufficiency stems from two facts 1) there is no reason a priori to believe that "sparing factors" will be the same for all late effects and 2) most studies have analyzed single end points against single methods of fractionation or chronic administration For example, it has been shown that fractionation reduces the life-shortening efficiency of radiation by a factor of approximately 2, but that fractionation of appropriate X ray doses increases their ability to induce permanent sterility in males

As one approach to this problem we are now conducting experiments which will analyze a series of late effects (carcinogenesis, life shortening, lens opacification, sterilization, and immunologic impairment) following exposure to acute, chronic, and fractionated gamma rays and fission neutrons In addition, the gamma-ray studies involve a series of total doses (48 to 384 R) received at a variety of dose rates (1 R/day through 1 R/second) From these latter studies we hope to be able to formulate equations which describe the incidence of late effects as a function of both dose and dose rate By combining these experiments with studies on the effects of age at exposure on the ability of single acute exposures to induce late effects, we should be able to determine the contributions of recovery, age, dose size per fraction, and latent periods required for expression to the observed "sparing factors" for chronic and fractionated exposure patterns

We do not propose that the resultant information can be used as a direct method of extrapolation to human populations, but rather it can establish general principles within animal model systems which can provide a rational guideline for the interpretation of probable risks in human populations exposed to low total doses at low dose rates

Mammalian Radiobiology

CARCINOGENESIS

CONSIDERATION OF CARCINOGENIC MECHANISMS IN THE PREDICTION OF LOW-LEVEL RADIATION EFFECTS

A M Brues

Argonne National Laboratory

Radiation carcinogenesis is not a self-sufficient field A unified theory requires a unified concept of carcinogenesis overall, and it is clear that this in turn requires more input from most of the newly developing areas of biology Nor will one approach suffice we find it useful to examine single molecular events that determine the malignant nature of a cell, but it is likely that any such event or combination of events occurs a great many times for every resulting malignant tumor Other determining factors that must be looked for lie in the interactions between a cell and its environment, either or both of which may be altered

Several developments in cancer biology have emphasized factors that were in more or less disrepute, or considered too specialized to be of much general importance To mention a few:

Viruses - A good deal has been learned about experimental viral carcinogenesis, but their relation to the human process is far from understood One human tumor is well understood to be associated with a virus which now seems to have an antigenic relation with some nonmalignant states It is now known that RNA viruses are capable of coding the host genome for homologous DNA synthesis, and so far this seems to be a peculiarity of tumor viruses

Immunologic reactions - Tumors seem clearly to have their own immunologic markers, immunologic tolerance seems to be increased by other carcinogens as well as radiation, and tumor-bearing patients tend to have increased tolerance

Carcinogenic transformation in vitro - This follows a long process of cultivation following which, after a period of depressed cell viability, changes occur in the intercellular relations and surface properties of the newly malignant cells

Plastic carcinogenesis - When tissue cells are separated by chemically nonspecific barriers so that they are no longer surrounded by other cells, this leads to delayed tumor development, the same conditions of cell separation (in terms of porosity of the barrier) appear to be critical in determining whether differentiation will occur in cultured embryo organs

It will be seen that in all of the above instances, host factors are involved at least at some point in the process

Among the matters that need to be discussed fully are (1) How do we define a tumor? Does invasiveness involve factors outside of the cell? (2) To what extent and on what level (cell and its environment) do aging processes and carcinogenesis interact? (3) Do carcinogenic agents act additively or synergistically? (4) How can the paradox of resistance of large animals to local effects be explained? (5) What are the actual rules governing variations in cancer susceptibility that are related to tissue growth and the age of host? (6) How much of cancer is actually "spontaneous"?

THE CARCINOGENIC ACTION OF SMALL DOSES OF DIFFERENT IONIZING RADIATIONS

G W Barendsen, J J Broerse, and C F Hollander

Radiobiological Institute and
Experimental Gerontology Unit, TNO,
Rijswijk, ZH, The Netherlands

The induction and development of malignant tumours after exposure to ionizing radiations involves a complex sequence of events, initiated by the absorption of energy from radiation in biological material, followed by biophysical, biochemical and biological changes which finally result in the observed neoplasm Because direct experimentation with very low doses presents great difficulties with respect to the number of animals required to obtain significant results, evaluation of the effectiveness of small doses must be based on adequate knowledge of shapes of dose-effect relations obtained with larger doses and extrapolation, with a suitable theory, to low doses and low dose rates Neither sufficient experimental data nor a generally accepted theory are available, however

In principle, dose-effect relations for the production of malignant tumours must depend on competition of two factors, namely the induction of changes in cells which can result in malignant transformation and the induction of cell reproductive death which will prevent part of the potentially transformed cells from contributing to tumour development For the investigations of the relative contributions of these factors, studies of the LET-dependence of the dose-effect relationships for tumour production by different types of radiations can be of great importance

Many biological effects of ionizing radiations in mammalian cells, including cell reproductive death and malignant transformation, are induced more effectively by radiations which cause high local energy densities, i e , through particles of high LET, than by X rays or γ rays For damage to the reproductive capacity of mammalian cells, dose-effect relations have been measured with a variety of radiations, e g , monoenergetic heavy ions and fast neutrons of different energies In view of the competition mentioned, it is clearly of great interest to compare dose effect relationships and the dependence of the relative biological effectiveness (RBE) on the radiation quality for impairment of cell proliferation with equivalent data for the carcinogenic action of ionizing radiations

In order to investigate the carcinogenic effectiveness of ionizing radiations with different distributions of local energy density, monoenergetic heavy ions cannot be used because of their limited penetration and changes of LET occurring along their path, if organs or whole organisms are irradiated It is necessary therefore to employ radiations, such as fast neutrons or π^- mesons, which produce in tissue secondary particles with a high mean LET

In studies of the carcinogenic action of ionizing radiation, two types of experiments may be distinguished, aimed at the elucidation of mechanisms operating either at the cellular level or in intact organisms In cases where the total body or a number of tissues in an organism are irradiated, the interpretation of results involves

an evaluation of the complex interactions of various types of damage to blood vessels, connective tissues and immunological and hormonal systems For studies of cellular aspects of radiation carcinogenesis, it is preferable to investigate the most simple systems in which tumours can be induced

A few results of studies of the carcinogenic effectiveness of fast neutrons of different energies in comparison with γ rays have already been obtained with rat skin [1] In the system used, a transplantation technique allowed the partial elimination of the influence of damage produced by penetrating radiations in subcutaneous tissues Further studies with this system will have to be complemented with investigations of the effectiveness of neutrons of different energies for tumour production by total body irradiation

Reference

1 G W Barendsen Tumour induction in rat skin by 300 kV X-rays and 15-MeV neutrons *Radiation-Induced Cancer* Int Atomic Energy Agency, 1969, pp 413-424

THE RELEVANCE OF MORTALITY AND CARCINOGENESIS AS CRITERIA FOR ASSESSMENT OF LOW-LEVEL RADIATION EFFECTIVENESS

D J Mewissen

University of Chicago Clinics

Assessment of radiation effects in biological systems is most accurately derived from dose response relationships involving a selected biological variate as a function of some radiation parameter(s) We intend to review briefly each of these components from the critical standpoints of information content and reliability

Although the influence of dose parameters in radiation injury is well known, some of their quantitative implications may be easily overlooked The absolute magnitude of exposure doses, or in many cases, of absorbed doses, is the usual piece of information at hand, although the spatial distribution on microscopic or submicroscopic scale is actually the critical factor (local energy density)

On the other hand, fractionation and/or protraction of dose are manipulated in an attempt to mimic actual human clinical situations For example, daily low-level exposure of mice is used as a model for chronic (but essentially discontinuous) exposure of human populations at risk In the resulting complex situation, the concepts of wasted radiation, potential and actual injury [1] are to be kept in mind for proper interpretation of data Accordingly, investigation of single doses may prove more rewarding and be given high priority

The specific nature of the dose-response function, and particularly the shape of the curve, is of lesser importance than selection and understanding of the variate (biological phenotypic end point) and of the independent variable (radiation dose) It is desirable, whenever possible, to end up with a linear regression, at least within a given dose range Metametric transformation of coordinates of the graph (probit, logit, log dose) are helpful, but one should realize that they introduce some a priori assumptions on basic mechanisms underlying the biological response In contradistinction with a widespread belief, linear versus nonlinear relationship has little, if any, relevance to the threshold problem A threshold or non-threshold situation can coexist with a linear, curvilinear or sigmoid curve [2]

As no one knows at what point the "low" dose range starts, back-extrapolation is invariably attempted The implication is that the function is assumed to be monotonic and continuous beyond the range of experimental data Furthermore, a no-response dose level is by no means an actual threshold level, as the frequency of an itemized response is contingent on sample size At the limit, the entire world population would seem to be the only acceptable sample size for testing a sufficiently infrequent event as a possible radiation response

A final word about the most popular variates, i e , aging and cancer Is aging a biological initiating process per se or an epiphenomenon resulting from distinct nosological entities? In many instances, aging graphically amounts to a shift of the lethality function along the time scale, with no significant alteration of the realm of diseases in control versus irradiated animals

A similar situation seems to prevail in radiation "induced" (?) cancer Recent studies [3] suggest that inbred strains of mice may, with improved environmental living conditions and enhanced survival, exhibit up to 70% of "spontaneous" tumor incidence It might be that with further extended longevity the 100% landmark would be approached more closely Such findings give further support to the theory of vertically transmitted oncogenes If so, radiation is no longer an initiating, but rather a triggering agent Similarly the fit (at least in a major portion) of

tumor incidence rates to a Gompertzian regression function would seem to indicate that carcinogenesis (spontaneous or radiation triggered) is dependent upon two interacting component mechanisms, one of phenotypic expression, acting at a constant rate of force throughout lifespan, and one of repression, gradually losing strength, also at a constant rate throughout lifespan. Obviously a number of biological processess (virus activation, virus incorporation or release, immunological competence) can be pinned on such a phenomenological frame.

References

1. Mewissen, D. J. et al. A formula for chronic radiation dosage versus shortening of lifespan: Application to a large mammal. Radiat. Res. *6*, 450-459 (1957).
2. Mewissen, D. J. La correlation dose-response des radioleucemies experimentale: le probit de marquage. Sang *29*, 764-789 (1958).
3. Mewissen, D. J. Dose-response relationship in radiation leukemia. Nature *183*, 401-402 (1959); Nature *184*, 1669-1670 (1959).

Mammalian Radiobiology

LARGE ANIMAL STUDIES

THE APPLICATION OF THE LOGISTIC DOSE-RESPONSE SURFACE IN EVALUATION OF TUMOR INCIDENCE FOLLOWING EXPOSURES TO INTERNAL EMITTERS

Marvin Goldman, L. S. Rosenblatt, and L. K. Bustad

University of California, Davis

and

N. H. Hetherington

University of California Radiation Laboratory, Livermore

Estimation of low-level radiation effects in human populations can be facilitated by the use of appropriate animal models. A method is described which permits what we believe to be a reasonable basis for extrapolating the radiation responses in animals at intermediate to high levels down to exceedingly low levels for which available data may be quite limited. The example chosen is only one of a large number which could be applied.

The long-term bone-seeking radionuclide studies at Davis and Salt Lake City cover a range of exposure doses of up to 10^3 and include over 2,000 beagles at risk for up to 17 years, the maximum lifespan for this breed. Although the Davis study is somewhat younger in time, both laboratories have demonstrated that the major effects attributed to radiation have been the induction of tumors in tissues within the range of irradiation flux. In addition to the tumors of bone induced by high levels of radium-226 and strontium-90, the sustained bone marrow dose from ^{90}Sr throughout early life adds a risk of inducing fatal myeloproliferative disorders in beagles at Davis. We have seen no other deleterious radionuclide effects on survival or reproduction at any of the levels tested, correcting the data for radiogenic carcinogenesis.

Analysis of the data utilized all of the animals at risk. In the analysis dose is related to cumulative incidence rates for each end point (e.g., bone tumor or marrow cancer). The Cutler-Ederer method was used to compute the cumulative survival rates for dogs on the ^{90}Sr and ^{226}Ra regimens. The modification of the life table method utilized considers mortality to consist only of those individuals manifesting the end point under study (e.g., osteosarcoma). Individuals dying of other causes are treated as "lost to the follow-up" but are considered to be at risk until they die. Individuals alive at the time of the analysis are also considered to be at risk for the total time that they are in the study. Computation of the cumulative survival rate (P_t) and its standard error (s_t) provides the estimate of the cumulative incidence rate, ($1-P_t$), whose standard error is also s_t because of symmetry. An essential

and salient feature of this analysis is the fact that all of the individuals are used in the estimation of cumulative incidence rates.

The cumulative incidence rates for osteosarcoma were computed for the pooled ^{226}Ra data from Davis and Salt Lake City. Only the SLC dogs extend beyond 7 years, and represent a very small population at risk. The injected radioactivities for each dosage level differed essentially by factors of 3. The family of cumulative incidence rates computed for each of the dose levels were generally "S" shaped and were not separated by equal intervals on the age scale. In addition, the relationship between decreasing dose and maximum cumulative incidence rate was nonlinear. The shape of these curves and their separation with regard to time suggest to us that the logistic (or growth) curve might provide the most appropriate representation of the data. Furthermore, analysis of cumulative incidence rates using the logistic curve suggested to us that the data could be related to age and log dose by a logistic response surface from which at least four different estimations might be attempted.

1. Fitting the logistic equation to individual dose level cumulative incidence rates provides an estimation of the maximum cumulative incidence, (M); a measure of the reserves of the individuals subjected to that particular dose level (1/B), which may be analogous to the potential for repair; and the rate constant (λ), which decreases the reserves per unit of time.

2. At any given age, provided that data exist, the cumulative incidence rates of the several dose levels are themselves related by a logistic, and may be extrapolated to estimate cumulative incidence at very low dose levels.

3. The estimated maximum cumulative incidence rates are also related by the logistic, and may be extrapolated to estimate M for very low dose levels.

4. The ages at which given cumulative incidence (e.g., 1 or 10%) occurs also follow a logistic and, again, extrapolations may be made to very low dose levels.

The logistic equation may assume many mathematical forms. Its most common form, $E = M/1 + Be^{\lambda t}$ was utilized here. In graduating the cumulative incidence rates, (E), t is taken as age. In graduating the maximum cumulative incidence rates (M), t is taken as ln dose and M is set equal to 1. No attempt is made here to describe other logistic relationships such as $dE/dt = aE + bE^2$. The significance of the mathematical constants in these equations relative to the biological parameters which they, in effect, attempt to estimate is a difficult and complex problem. Henry Eyring and Betsy Stover at Salt Lake City have suggested a similar logistic approach utilizing the principles of chemical kinetics to evaluate radiation dose-effect relationships.

Although the examples cited above were restricted to the effects of bone-seeking radionuclides on the specific cells at risk with the only end points considered being the induction of tumors, this model has wider applicability. We would like to suggest that the model can be utilized for any all-or-none response, provided that the cells at risk remain at risk for the lifespan of the individual. The response surface produced by this model as applied to radiation effects evaluation utilizes the interrelationship of dose, time, and incidence. For the system under study, a practical threshold is provided by the finite limitation (e.g., lifespan) associated with the temporal axis. We look forward to possible application of this approach to evaluating the dose response of biologic systems other than tumors of bone. In addition, we are currently evaluating variations of this model which consider changes in dose rate and local dose distribution in tissues at risk throughout the individual's lifespan.

DOSE-RESPONSE RELATIONSHIPS IN THE INDUCTION OF BONE SARCOMAS BY RADIONUCLIDES

C. W. Mays

University of Utah

The incidence of bone sarcomas vs. dose has been examined in 11 different studies. *None* of the β-emitter experiments supports a linear dose-response relationship: at low β doses a sigmoid relationship or a "practical threshold" relationship is more probable.

For skeletal irradiation by α emitters, the response is more varied: some α studies support a linear relationship, whereas others support the sigmoid or "practical threshold" concepts, where at low doses few, if any, bone sarcomas are induced.

In the following table, the observed numbers of cases with bone sarcomas at low doses are compared with the numbers predicted by (a) the threshold model (natural incidence only) and (b) the linear model in which a radiation-induced incidence (assumed proportional to dose) was added to the natural incidence.

"P" values shown in the last column are the probability that *if* the linear model were correct, the observed cases (or fewer) could have occurred by chance. The detailed data, to which the linear relationships were fitted, are available from C. W. Mays [1-3].

TABLE 1. Observed and Predicted Cases at Lower Doses

	Observed Cases	Threshold Prediction	Linear Prediction	P
β-PARTICLE IRRADIATION				
^{90}Sr in 328 mice	9	7	28	$<10^{-4}$
^{45}Ca in 379 mice	7	4	26	$<10^{-5}$
^{90}Sr in 2718 rats	2	0	36	$<10^{-13}$
^{90}Sr in 30 beagles	0	0	2.5	0.07
^{90}Sr in 74 pigs	0	0	1.8	0.16
α-PARTICLE IRRADIATION				
^{226}Ra in 1436 mice	115	17	109	
^{224}Ra in 222 humans	0	~0.1	1.1	0.33
^{226}Ra in 11 beagles	0	0	0.7	
^{228}Ra in 4 beagles	0	0	1.2	0.06
^{228}Th in 6 beagles	0	0	0.7	
^{239}Pu in beagles		(insufficient observation time)		

References

1. Mays, C. W. and R. D. Lloyd. Bone sarcoma incidence vs. radionuclide dose. *The Radiobiology of Plutonium*. Ed. B. J. Stover and W. S. S. Jee, to be published.

2. Mays, C. W. and R. D. Lloyd. Bone sarcoma risk from ^{90}Sr. *Biomedical Implications of Radiostrontium Exposure*. Ed. L. K. Bustad and M. Goldman, to be published by the U. S. Atomic Energy Commission Division of Technical Information.

3. Mays, C. W. et al. Bone cancer induction by radionuclides: incidence vs. dose. Hearings on environmental effects of producing electric power. Joint Congressional Committee on Atomic Energy, Vol. II, part 2, pp. 2192-2210 (Jan. 27-30 and Feb. 24-26, 1970), also in Research in Radiobiology; University of Utah Report C00-119-242, pp. 385-401 (March 1970).

ANIMAL STUDIES TO ESTIMATE LOW-LEVEL RADIATION EFFECTS IN HUMAN POPULATIONS

S. M. Michaelson

University of Rochester

Concern about proliferation of man-made sources of electromagnetic radiation and "environmental pollution" has provoked reexamination of present Radiation Protection Guides. In an upsurge of semantical arguments fundamental concepts, scientific facts and philosophic principles are obscured in an attempt to find ready answers in an area which is not black and white but many shades of grey.

What are the scientific facts; how can they or should they be made compatible with political, sociological and economic factors? How does one reconcile the benefit vs. risk concept with the voluntary risks which society can and is willing to accept for an improved "quality of life"?

The information presently available, although incomplete, does provide a basis for setting public safety standards for radiation. The present standards are conservative and have not been shown to result in any injurious effects. In the meantime, we must develop concepts and criteria and pursue well-conceived, properly performed, adequately controlled studies in animals and man to answer some of the unresolved problems.

We should differentiate between biologic effect per se, which is non-injurious and quickly and fully recoverable, and injury which is slowly recoverable or irreparable. We should attempt to resolve the questions of threshold, curvilinear or linear response to low-dose radiation exposure.

In considering the use of "large animal" studies to estimate low-level effects in man, several approaches are suggested.

1. A concerted effort should be made to review in a systematic manner the accumulated reported

and unreported data obtained in past studies on large animals. By using newer analytic techniques, examining the information in a comparative manner in relation to animals and man according to common physiologic parameters and correlating information pertinent to the low-level effects problem, it is very possible that many of the answers we are now seeking may already be available.

2. Planning of additional studies to fill in gaps in the existing information.

3. Correlation of data from "large animal" investigations with retrospective and prospective studies in man.

It should be recognized that no single animal species can represent the ideal model and no experimental procedure is universally suited to all forseeable uses. In selection of the experimental animal, the specific attributes of various species should be evaluated.

Study of several species using a Systems Physiology approach based on various levels of biological organization can provide the most reliable extrapolation factors for man. From a spectrum of species such as the mouse or rat, dog, and pig or sheep, basic information on the comparative reaction of biologic systems can be acquired to elucidate mechanisms of action. A common parameter such as metabolic rate could be utilized to provide an index of extrapolation between species.

ESTIMATION OF LOW-LEVEL RADIATION EFFECTS OF INHALED PLUTONIUM AND URANIUM MINE AIR CONTAMINANTS IN HUMAN POPULATIONS

J. F. Park

Battelle-Northwest Laboratory

The present state of knowledge and confidence in the assessment of the low-level effects of inhaled plutonium and uranium mine air contaminants demonstrates contrasting situations. Inhaled plutonium has caused pulmonary neoplasia and lymph node, liver, skeleton, and hematological pathology in experimental animals at high dose levels, while studies at lower doses are not completed and biological effects have not been reported in exposed human populations. Epidemiologic studies have shown an increased incidence of pulmonary neoplasia in uranium miners; however experimental animal studies have thus far not developed animal models causing the observed human effect.

Low-level inhalation studies with "soluble" and "insoluble" plutonium in long-lived experimental animals are required to determine the critical tissues and dose-effect relationships. Studies in short-lived species will provide needed data, and comparison of the two or more species could aid in developing a much needed more meaningful method of expressing the radiation dose-effect relationship so results of the animal studies could be more adequately extrapolated to man. The role of the chemical and physical form of the inhaled material on the observed effect must be evaluated in experimental animals. Methods are required to accurately determine the in vivo body burden and distribution of inhaled plutonium in both animals and man. Epidemiologic studies of plutonium workers should include special exposure, clinical and post-mortem evaluation of humans with known body burdens. These known-exposure cases, if properly studied, should provide the most reliable information for estimating low level effects. Consideration should be given to experimental studies in humans using plutonium isotopes such as ^{237}Pu to evaluate inhaled plutonium metabolism in humans.

Since uranium miners are exposed to a combination of potentially carcinogenic agents, animal experiments are required to identify the primary etiological agents or combination of agents and evaluate the dose-effect response. An adequate method of expressing the dose-effect relationship must be developed for utilization of the animal data to evaluate human exposures. Human studies should be expanded not only in number of epidemiologic observations but also emphasizing more accurate dosimetry and extensive study of the exposed populations.

The lungs of a large segment of the human population are routinely exposed to harmful materials including tobacco smoke and other pollutants; therefore the combined effect of low-level radiation and other agents must be evaluated in human and animal studies to properly estimate the effects of low-level radiation on human populations.

When low-level effects are observed, calculated or estimated, some consideration must be given to the "significance" of the effect.

Mammalian Radiobiology

TISSUES AND CELLS IN VIVO

LATE RADIATION EFFECTS: COMMENTS ON IN VIVO SYSTEMS

E. J. Ainsworth

Argonne National Laboratory

One approach to the challenge of the estimation of low-level radiation effects in humans is by interspecies comparisons of life shortening, and of radiation effects in selected physiological systems. Such studies may permit generalizations from a broad phenomenological base which could bear more directly on estimation of human hazard than would studies with mice or rats alone. It is clear that marked species differences exist with regard to potential for repair-recovery after acute sublethal exposure or during continuous low-level exposure. Moreover, phenomena have been encountered, such as, in sheep, a complete inhibition of recovery during continuous exposure immediately following a sublethal acute exposure, which are not described for laboratory rodents. The extent to which species differences based on measurements of short-term end points also apply to late effects is unclear but deserves attention. Perhaps one of the most important findings from the interspecies studies is the great difficulty encountered in arriving at broad generalizations. This cautionary facet adds an important perspective to our consideration of extrapolation to man.

One complication of interspecies studies involving large animals concerns the difficulty of in vivo measurements of cell and tissue injury. This is but one of many reasons that the laboratory mouse may be used to advantage, since a combined approach involving both epidemiological and physiological description of the populations' responses to low-level irradiation is feasible and rewarding. One in vivo system suitable for estimation of damage to the hematopoietic system involves measurement of changes in the marrow population of colony-forming cells (CFC) together with estimations of the ability of transplanted marrow to produce erythrocytes and granulocytes. In this way, insight may be gained into the compensatory responses, at the tissue and cell level, which are made by irradiated mice. By experimentally inducing proliferation within the hematopoietic system, it may be possible to detect late radiation effects on regulatory systems. Studies of compensatory or regulatory capability are of importance, since in the context of low-level radiation effects, stem cell death per se, in some critical systems, is important only to the extent that the stem cell population is not reconstituted. Preliminary results show femur CFC content is significantly decreased among aged survivors 700 to 900 days after exposure to neutron or X radiation. Studies of cell population changes in marrow after fractionated exposure are in progress.

It will be of particular interest to investigate compensatory potential and regulatory systems in mice exposed at low radiation levels when no significant life shortening is detected. Have repair or recuperative process indeed been complete, or will test procedures measuring compensatory responses reveal injury to homeostatic mechanisms? Were such effects detected, our views on hazards of low-level exposure might be modified, especially when considering the compensatory responses required of human populations exposed to many other environmental hazards. Consideration of the combined effects of low-level irradiation and other environmental contaminants may therefore be in order.

RELATIVE IMPORTANCE AMONG VARIOUS LOW-LEVEL EFFECTS IN MAN

J. L. Bateman

Brookhaven National Laboratory

A rigorous investigation of a single low-level cause and effect, as is generally recognized, will involve either or both 1) extrapolation downward to the doses of interest from the nearest (higher dose) data in man, and 2) parallel experimental animal studies of the effect of concern at the doses of interest. The former technique suffers the disadvantage that the extrapolations involved are often long and tenuous, while the latter technique is handicapped by the difficulty of utilizing samples of sufficient size (for statistical validity) with

organisms close to man on the phylogenetic scale. With either type of approach, a clear determination must be made of 1) the biological nature of the effect under consideration, 2) the degree of effect, and its causes, in the control population, 3) the degree of effect in the test population, and 4) the physical nature and magnitude of the perturbing influence. Finally, statistical analytical procedures must be able to determine accurately the likelihood that the observed effect is not due to chance.

(The studies, to be described, of radiation-induced lens opacification in the mouse fulfill several, but not all, of the above criteria.)

A comprehensive approach to the problem, however, should not be confined to the scope embraced by the factors above. In fact, the precision of determination of a given effect caused by a given influence (e.g., induction of myelogenous leukemia by gamma rays) may become relatively less important if either 1) the same effect can be more readily produced by another influence or 2) a different effect produced by a different influence (e.g., induction of bronchogenic carcinoma by the atmospheric pollutant 3,4-benzpyrene) is of greater clinical significance and incidence.

Protection of the human population from deleterious influences will be more rapid and effective if the relative importance of these influences (whether physical, chemical or radiant) is determined, and corresponding priority assigned for investigation of the hazard and development of protective measures.

IN VIVO MAMMALIAN RADIOBIOLOGY AND SPECIFIC SYSTEMS

E. B. Darden, Jr.

Oak Ridge National Laboratory

Several statements in the Conference present views on the relevance of animal studies in general for the estimation of the effects of low levels of ionizing radiation on the human population. As H. H. Rossi has commented recently, permissible doses have usually been reduced about a decade below the level of observable effects. Direct examination of the consequences, if any, of these small amounts of radiation has been nearly impossible, even in animals. My comments are directed toward the importance of studying in the intact mammal effects of radiation on specific radiosensitive systems or on the induction of specific lesions. It seems to me that selected in vivo systems can serve one or both of two important purposes: provide a response capable of being evaluated quantitatively at small enough doses to reduce substantially the uncertainty of extrapolating below detectable levels of effect, and provide a model for the study of mechanisms, hopefully with some general applicability to low-level effects.

We are studying factors affecting dose response and RBE in two relatively sensitive systems in the mouse, (1) the zygote (a joint project with the Federal Aviation Administration) and (2) the lens. In the first, embryo mortality as determined at 16 days' gestation is used as a measure of the effect of radiation given early in the preimplantation stage. A statistically observable effect is obtained at doses below 5 rads of fission neutrons. Relative survival is approximately exponential with D_0 of 16 rads or an LD_{50} of 14 rads. The RBE with respect to X rays from 5 to 20 rads is about 4 for single doses delivered within a few minutes. Some of the surviving offspring of irradiated mothers are being kept for observation of any late effects. The practical consequences of the study may be related to the effects of radiation in the human female at an analogous time after conception when pregnancy may not be suspected.

The graded response of the mouse lens to radiation provides a highly reproducible assay (and a nondestructive one) over a wide span of doses with a degree of precision unusual in mammalian radiobiology. In current studies we are examining dose effect in terms of latency and of opacification level for fission neutrons and X rays. The response can be followed over more than a five-hundred-fold neutron dose range down to less than 0.5 rad. In addition to supplying basic information about factors influencing radiation cataractogenesis, the system shows promising results in providing experimental comparison to theoretical models such as the 1-2 hit theory proposed recently by Rossi.

SOME ASPECTS OF ANIMAL AND CELL POPULATION EXPERIMENTS

R. J. M. Fry

Argonne National Laboratory

The development of late effects obviously involves complex mechanisms which allow for many interactions of the various regulating systems [1]. In the realm of animal experiments and their role in providing information relevant to human populations, useful generalizations can be sought from data obtained deliberately on a sufficient number of different species. The species differences in sensitivity to late effects, such as tumors and lens opacification, have both defied explanation and been a reason for varied animal studies. The differences in sensitivity between tissues in the same animal are equally obscure. Comparisons, interspecies or interanimal, are made on an organ basis and not related to the number of cells in the respective tissue. The use of estimates of numbers cells at risk for neoplastic transformation for comparisons between organs, within and between species, may be singularly naive, but perhaps it would focus on the possible reasons for the differences. There is reason to believe that for either tumor induction or lens opacification sensitivity is negatively correlated to the number of cells at risk when large and small animals are compared. Mole [2], however, has suggested that the whole endosteum of different species is equally radiosensitive for sarcoma induction. The statement is productive, largely because it is provocative–especially as he points out that one cannot distinguish between the hypothesis that there are the same number of potential cancer cells in the various species or the hypothesis that the cells, while greater in number in larger animals, are less sensitive. The estimate of the number of cells at risk for a tissue would probably be only of use for comparison, of say, a transformation index of cells in vivo and in vitro, or perhaps the changes with age in number and sensitivity. It is clear that for meaningful comparisons such "local" factors as repair, the efficiency of removal of abnormal cells, which varies with turnover rate, and postexposure proliferative activity would all have to be determined and incorporated. The comparison of local and whole-body irradiation would be necessary to establish the comparative importance of the interactions. For example, the immunological aspects of suppression of tumor expression may show variation between species and with ages in unirradiated and irradiated animals. In the lens, no tumors occur, but the opacities are thought to be the product of aberrant cells. In this system, interactions with the immune system have not got the same importance. Therefore, studies of the relationships of cell killing, chromosomal abnormalities and the resultant incidence of opacities on an interspecies basis should provide results uninfluenced by cellular responses elsewhere in the body. Lastly, comparative studies on somatic mutation appear to be necessary. All that this has said is that much hard-won phenomenological information is needed, and will not be collected in a day.

References

1. Brues, A. M. Critique of the linear theory of carcinogenesis. Science *128*, 693-699 (1958).
2. Mole, R. H. Endosteal sensitivity to tumor induction by radiation in different species: A partial answer to an unsolved question. *Delayed Effects of Bone-Seeking Radionuclides*. Ed. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor. University of Utah Press, Salt Lake City, 1969, pp. 249-261.

Genetics and Cellular Radiobiology

GENETICS

GENETIC EFFECTS OF LOW-LEVEL RADIATION IN HUMAN POPULATIONS. STUDIES WITH *DROSOPHILA MELANOGASTER*

Seymour Abrahamson

University of Wisconsin

The principle of linearity of radiation dose-mutation relationships has been the view long put forth by geneticists in estimating genetic risk from low doses of irradiation. This is a conservative view only if mutation

rate is proportional to dose or if there were to be a threshold found at very low doses On the other hand, if there were an extremely sensitive and substantially sized population of important germ cells (e g , gonial) which were both highly mutable and killed by low doses or irradiation, then in fact the concept of linearity might underestimate the hazards of low doses when extrapolations from intermediate or high doses are carried out For this reason it becomes important to obtain critical low-dose information on the induction of mutations in critical stages of germ cells in Drosophila and mammals Work in our laboratory at present indicates that oogonial cells do not possess a detectably sensitive population of cells that would lead to a departure upwards from the expected linearity at low doses In fact, a test of over 77,000 X-chromosomes fails to show a significant increase in the induction of sex-linked lethal mutations for doses of 20, 100, and 500 R as compared to the control On the other hand, the work of Oftedal does suggest that Drosophila spermatogonia possess a sensitive fraction of germ cells I am uncertain at present whether this population would contribute a substantial mutation component that would significantly alter the estimated mutation rates for human populations at low doses (i e , 170 millirads per year) if an equivalently sensitive population existed for human cells

Other studies in our laboratory on the induction of translocations in *mature oocytes* at doses of 0, 10, 50, 150, 250, and 500 R demonstrate the following important points

1 Ten roentgens significantly increases (by more than doubling) the rearrangement frequency

2 Rearrangements are induced in a linear manner up to a dose of 50 R and in a quadratic fashion above 50 R This extends and corroborates the work in mature sperm of Drosophila, bone marrow cells of man, and spermatogonia of the mouse

3 Linearity at low doses suggests that factors such as dose rate and dose fractionation will be unimportant in the mutation or rearrangement process, since the induction event results from a single ionization track

A PROPOSAL TO ESTABLISH VITAL STATISTICAL MONITORING SAMPLES IN SELECTED GEO-ECONOMIC REGIONS OF THE CONTINENTAL UNITED STATES TO DETECT POTENTIAL DETRIMENTAL EFFECTS OF LOW-LEVEL ENVIRONMENTAL HAZARDS

Douglas Grahn

Argonne National Laboratory

In recent years, standard vital statistical data have been exploited to demonstrate alleged radiation effects (at fractions of natural background levels) in terms of increases or time-trend changes in fetal and infant mortality rates, and adult mortality patterns Under most circumstances, gross unadjusted mortality rates are relatively insensitive to minor perturbations in the normal array of environmental, cultural, and biological factors that influence mortality Although some causes of death may be responsive, most analyses put forward today are grossly deficient in their simple recognition of the impact of many common socioeconomic and racial variables on mortality Because vital statistical data are cheap and plentiful, though not without some troublesome inaccuracies, the question becomes, what can be done to make such statistics a more valuable and sensitive continuous monitoring system of the biological effects of environmental agents?

To start, all factors known to influence mortality need to be clearly defined, so the uninitiated will give more thought to the interpretation of variations The intrinsic variance, or random component, needs to be quantitated The relative sensitivity of different end points to changes in the major independent variables also requires some elaboration All of this, however, merely precedes what should be done--the establishment of selected representative master samples or sampling regions that can be used for longitudinal study of the vital statistical parameters that may be significant indicators of injury produced by persistent low levels of environmental stress

The selected samples should represent the major geo-economic regions of the continental United States, for example, New England, the industrial Midatlantic, the racially and economically heterogeneous Southeast, the cash-grain crop Midwestern region, and others Regional patterns of mortality and significant socioeconomic variables should be identified A general environmental monitoring program should be set up to evaluate changes at least in the following water supply, air-borne contaminants, therapeutic drug usage, occupational patterns, migration, racial components, income, education, and medical support programs Age and cause-specific mortality in infants and adults can then be baselined for longitudinal, inter-regional, or other comparisons As no true "control" population is available, each sample region becomes its own control in time If a

question should arise about the possible detrimental effect of a nuclear power station, for example, the necessary data will be instantly available.

More sophisticated monitoring systems have also been recommended recently by Neel [1,2]. A set of regional master samples, as recommended here, could provide the material to fulfill Neel's suggested requirements for the detection of cytogenetic and biochemical genetic changes. Neel considers that only a few selected vital statistical events can be dependably monitored for changes in mutational pressure. This may be the case, but present-day environmental problems have both somatic and genetic damage potential. As recently noted by the Assistant Surgeon General of the U. S., exposed individuals are seriously threatened by the synergistic action of two or more factors, and cause-specific death rates may, therefore, detect somatic injury very efficiently. The fact that crude measures of infant mortality are now being used to measure alleged radiation effects makes it imperative to establish the basic mortality patterns and control factors, as it is certain these statistics will continue to be used both wisely and unwisely. Lastly, it would be ideal to coordinate genetic and somatic measures of injury in the population, if any sensible estimate of the biological effects of long-term multigeneration, low-level environmental stress is to be made.

References

1. Neel, J. V. Evaluation of some genetic consequences of a deteriorating environment. Testimony before Subcommitte on Intergovernmental Relations, U. S. Congress, April 24, 1969.
2. Neel, J. V. Lessons from a "primitive" people. Science *170*, 815-822 (1970).

Genetics and Cellular Radiobiology

CYTOGENETICS

CYTOGENETICS

A. B. Reiskin

The University of Connecticut

A review of the cytogenetic literature indicates that most radiobiological phenomena apply to structural changes in chromosomes as well as to intact cells. The degree of damage or number of aberrations varies as a function of the total dose, radiation quality, time and method of sampling, conditions at the time of exposure, dose rate (depending on quality), cell age and other factors. The oxygen effect and/or protection by inert gases may be an important exception.

Cytogenetic end points, however, often only reflect the initiation of some metabolic, oncogenic, genetic, or other process and in themselves may be of little direct consequence. Dulbecco has pointed out that radiation-induced breaks in DNA may be the insertion sites for tumor viruses, and there seems to be developing evidence that viral antigens sometimes appear in tissues after irradiation. It is already clear that radiation enhances transformation by viruses, but the mechanics are poorly understood. It has also been recently demonstrated that stable cell lines with chromosome-specific biochemical lesions can develop as a consequence of irradiation. Again, the qualitative and quantitative relationships between radiation-induced chromosome changes and these phenomena are unclear. The problem is further compounded by the fact that in the areas of greatest concern, namely, low dose partial body exposure, the required samples are large and difficult to obtain.

The nature of the problem indicates a need for two lines of attack. Assuming a model in which radiation-induced chromosome changes lead to cell death, or to alterations in normal function, the first step is satisfying a requirement for a precise definition of the time, dose, and quality functions of aberration production. Precision, particularly in the case of small, low-frequency events, is beyond the scope of manual evaluation and will require automated analytical techniques. The automation of karyotype analysis is advancing rapidly, but it will be necessary to define the parameters relevant to radiation effects since they may differ from those required for other purposes. Second, assumptions linking structural changes in chromosomes to tumor induction, metabolic disease or other sequelae can and should be experimentally tested.

STATEMENT ON CYTOGENETIC EFFECTS OF LOW-LEVEL RADIATION

Sheldon Wolff

University of California Medical Center

Over the years, many effects of radiation have been studied rather extensively, but among the most extensively studied has been the induction of chromosome aberrations. It is generally believed that when cells are killed by low doses of radiation, the sensitive target is the cell nucleus, i.e., that it is damage to the genetic material of the cell that results in cell death.

Arguments have been constructed showing that, of the various types of nuclear damage, only chromosome aberrations can quantitatively account for the changes in cell survival. There are other arguments indicating that almost all mutational events, be they true point mutations or chromosome aberrations, are detrimental or deleterious. Consequently, almost all geneticists agree that radiation-induced mutations are harmful, and that any increased amount of radiation which will increase the number of mutations, will also be harmful. In spite of this, and in spite of the fact that over the years very much work has been performed in this area, we still have the problem that we do not know exactly how much genetic damage will be caused by very low doses of radiation, nor can we tell exactly how harmful this damage will be.

The reasons for this are manifold. For instance, dicentrics comprise one of the major types of chromosome aberrations studied cytologically. In human cells, these aberrations have to be observed in metaphase preparations that have 46 chromosomes. The chromosomes have to be counted and studied individually in order to pick out such dicentrics, and consequently the preparations have to be of very high quality. At this time, this has become somewhat easier, but in the past it was rather difficult. Earlier, people looked at only some 50 human cells per point. It was much easier to deal with plant cells that had much larger chromosomes, and then to make extrapolations to the human case. Now that mammalian cytology has improved, this is no longer as serious a problem as it was, but at low levels of radiations, where the aberration yields are low, it is still very arduous to obtain statistically significant results.

This can be readily seen when one considers the shape of the dose curves for the induction of dicentric chromosome aberrations that require two breaks. With sparsely ionizing radiations, these aberrations increase approximately as the square of the dose. Therefore, at very low doses, there are very few aberrations. Thus, even with good preparations, it is very difficult to obtain enough of these aberrations after low doses to determine the difference from controls with any statistical precision. To fix our ideas on this, we can note that with a dose of 5 rads we might expect only 0.00032 dicentrics per cell, which is very difficult to distinguish from the spontaneous yield.

At least three different studies carried out on aberrations in radiation workers have suffered from such difficulty. Although, in general, such studies can show how low level doses of radiation are able to induce aberrations in humans, it takes very large numbers of cells to determine whether the level is higher than in the controls. Furthermore, there is a great deal of variability from person to person irradiated.

All of this is further complicated by the fact that dicentric aberrations, which are among the most common, are subject to an intensity effect, with fewer dicentrics being formed at low intensities of irradiation than after acute doses. Since most low-level experiments are carried out at low intensities, this tends to reduce the number of dicentrics even more, and thus make it even more difficult to obtain statistical differences. In addition, it is difficult to obtain a control value because the individuals who comprise the control population frequently have been exposed to dental X rays, medical X rays, caffeine, chemical and environmental pollutants, or viruses that can break chromosomes.

But even if we did know exactly what the yield of chromosome aberrations was, especially after low doses and low dose rates, geneticists still couldn't tell you how bad this is. The reason is that most chromosomal aberrations of the type that are scorable in cytogenetic preparations are not passed on to succeeding generations. As a matter of fact, they are not even passed through very many cell divisions in somatic cells. These aberrations have been called unstable aberrations and are actively selected against. That is, they lead to cell death either because a fragment with a large number of genes is not included in the daughter cells or because the aberrations form bridges that prevent cell division.

Consequently, it is seen that the problem is twofold. First, it is extremely difficult to obtain the data necessary to establish statistically significant differences between control populations and those exposed to low levels of radiation; and secondly, it is difficult to make a precise estimate of the degree of damage associated with

such aberrations that are actively selected against and replaced with normal cells. The developmental changes that occur because of such selection are largely, if not completely, unknown.

Genetics and Cellular Radiobiology

CELLULAR RADIATION BIOLOGY

CELL CULTURE STUDIES RELATIVE TO MUTATION AND TRANSFORMATION

M. M. Elkind

Brookhaven National Laboratory

Assessment of present state of knowledge

Mammalian cells grown in culture are currently being used to study mutation production. Cell transformation is also being studied in the contexts of cell-to-cell controls of proliferation, the role of chemicals and viruses, and the use of the transformation end point in connection with mechanisms of carcinogenesis. In reference to transformation studies, some results have been published demonstrating an enhanced effect of ionizing radiation [1–3] although this is not always observed [4].

Concerning cell transformation, a comprehensive picture is not available as yet, nor is the role of radiation clear. Futher, studies of repair of radiation induced cell transformation (or mutation production for that matter) are few and as yet not very enlightening. As might be expected with the limited data available, even less is known about whether or not drugs and/or viruses can act synergistically with radiation. Finally, little is known about a possible dependence of mutation and carcinogenesis on radiation quality.

Evaluation of future courses of action

Three kinds of related departures are worth pursuing with mammalian cells in vitro.

First, there is need for the development and/or improvement of end points with which to assay mutation and carcinogenesis more rapidly than can be done in animal systems.

Second, with current and/or improved end points, dose dependencies need measurement, and the role of radiation quality needs assessment.

Third, as one important approach for the study of mechanisms, for the guidance of animal studies and for the estimation of incidences at low dose and low dose rate, a search for repair processes and their relation to repair relative to other end points should be pursued. This should be done as a function of LET to help develop a comprehensive understanding of the forward and back reactions. This third departure relates to the "threshold question." Its relevance to this conference is evident.

References

1. Stoker, M. Nature *200*, 756 (1963).
2. Borek, C. and L. Sachs. Proc. Natl. Acad. Sci. 57, 1522 (1967).
3. Pollock, E. and G. Todaro. Nature *219*, 520 (1968).
4. Klein, J. C. J. Nat. Cancer Inst. *37*, 655 (1966).

CELLULAR RADIOBIOLOGY AND LOW-LEVEL RADIATION EFFECTS ON HUMANS

W. K. Sinclair

Argonne National Laboratory

Studies on single mammalian cells in vitro [1, 2] have been very successful in quantitating radiation responses such as lethality, division delay, and various biochemical changes. Most of the data pertaining to

the shape and parameters of mammalian cell survival curves, and the manner in which they are modified by radiation features (dose rate, LET, fractionation, etc), physiological parameters (oxygen, temperature, position in cell cycle), or inhibitors, sensitizers, protective agents, etc have been obtained by studies in cellular systems in vitro [3] Corresponding, but usually less precise, experiments in vivo have rendered in vitro data useful and applicable, within limits, to some in vivo cell compartments (much more is, however, needed here) Cellular models may then be developed [4] which, in certain instances, can predict or explain responses in whole animal systems For example, experiments on the effects of X rays and fast neutrons from the JANUS reactor on mammalian cells in vitro indicate that *it is likely* that recovery occurs in mice exposed to fast neutrons, but to a considerably lesser degree than after X or gamma rays

With respect to low-level radiation effects in humans, two aspects of cellular studies in vitro are of particular significance

First, the effect of low doses of radiation has been quantitated in some cellular systems, and these data may have some predictive value for whole organisms The multitarget, single hit model commonly employed to fit mammalian cell survival curves [5] predicts that at very low doses (i e , at the origin) the survival curve should have zero slope Experimental studies indicate that this is probably not the case Several workers have found in asynchronous cells that survival data are better fitted by a two-part model in which a low initial slope (with n=1) is followed by a later steeper slope [5–8] Differences in D_0 amount to a factor of 2 or 3 To avoid the complications of mixed responses in asynchronous populations, Morton and I examined synchronized Chinese hamster cells in late S in the region above 50% survival [9] We found that the slope near the origin was not zero, but corresponded to a $D_0 \sim 550$ rads initially, compared to a final slope with $D_0 \sim 190$-200 rads

Thus, (1) even at the lowest dose some effect was observed, and presumably this continues to very low doses, and (2) ignoring other interpretations of the model, the response of these cells has two parts, a small but positive initial dependence on dose, followed at higher doses by a greater dose dependence *The response is evidently not uniform over the whole dose range*

Extension of these experiments into the very low dose region requires, for statistical reasons, a "megaplate" experiment Nevertheless, some further extension would be desirable

Second, the response of most current concern at low doses is the incidence of tumors Little is known about the cellular basis of carcinogenesis For example, the transformation of a normal cell into a malignant one by radiation must be a sublethal event, but what this event involves has been little investigated This is partly because the identification of malignant changes in cultured cells still requires further development, including confirmation of the capacity of transformed cells to induce tumors in animals The method has so far been more useful for the study of chemical carcinogens than for radiation [10] However, development of this end point in culture would be an important step in the further investigation of cellular carcinogenesis and of low level radiation effects

Thus, I identify the important problems for the future in the cellular area as (1) further development of methods of translating data from in vitro experiments to in vivo situations, (2) further low dose and low dose rate investigations in culture, (3) the development of appropriate assay methods for transformed cells in culture, and (4) the investigation of the cellular basis of radiation carcinogenesis using these assay methods

References

1 Puck, T T and P I Marcus Proc Nat Acad Sci *41*, 432 (1955)

2 Elkind, M M and G F Whitmore *Radiobiology of Cultured Mammalian Cells* Gordon and Breech, New York, 1967

3 Sinclair, W K X ray survival of mammalian cells in culture *Comparative Cellular and Species Radiosensitivity* Proc Symp , Ed V P Bond and T Sugahara Igaku Shoin, Tokyo, 1969, pp 65-78

4 Elkind, M M Fundamental Aspects of Radiosensitivity Brookhaven Symposia in Biology *14*, 220-245 (1961)

5 Sinclair, W K The shape of survival curves of mammalian cells in vitro IAEA Technical Report, No 58, Int Atomic Energy Agency, Vienna, 1966, p 21

6 Bender, M A and P C Gooch Int J Rad Biol *5*, 133 (1962)

7 Barendsen, G W and H M D Walter Radiat Res *21*, 314 (1964)

8 Hall, E J NCI-AEC Conference, Brookhaven National Laboratory Report BNL-50203 (1970)

9 Sinclair, W K and R A Morton Radiat Res *29*, 450 (1966)

10 Klein, J C *Radiation Induced Cancer* Int Atomic Energy Agency, Vienna, 1969

IN VITRO STUDIES OF GENETIC AND CARCINOGENIC EFFECTS OF RADIATION

G. F. Whitmore

Ontario Cancer Institute

The growing awareness of the potential genetic and carcinogenic hazards arising from radiation and a host of other environmental pollutants requires the development of methods for screening for the effects of such agents. While in some instances it may be necessary to carry out such studies in small mammals, considerations of cost and convenience suggest the use of mammalian cells in vitro. Partly as a result of the growing awareness of this need, and partly for various other reasons, a number of groups have begun the study of various aspects of mammalian cell genetics in vitro. To date most of these studies have been concerned with isolating and describing the properties of both drug-resistant and auxotrophic mutants, and techniques have been described for the isolation of mutants of both classes. In addition, there have been several reports of attempts to use these systems in initial attempts to determine the mutagenic efficiency of both ultraviolet and ionizing radiation, and also of a group of known mutagenic agents. From the studies already reported it is obvious that the system suffers from a number of difficulties. With most cell lines in culture there is still considerable question as to the genetic composition, including frequency of monosomic regions, etc. Also, there is considerable uncertainty concerning overall genetic stability during growth in vitro. In addition to these uncertainties, there are technical problems in that the mutation frequency observed depends upon factors such as the initial cell population size in the test dish, the time allowed between mutagenesis and expression, and the level of the selecting drug used in the selection procedure. It is doubtful, however, if even this array of potential difficulties can explain the apparent discrepancies between the values reported for the mutagenic efficiencies of X rays in two mammalian test systems, one looking at drug resistance and the other at the induction of a glycine deficiency. Obviously a great deal of work remains to be done on the development of the system. Nevertheless the beginnings of a useful system appear to be at hand.

In addition to the spectre of radiation-induced mutations introduced into large populations exposed to low levels of radiation, there is also the spectre of radiation-induced malignancy. Here again, there are possibilities that certain aspects of this can be investigated with in vitro systems. The development of in vitro assays for viral transformation open up the possibility of using the same assay systems for studying radiation-induced transformation. In this connection, one aspect which would appear to deserve a great deal more attention is the possible interaction between viruses and radiation in the production of malignancy. Most DNA tumor viruses would appear to require incorporation into the cell's genetic apparatus before they can bring about transformation. Evidence is accumulating that this incorporation can be fostered by the presence of nicks in the DNA introduced by chemical agents, including a variety of known carcinogens. Since it is known that radiation can also produce such nicks, there would appear to be a possibility of a synergistic effect here also, an effect that might also be investigated in vitro.

Based on the above reasoning, there would seem to be a great deal of merit at the present time in the further development of in vitro systems for testing both for mutagenic and for oncogenic effects of low levels of radiation.

Human Epidemiology

FOLLOW-UP OF EXPOSED POPULATIONS

HUMAN EPIDEMIOLOGY

R. E. Albert

New York University Medical Center

There is a strong suggestion of an approximately linear nonthreshold dose-effect relationship for leukemia in Japanese atom bomb survivors as well as X-irradiated spondylitics. Although the "threshold" form of dose-effect curve is observed in most experimental studies relating carcinogen dose to tumor incidence, any doubt

that there is such a thing as a linear nonthreshold tumor response is dispelled by the data relating lung cancer in humans to the daily consumption of cigarettes The practical implications of a nonthreshold dose-response relationship are repellent because it inevitably produces the dilemma of attempting to equate the cost in human life against the amenities of life produced by technology

Although it may be wishful thinking, there is one consideration that might lead to a practical amelioration of the problem, namely, if the apparent nonthreshold dose-response relationship were really the composite response of a series of subpopulations of graded susceptibility If so, the identification and special protection of such high risk populations might significantly reduce the cost in lives associated with any given level of carcinogen exposure That such high-risk subgroups exist is clearly illustrated by the well-known genetically determined disease, xeroderma pigmentosa, which involves a defective mechanism for repair of DNA injury caused by ultraviolet radiation, together with a remarkably high susceptibility to skin cancer induced by sunlight

These considerations lead to the issue of how the degree of susceptibility to a particular carcinogen for a given form of cancer relates to the spontaneous incidence of that cancer One gains the impression from experimental data that a nonthreshold type of tumor response to a carcinogen occurs where there is a relatively high spontaneous incidence of the particular cancer under study If an approximately constant radiation dose were required to double the spontaneous incidence of any type of cancer, it is clear that the spontaneous incidence of a cancer would have a strong effect on the shape of the response curve and the existence of an apparent dose threshold

THE EFFECTS OF RADIATION ON THE FETUS

M L Griem

University of Chicago Clinics

In 1968 in the Journal of Reproductive Medicine I took the following position in the summary of a review article on the effects of radiation on the fetus

1 High doses of ionizing radiation above 50 rads will result in gross congenital malformations These malformations will vary with the stage of gestation at which exposure to X ray occurs

2 The developing central nervous system is very sensitive to ionizing radiation, and doses above 15 rads will result in frank abnormalities

3 Exposures of 1 5 to 3 rads may result in an increased frequency of tumors, either benign or malignant

4 Below doses of 1 rad there seems to be little evidence that the fetus is injured

5 Radioactive isotopes administered to the mother can cross the placental barrier and result in injury to the fetus

6 Diagnostic X ray exposures of the maternal pelvis should be avoided, especially during the first trimester of pregnancy

7 Diagnostic chest X rays and X rays of the skull and extremities have not been implicated in radiation injury to the fetus

This position can be modified two years later by additional data supplied by L Jacobsen who has evaluated the somatic effects of radiation on the fetus and has extended the observations of the Russells in a monograph entitled "Low-Dose X-Radiation and Teratogenesis " The other area which has changed somewhat in the past two years is that of carcinogenesis Three interesting papers have been presented One is by Robert W Gibson and co-workers pointing out the increase in leukemia in children exposed to multiple risk factors, one of which includes in utero radiation of the child Alice Stewart has added some additional information to the concept that radiation may induce cancer On the other hand, recent work by Jablon and Kato analyzing almost 1300 children exposed prenatally to the atomic bombs has not demonstrated an excess mortality from leukemia and other cancers These most recent data in the prospective study of Jablon raise some questions concerning the previous retrospective studies by Gibson, Stewart, and MacMahon

The position one might take now with relation to fetal irradiation and carcinogenesis is that the risk is less and that the frequency of tumors induced by prenatal radiation is less than previously expected Brent has added additional data concerning the lack of effects on the central nervous system as measured by changes in nervous function A number of others have contributed to the growing body of data about which isotopes cross the placental barrier and enter the fetus This work has been reviewed by Sikov

LOW-LEVEL RADIATION EFFECTS IN HUMAN POPULATIONS

L. H. Hempelmann

Strong Memorial Hospital

Assessment of present state of knowledge and confidence

Almost all of the predictions of the effects of low-level exposure to ionizing radiation in man are based on extrapolation of data from human populations exposed to relatively high doses (usually over 100 R) delivered at a high dose rate (over 50 R/minute or more), often to a limited portion of the body. The only populations at present available for direct study of low dose effects are (1) human fetuses exposed to a few rads of X rays at high dose rates, (2) hyperthyroid patients treated with ^{131}I with a resultant total-body dosage of several tens of rads at a relatively slow dose rate (plus a large thyroid dose), (3) a few hundred Marshall Islanders exposed to rather uncertain doses of external and internal radiation at a relatively high dose rate from radioactive fallout, and (4) a large population of Japanese at some distance from the hypocenter of the nuclear explosions, with resultant exposure to small doses of uncertain magnitude delivered at a high dose rate.

Since the results of all of these studies are at best uncertain in one aspect or another, we must use the available data on persons exposed to relatively high doses at high dose rates to assess the risks of low level exposures. In keeping with the usual policy of maximizing estimated risks, we make the most conservative assumptions in extrapolating the values to low dose levels, namely, we assume that the linear dose response observed at the high dose levels and high dose rates also holds at low levels of doses and dose rate. In other words, we assume that no recovery occurs at low doses and dose rates, a pessimistic assumption in view of the demonstrable recovery of cellular damage in animal and tissue culture experiments. As far as the confidence in the extrapolated risk values is concerned, we are certain that these estimates are at the upper limit of the possible effects if one extrapolates from the rapidly ascending part of a valid linear dose-effect curve. We have no idea how much less than the maximum the actual risks may be. The confidence limits, then, are between the upper estimated risk and zero.

Evaluation of future course of action

In my opinion, the following course should be pursued to solidify the data on risks of low-level radiation exposure.

1. Intensify mathematical treatment of dose-effect relations extrapolated to low doses.
2. Set up intensive experimental studies of the shape of the dose-response curve at low doses and dose rates, and of the mechanisms of cancer induction under these conditions.
3. Continue animal experiments comparing effects of the same doses of ^{131}I and X rays, such as have been done for cell killing and oncogenesis in rat thyroid.
4. Continue and extend existing epidemiological studies.
5. Look for new study populations, preferably irradiated at low levels, e.g., technical and supportive staff exposed to fallout at the 1951 Eniwetok tests, children given tracer doses ^{131}I, etc.
6. Set up a panel to evaluate objectively the comparative risks of nuclear vs. other power sources. This should be composed of distinugished scientists who have not previously been associated with the radiation field, but who think in terms of probabilities and who can analyze data objectively.

SOME RECOMMENDATIONS FOR EPIDEMIOLOGICAL STUDIES

E. L. Saenger

University of Cincinnati College of Medicine

The probability of isolating additional unique low-level effects attributable to radiation by experimental methods seems low. Historically, the only data which contribute to our understanding of somatic effects, insofar as radiation standards are concerned, are human data; and of these by far the most useful data are obtained from epidemiological investigations.

My personal view continues to be that the present radiation standards are entirely adequate [1, 2] and that no changes should be made until new information becomes available which indicates clearly the need for further modification. Based on existing data one can show the reasonable possibility that certain present standards are too rigid just as well as one can consider that the same standards are too high. These statements do not indicate an opposition to the search for effects associated with low-level radiation: well planned studies are highly desirable, particularly in view of current public apprehension.

A principal source of confusion of some recent studies lies in the practice of comparing populations with grossly dissimilar characteristics, usually a diseased group vs. the population at large. In general, retrospective studies have been of only suggestive help in identifying association [3]. Usually their appeal is an economic one. It will be necessary to identify prospectively populations receiving low doses (0.1 to 20 rem) and arrange long-term followup both of the irradiated and comparison cohorts.

Specific study areas include further investigation of alterations of sex ratio, abnormalities of development following diagnostic X irradiation early in pregnancy, and abnormalities in children receiving "high" doses to the genitourinary tract. Further correlation between cytogenetic changes in irradiated children and subsequent manifestations of such abnormalities should be considered. Most investigations of these kinds will require collaboration between many large centers.

The earlier record-keeping proposals of AEC should be re-examined. It should be possible to follow individuals who receive 1 to 5 rem/yr, if they are properly identified. Again, it will be necessary to identify appropriate comparison groups. Adequate follow-up must be assured. Access to Social Security records should be simplified greatly, so as to make appropriate follow-up more precise and less costly.

The concept of benefit vs. risk is so loosely used that this matter needs thorough re-evaluation so that a language of benefits can be developed. Consultation with clinical epidemiologists and actuaries will be helpful in this regard.

Finally the relatively high costs of these programs should be considered. They will probably be less costly than the expense of making standards more rigid in the absence of scientific evidence. It is essential that we be right for the right reasons.

References

1. Saenger, E. L. Radiologists, medical radiation, and the public health. Radiology 92(4), 681-699 (March 1969).
2. Saenger, E. L. and W. Stumpe. The future of radioisotopes in medicine: Benefit vs. risk. Medical Radionuclides: Radiation Dose and Effects, Proc. Symp. held at the Oak Ridge Associated Universities, December 8-11, 1969. U. S. Atomic Energy Commission Symposium Series 20 (June 1970), pp. 491-507.
3. Feinstein, A. R. *Clinical Judgement*. Williams and Wilkins Co., Baltimore, 1967, p. 271.

Human Epidemiology

EPIDEMIOLOGY OF ENVIRONMENTAL EFFECTS

WHAT CAN BE LEARNED ABOUT LOW-LEVEL RADIATION EFFECTS FROM THE RADIUM CASES?

R. E. Rowland

Argonne National Laboratory

The study of the effects of internally deposited radium isotopes began long before accelerator or fission-produced radioisotopes were created. Human exposures from radium, acquired either through industrial exposures or iatrogenically, have provided a great wealth of information on the effects of radiation on man. However, most of the emphasis has been placed on the effects of high levels of radium.

Exposure to radium, however, has produced a complete spectrum of levels of internal contamination. The exposed population consists, therefore, not only of the high level cases where the majority have died as a result of their exposure, but also a large number of low-level cases where few, if any, consequences of the radiation exposure have been detected.

Since the formation of the Center for Human Radiobiology within the Radiological Physics Division of Argonne Laboratory, we have acquired case records for most of the radium cases that have been located within this country. From some 2000 records, we have identified a group of 777 cases who have a measured body burden, and for whom total doses have been calculated. These cases experienced a total of 71 malignancies presumed to be radiation induced.

Various dose response functions have been fitted to these data. The function yielding the most satisfactory fit for the entire range of doses is of the form

$$\text{Tumor Incidence} = K(\text{Dose})^2 e^{-\text{Dose}/D_0},$$

where the Dose is the average skeletal dose.

For this discussion the region below 1000 rads, where there are 584 cases with no malignancies to date, is of most interest. Assuming that a linear response applies in this region, there is a 90% probability that the relation of incidence to dose is

$$\text{Tumor Incidence} \leq 0.3\% \text{ per } 100 \text{ rads.}$$

Future studies on the population of radium cases will include:

1. All possible efforts to increase the number of cases available for study.
2. Complete follow-up of all living cases for the remainder of their lifetimes. Of our population of 777 cases, some 580 are alive today, most of whom have now carried radium within their bodies for over 40 years.

It is the alpha-ray dose to the soft tissues adjacent to bone which is usually considered when evaluating the effects of internally deposited radium. The following features, usually ignored, are also to be considered:

1. Most of the radon formed diffuses out of bone into the blood stream, and thus throughout all organs of the body. Radon decay may thereby result in the irradiation of all organs of the body.
2. The radium daughter products which do remain within bone emit, in addition to alpha particles, beta and gamma radiations, which effectively deliver a small dose to all of the contents of the marrow cavity and surrounding tissues.

Thus the living radium cases have experienced not only intense alpha radiation adjacent to bone, but continuous low-level irradiation of all the tissues. The study of this population, therefore, may yield a background of information applicable to low-level radiation exposure to the entire body.

EPIDEMIOLOGY OF ENVIRONMENTAL EFFECTS

P. E. Sartwell

Johns Hopkins School of Hygiene and Public Health

It is difficult to think of epidemiological studies of low-level radiation effects which do not involve the follow-up of exposed populations, a topic allotted to another group. Two kinds of situation have provided most of the direct information on human effects. These are occupational exposures, and diagnostic or therapeutic exposures. Occupational groups which have yielded valuable information include the Colorado plateau uranium miners, radium workers, and radiologists. A common deficiency in such studies is limited information as to dosage. Occupational risks have probably become much smaller than heretofore.

Medical exposures which have been well studied include X-ray pelvimetry in pregnancy, and treatment of ankylosing spondylitis. Other situations have been less well investigated. In particular, tuberculosis patients who received pneumothorax treatment in the nineteen-thirties and forties should be followed up, since they received heavy fluoroscopic exposures. Suitable controls would be patients with similar lesions who could not receive pneumothorax. Such a study would be difficult because of the long elapsed time, but nevertheless offers promise.

No information is available, to my knowledge, on the effects of living in sites where natural background radiation is very high. India and Brazil are said to have such regions. It would seem feasible to make such studies, which might yield information as to possible increases in mutations, congenital defects, intrauterine death, cancer incidence and general mortality.

More can be learned about the longevity, reproductive experience, diseases and causes of death of radiologists in comparison with other medical specialists In particular, we need to learn if the excess mortality which we attributed to occupational exposure is still in evidence Two studies--one based upon a registry of radiologists and pathologists, the other an analysis of mortality experience of several medical specialist groups--are under way to answer these questions

The investigations mentioned above are of the longitudinal or cohort type Another approach is to select a disease suspected of being radiation induced and conduct a case-control study This approach has been used effectively in studies of leukemia, lung, breast and cervical cancer and other diseases It permits the estimation of relative risks of a selected disease among those who have had a particular exposure, such as radiation

The acceleration of aging by radiation is a phenomenon established in animal experiments but not yet clearly indicated in man It is perhaps the most important, as well as difficult, low-level radiation effect to evaluate In addition to clinical evidence, an excessive age-specific mortality beyond age 45 attributed to cancer, arteriosclerotic heart disease and some other causes would be evidence for accelerated aging in exposed human populations

In epidemiologic studies it is important to take account of other environmental and host qualities which may also influence disease incidence An example of this is the importance which cigarette smoking appeared to exert in amplifying the effect of radiation in inducing lung cancer of uranium miners

EPIDEMIOLOGY OF ENVIRONMENTAL EFFECTS

Raymond Seltser

Johns Hopkins School of Hygiene and Public Health

The specific charge to each participant of this conference was to bring a concise statement of his views about ways to improve the estimation of low-level effects in human populations It was to deal explicitly with the following two points 1) assessment of the present state of knowledge and confidence and 2) evaluation of future courses of action

The type of radiation hazards from "environment effects" can be classified according to the *source* of the radiation exposure, i e , air, water, or soil It is relatively easy at this point to assess the present state of knowledge concerning low-level effects attributable to air, water, or soil exposures The controversy over the interpretation of vital statistics--and the need to rely on such imprecise measurements at all in attempting to detect radiation effects in human populations--is an indictment of the failure to develop and maintain adequate study populations which might serve as indicators of these effects There is limited knowledge available from the Marshallese data and the Nevada test data, but these are so scanty, controversial, and selective as to be almost worthless for specific inferential use

How, then, should this problem be attacked? What can we do now and in the future? I believe that there is the need for the development of a National Environmental Effects Surveillance Center, charged with the responsibility of

1 Monitoring through appropriate sampling schemes for the existence of "high risk" areas and/or populations where the levels of any environmental toxic agent (whether it is radiation or other pollutant) exceeds an established minimum,

2 Surveillance of such high risk areas and populations, developing whatever specific studies are needed to determine dose-effect relationships between the "agent" and the host

I believe that such studies and such populations must no longer be allowed to develop at the "whims" of individual investigators All such identified groups should be considered "national resources" and as such, follow-up should be under the aegis of some central group It is likely that much of the actual work on these groups could be carried out by university personnel or other interested groups under contract to the central unit

I cannot overemphasize the importance of attempting to tie in the surveillance for radiation effects with similar activities for other biological effects induced by other environmental hazards The techniques of study and the problems of follow-up are similar for all these agents--even though each study would require different types of scientific and technical expertise on the study team The common denominator, however, is the epidemiologist whose forte is the techniques of hypothesis testing in human population groups

ROLE OF THE RADIOBIOLOGIST IN SETTING GUIDELINES

A. R. Tamplin

Lawrence Radiation Laboratory

For the purpose of setting guidelines for the exposure of individuals by ionizing radiation, the reasonable public-health approach is to use a linear extrapolation beyond the point where data exist. This, it can be said, is my opinion and it involves certain value judgments that lie outside my scientific discipline. With this I would agree.

At the same time, I think this illustrates the role of scientists in setting the guidelines. His role, as a scientist per se, stops where valid scientific evidence ends. At that point he has one additional input and that is to define the nature of the experiments, the time required and the money needed to resolve the uncertainties.

I think the present data are sufficient to set the guidelines. To do further experiments for the sole purpose of setting the guidelines would appear to be counter-productive. For the most part, the study of low-level radiation effects entered the baroque period some years ago. By this I mean that the experimental approach has been to study larger groups of animals at lower dosages. These studies now show linearity down to 10 rads. Further extension solely for guideline purposes would seem unwarranted.

The future of radiobiology would seem to lie in different pursuits such as investigating the mechanism of radiation carcinogenesis. Here it seems to me that more experiments involving synergism and co-carcinogenesis should be undertaken. I think the same thing applies to the genetic effects, for example, investigating the different behavior of the mouse oocytes. Also more effort should be applied to the role of the chromosome alterations in both carcinogenesis and genetics. The newer techniques for studying chromosomes would suggest that this area is ripe for detailed study both in animals and man.

Physics and Models

DOSIMETRY STANDARDIZATION--COOPERATION IN LATE EFFECTS RESEARCH IN EUROPE

J. J. Broerse

Radiobiological Institute, TNO

Progress on the estimation of low-level radiation effects requires large-scale experiments and long-term commitments of personnel and facilities. Such requirements are in general beyond the scope of an individual laboratory, because of limitations with respect to finances and technical facilities. In the past, the lack of standardized experimental material and variation in methodology and in quantitation of end points, have made interlaboratory comparisons extremely difficult. A solution to these limitations, providing the possibility of more rapid advances in the field of late effects studies, has been found in a coordination of projects of several European laboratories organized in an European Late Effects Project Group (EULEP).

A cooperative research program requires the standardization of methods used in the participating laboratories [1]. A few areas can be distinguished where the standardization of methods is of paramount importance, namely, dosimetry, experimental animals, and special auxiliary methods used in experimental and clinical studies. Such a standardization will facilitate the comparison of results obtained as well as their evaluation and interpretation.

For a quantitative assessment of the effects of external irradiation, the exposure procedures have to be standardized and the absolute dosimetry has to be consistent within the participating laboratories. For internal irradiations, it will be necessary that the participating laboratories apply the same models and the same physical and biological data for their dose calculations. For the standardization of dosimetry in these laboratories, a special dosimetry committee has been appointed to assist in dosimetric problems and to suggest improvements in existing methods. At present the committee has given recommendations for the standardization of X ray dosimetry [2], and is carrying out dosimetry intercomparisons. A mail service of thermoluminescent dosimeters has been organized. The preliminary results of the EULEP X ray dosimetry intercomparisons are shown in Table 2.

TABLE 2. Preliminary Results of X Ray Dosimetry Intercomparison

Institute - blind coded	Difference between highest and lowest readings of three TL dosimeters, %	Mean value for first intercomparison, %	Mean value for second intercomparison, %
A (Rijswijk)	0.4	102	101
B	2.1	90	101
C (Bilthoven, standardized) (on NBS and NPL)	0.9	98	100
D	5.6	97	91
E	1.9	97	102
F	2.9	116	-
G	1.7	106	107
H	4.5	99	98
K	0.1	101	100
L	2.1	94	95
M	4.9	107	114
N	0.6	91	90
O	0.5	105	101
P	2.3	81	77
Q	1.5	107	110

References

1. EULEP (European Late Effects Project Group). Proposal for the performance of a cooperative research project on late somatic effects of ionizing radiation in mammalian organisms, to be published in 1971.
2. EULEP. Recommendations for the standardization of X ray dosimetry, to be published in 1971.

A STATEMENT ON LOW-LEVEL EFFECTS IN HUMAN POPULATIONS

H. H. Rossi

Columbia University

I believe that we are in the process of formulating the basic nature of the radiation lesion in the mammalian cell to the point where the kinetics of a particular inactivation or injury can be defined in terms of two or three characteristic quantities. Short-term research goals should be concerned with the measurement of these parameters in order to achieve the ability to predict effects at low doses and, in particular, to identify the magnitude of the linear term in the relation between dose and cellular effect. Research suitable for this purpose is concerned with an assessment of the effects of radiation quality and of dose rate, particularly at low doses. An important larger experiment should be a comparison of the effects of chronic exposure of animal populations to high (^{60}Co) and low (^{170}Tm) energy gamma rays and to neutrons (^{252}Cf). This should provide many of the needed data, even with observations at doses that considerably exceed permissible levels. Extrapolations or mathematical analysis of the dose-effect relation for any one radiation are likely to be sterile or misleading.

The biophysical approach mentioned above provides only a limited pragmatic understanding of the action of radiation on the cell. It is unlikely to solve such fundamental problems as the biochemical identity of the radiation lesion or the interrelation between cellular and tissue effects. The answer to the first of these questions is not immediately required for radiation protection. The answer to the second has considerable bearing on whether permissible doses based on cellular response are too low but not on whether they are too high, since injury to more than one cell must exhibit a dose-response relation in which linear terms are suppressed or absent. To overestimate radiation hazards might be as harmful to progress as to underestimate them. Thus research designed to elucidate the relation between cellular injury and pathological response to radiation should have high priority.

THE DOSE-EFFECTIVENESS FUNCTION (DEF). DEFINITION, DATA, AND A CYTOGENETIC MODEL

G. A. Sacher

Argonne National Laboratory

The DEF is defined for each end point as the functional dependence of yield on dose, with yield expressed per unit dose. The validation of each empirical DEF estimate depends on demonstration that the derived curve is not distorted by interactions with other parameters.

Analysis of life shortening data for rodents given single, fractionated or lifetime exposures to γ rays, X rays or fission neutrons establishes the following properties for the DEF: 1) over a γ-ray dose range extending from about 10 R up to about 100 R, the DEF increases as the first power of the dose; 2) below 10 R, the DEF is constant, with a nominal value of 0.0004 R^{-1}, above 100 R, the DEF rolls over to an upper plateau with a value of about 0.003 R^{-1}, so the high- and low-dose effectiveness values are in ratio of about 8:1; 3) the DEF for fission neutrons is nearly constant over the entire range, so the reciprocal of the DEF is approximately the RBE function for fission neutrons relative to gamma rays.

It was conjectured that the middle and upper branches of the DEF are due to cell injury and death arising from inviable rearrangements of broken chromosomes. A computer-aided mathematical analysis of chromosome breakage and reunion is being developed which permits the kinetics of these processes to be modeled. The computer model can deal with 40 or more simultaneous chromosome fragments per cell. The first cases modeled are found to fit the two upper branches of the DEF when the two adjustable parameters are assigned values consistent with the data of cell radiobiology.

Further study of the properties of DEF's for various end points, and of the cytogenetic theory, should be given priority because they promise to provide a basis for evaluating the parameters of the low-dose branch for effects on man. Some first objectives at the phenomenological level are: 1) measure DEF's for various somatic end points, especially leukemia, making use of the relation between DEF and RBE curves; 2) in particular, determine in each case whether a low-dose branch exists, and whether it has a consistent ratio to the high dose branch (this ratio is so far known for only one end point); 3) determine the DEF's for species differing in sensitivity, and their parametric differences (e.g., guinea pig and mouse DEF's differ only in the recovery rate parameter); 4) seek further evidence on the quantitative relation of somatic disease and death to cell death; and 5) pursue the relation of cell death to chromosome lesions, especially the mechanisms of the first-power dose dependence at low doses.

A great effort will be needed to match the chromosome aberration theory to the complex phenomenology of the cell cycle, but significant advances can be made independent of that development. For example, the theory has already suggested new experiments on the effects of fractionation and neutron-gamma mixtures, which may have important consequences.

Exposure Guidelines: The Process

THE DEVELOPMENT OF EXPOSURE GUIDELINES

Lauriston Taylor

National Academy of Sciences, Washington, D. C.

A numerical value for a standard of effect implies a knowledge of the effect produced at a given level of stress, and that both effect and stress are measurable. At modest doses of a few tens of rads delivered in a short time period the statistical identification of certain cause-related effects becomes possible; no observations have been possible for levels below a few rads. Because of this, many questions arise.

Any protection specification requires an indication of the object to which the standard applies. If the object is man, is it *all* men, and are we by such protection depriving him of something he needs and desires--like more life at some level of health and comfort, or perhaps just some more comfort, or something material? And who

evaluates his needs and desires and decides upon the level of their fulfillment? These questions have to be answered before we can assess the value of our state of knowledge because unless, and until, we have some basis for a relationship between whom we are protecting and what we are protecting against, we are largely in an atmosphere of personal opinion and we can more easily settle the problem by voting--except that a consensus in ignorance does not produce wisdom

Another problem is the definition of what an "effect" is and whether it can ultimately be shown to modify man's "way of life" or that of his offspring

It is reasonable to suppose that an allowable exposure of population groups to ionizing radiation originating from a controllable source would be at some level less than that causing an observed effect For exposures above the minimum, E_0, to cause an observed effect, there are various dose-effect relationships that may vary with the effect and the manner in which the dose is delivered However, the population doses, E_p, for which there is concern, are a small fraction of E_0- doses generally of the order of that from natural radiation E_n, or much less $E_p \ll E_n < E_0$ The allowable dose might be arbitrarily set as low as zero, where there is clearly no direct or indirect benefit to anyone A level above zero would be set in consideration of possible needs, benefits, risks and costs The question is how to evaluate or postulate the effects or risks in the dose region below the level of E_0 in which no cases are likely to be found within the forseeable future How then is an allowable dose level set?

The method used in toxicology is to make no assumptions about dose effects in the region where there are no observed effects and choose an allowable level at some fraction of E_0 It is a simple "safety factor" method One alternative would be to postulate a linear dose-effect relationship in the dose range between E_0 and zero dose, disregarding repair and recovery There is little foundation based on observations for such an extrapolation, and since there *is* some biological repair and recovery any such plot would, at most, represent extreme upper values for effect Such an extrapolated curve, alone, is not only valueless but seriously misleading when used as a basis for calculating or predicting radiation risks, injuries or deaths

Thus, neither the safety factor nor extrapolation method can be used for quantitative evaluations of either effects or risks The main virtue of the second method is that the extrapolation may provide a useful line of departure for the study of effects when new techniques or large statistical samples may yield some significant data in the low-dose region In the meantime for doses $< E_0$ it must be clear that the effects have faded into insignificance A definition of "insignificance" is essential

Chairman's Committee Report

ON THE DOUBLING DOSE CONCEPT

C W Mays

University of Utah

By analogy with the induction of genetic mutations, some individuals [1,2] have assumed that the incidence of radiation-induced cancer is directly proportional to both its "natural" incidence and the radiation dose

$$I_r = I_0 \frac{x}{D} \qquad (1)$$

where

I_r = radiation-induced incidence
I_0 = natural incidence
x = radiation dose
D = doubling dose (assumed constant)

However, the same individuals proposing the above relationship have indicated that the so-called natural incidence is not a fixed quantity, but can be influenced by various factors such as country of residence [1], cigarette smoking [1], exposure to asbestos [1], and background radiation [2] For example, they present data indicating that for radiation-induced lung cancer, the incidence per rad is about 10 times higher in cigarette smokers than in nonsmokers, and ascribe this to the 10-fold higher natural incidence among the cigarette smokers [1]

Furthermore, they claim that the average background of about 0 1 rad per year causes about 3% of the naturally-occurring cancers If this were true and if the dose-response were linear, then from this factor alone the predicted natural incidence in some regions should be 4 times average, since background radiation in some inhabited parts of the world ranges up to about 10 rads per year, which is 100-fold higher than average [3] Predicted natural incidence for such regions of high background

Radiation induced	≅ 100 X 3% = 300%
Nonradiation induced	≅ 100%
Total natural incidence	≅ 400%

Thus, (from Equation 1) the increased incidence per additional rad in such regions of high natural background is predicted to be about 4 times greater than if background-equivalent radiation had been artificially given This suggests that Equation 1 is inconsistent since tissues cannot distinguish between radiations which differ only in their natural vs artificial origin

It seems more consistent to assume that the additional incidence (dI) *from additional dose* (dx) *is* proportional to the total incidence (I) which would result from the previous radiation doses and natural causes

$$\frac{dI}{dx} = kI, \tag{2}$$

where (k) is a constant of proportionality The solution to Equation 2 is

$$I = I_0 e^{kx}, \tag{3}$$

where natural incidence (I_0) is assumed constant for fixed conditions Since the total incidence (I) equals radiation-induced incidence (I_r) plus natural incidence (I_0),

$$I_r = I_0(e^{kx} - 1) \tag{4}$$

In Equation 4, the predicted incidence of radiation-induced cancer increases not linearly, but as an exponential function of dose However, the higher the natural incidence, the more closely the exponential Equation 4 approaches a linear relationship, as has been shown in a more detailed analysis on this topic [4]

But one must realize that the fundamental mechanisms by which radiation induces cancer may be quite complex, and any relation as simple as Equation 4 should not be expected to describe accurately the actual incidence over a wide dose range For example, it must break down at very high doses because of the radiation killing of potentially malignant cells It may, however, prove useful in testing hypotheses against experimental data, and it may give insight into alternative models which may more closely approximate that elusive goal called reality

I am grateful to Austin Brues for first pointing out at this conference the nonlinear interpretation inherent in the "doubling dose" concept, to Roy Albert for asking me to write it up, and to George Sacher for including it in these proceedings

References

1 Gofman, J W and A H Tamplin Major fallacies in the AEC staff comments on the Gofman-Tamplin papers and congressional testimony *Environmental Effects of Producing Electric Power*, Hearings of the Joint Committee on Atomic Energy, Part 2, Vol II (Jan 27-30 and Feb 24-26, 1970) pp 2113-2127

2 Gofman, J W and A. H Tamplin, Low dose radiation, chromosomes and cancer *Environmental Effects of Producing Electric Power*, Hearings before the Joint Committee on Atomic Energy, Part 1, (Oct 28-31 and Nov 4-7, 1969), pp 641-652

3 Penna-Franca, E , J C Almeyda, Johanne Becker, et al Status of investigations in the Brazilian areas of high natural radioactivity Health Phys *11*, 699-712 (1965)

4 Mays, C W A nonlinear interpretation to the doubling dose concept *Research in Radiobiology*, University of Utah Report C00-119-244 (March 1971, in press)

Documents Distributed during the Conference but Not Included in These Proceedings

Abrahamson, S., P. Gullifor, E. Sabol, and J. Voigtlander. The induction of translocations in mature Drosophila oocytes over a dose range of 10-500 R of X rays.

Kellerer, A. M., and H. H. Rossi. RBE and the primary mechanism of radiation action.

Goldman, M., N. H. Hetherington, L. S. Rosenblatt, and L. K. Bustad. Quantitative evaluation of dose-effect relationships following exposure of dogs to internal emitters.

Rowland, R. E., P. M. Failla, A. T. Keane, and A. F. Stehney. Some dose-response relationships for tumor incidence in radium patients.

RAPPORTEURS' ACCOUNTS

Mammalian Radiobiology

SYSTEMIC AND PHYSICAL FACTORS

J B Storer and J M Yuhas

Oak Ridge National Laboratory

The session on systemic and physical factors covered two broad questions the role of animal experimentation in the estimation of low-level radiation hazards for man, and the type of animal experimentation which would most adequately fulfill this role Since animal experimentation will not in itself allow us to evaluate radiation standards, its role is largely that of establishing general principles which relate to the overall problem Experiments designed to test smaller and smaller doses of radiation through the use of larger and larger populations of animals should be avoided, owing to their lack of generality, unless specific hypotheses are being tested which go beyond "late effects surveys" In order to be relevant, animal experimentation should concern itself with mechanisms or processes which are known to be species-independent, or which can be related logically to biological characteristics for an interspecies comparison

Specific areas which merit further investigation include

1 the role of the immune system in the control of radiation-induced cancers, especially in the low-dose-rate range,

2 the quantitative relationships which exist between activated viruses and the resultant cancers,

3 the toxicology of internal emitters which may be encountered by man, including tritium and krypton

4 the relationship between total dose, dose rate, and the incidence of late effects, including analyses of the role of single and multiple event phenomena in the induction of specific disease entities

CARCINOGENESIS

A M Brues and C F Hollander

Argonne National Laboratory and Experimental Gerontology Unit, TNO

The opinion was expressed that normal effects are accelerated by treatment, more attention should be paid to morbidity than to mortality, life shortening is not the most valuable parameter unless it is related to specific death rates for specific diseases Some tumors (lung adenomas) are present for a long time in living animals so that the morbidity rates are not estimated by autopsying animals as they die The plot of the logarithm of the rate of tumor morbidity against time shows a decreasing slope later in life The decrease occurs later and is less marked in pathogenfree mice

The carcinogenic process reflects a competition of two factors tumor induction in cells and killing of cells It has been useful to use monoenergetic ions to study carcinogenetic action, as this controls the site of radiation action The question of direct effect has been studied by skin transplantation, tumors are shown to arise from the irradiated skin, and not from the skin of the unirradiated recipient, even after a third transplant generation

There are various studies, using carcinogens in general as well as radiation, which indicate that host factors are important as well as the cells that are the origin of the tumor This is suggested by viral carcinogenesis and the role of immune factors, and by plastic carcinogenesis, which has not been shown to be enhanced by radiation, and which has resemblances to transformation of cell cultures and to the conditions preventing differentiation of embryo organ cultures An example of a host factor in co-carcinogenesis is the inhibition of ciliary action in the lung by tobacco smoke, favoring retention of inhaled particles Care must be taken to distinguish between carcinoma *in situ*, benign tumors and invasive malignancy

It was noted that the evidence for co-carcinogenesis by smoking in uranium miners is not complete at present The existence of chemical agents in miners, in addition to radon, was indicated

LARGE ANIMAL STUDIES

Marvin Goldman and S. M. Michaelson

University of California and University of Rochester

The discussion relating to research on large animal radiation effects suggests that they provide valuable model systems extrapolatable to man. For example, there are data which show that dogs manifest a spectrum of responses to ^{226}Ra similar to what has been reported for man. A consistent finding in large animal studies is that the dose effectiveness for cell or tissue "injury" and cancer incidence is nonlinear in each study in which all the data are included in the analyses. The discussion pointed out some discontinuities or deficiencies which appear to be related to (1) the nonuniform distribution of dose over time, and over the cells at risk and the tissue or organ system under study, and (2) the uncertainty about the fraction of the absorbed tissue dose that is unavailable to cells at risk, either because the cells were previously killed or are not in the range of the ionizing events. An additional example was a discussion of the nonuniformity of local dose distribution and tissue response of lungs of dogs following inhalation of high levels of ^{239}Pu.

It was also noted that lung pathology, not radiation related, also often manifests a nonuniform distribution throughout the organ. These observations may be showing us valuable data on the actual distribution of types of cells at risk. In this context, some of the radionuclide effects studies are of particular value for determining the distribution of cells at risk by evaluating cell injury or death, and incidence of neoplasms spatially and temporally, with regard to their *specific* dose rate pattern. The data do not suggest unique radiation carcinogenetic effects in tissues not being directly irradiated.

The problem of interspecies comparisons is also related to the above. It would appear important that some species scaling is possible, and data exist for cell, tissue and organ systems receiving *comparable* doses of radiation, independent of and parallel with such data as relative body mass, metabolism and lifespan. The use of systems physiology, based on various levels of biological organization in several animal species with specific and well-known attributes, is invaluable in extrapolation to possible human hazards from radiation.

There is an obvious need to carefully extract and evaluate the costly and painfully obtained data that already exist on radiation effects in large (long lived) animals, so as to assure the best possible analyses in relation to assessment of linear vs. nonlinear response characteristics.

TISSUES AND CELLS IN VIVO

E. B. Darden, Jr. and R. J. M. Fry

Oak Ridge National Laboratory and Argonne National Laboratory

The first tissue considered was the mouse lens, which can be examined serially to record the development of tiny opaque defects (termed *flecks*) which electron micrographs suggest to be defective portions of single lens fibers. Normal fibers are produced by proliferation of the lens epithelial margin, throughout life at a declining rate. Progeny cells migrate to the lens equator and mature into adult fibers. The time interval (six weeks) from division to maturation is equal to that from irradiation to an increase in flecks, evidence that the site of injury may be the lens germinal cell. Flecks in the nonirradiated controls begin to appear at 13 weeks of age and increase with time, suggesting the presence of abnormal but viable germinal cells in the normal lens epithelium. If irradiated at six weeks of age, mice reveal fleck counts which also appear at 13 weeks of age, but increase at a faster rate. Dose dependent RBE values have been obtained, being 55 for 0.5 rad of 0.43-MeV neutrons and 6 for 5 rads of 14-MeV neutrons. X-ray dose response appears sigmoid, whereas 12 rads of X rays produced a detectable effect, 4.5 rads did not. The incidence of flecks is being studied in the Marshallese and several women who received 175 rads from fallout radiation in adolescence have shown an incidence of flecks above the control level. (A generally accepted ratio of lens radiosensitivity in man:rabbit:mouse is 1:4:16, respectively.)

The interspecies comparison appears to show that the larger eyes are less susceptible to induction of lens opacities. The reason for the differences in sensitivity are unknown, although it was suggested they may be related to differences in growth rate and therefore proliferative rate.

Studies of the relationships of cell killing, chromosomal abnormalities and the incidence of

opacities on an interspecies basis appear a possibility There would be the advantage that the results would be almost independent of cellular responses elsewhere in the body The system is also useful in providing experimental data for comparison to theoretical models The second sensitive system was the mouse zygote Irradiation is given shortly after timed mating, in the early pre-implantation stage Sixteen days later the uteri are examined With relative embryo survival as the end point the effect of <5 rads of neutrons can be detected Survival at higher doses appears to be exponential, at least to 20 rads, with a D_0 of 18 rads The RBE with respect to X rays is about 4 over this dose range The importance of interspecies studies was emphasized for the determination of the relationship of changes in cell systems, such as colony-forming cells of the bone marrow, to life shortening There are marked species differences which are likely to be of importance in the elucidation of the ability for repair and recovery after acute exposure and chronic low dose exposures An understanding of these species differences would appear to be necessary for extrapolation of data from small animals to man Adequate comparative studies are difficult to carry out, and for some time it will be necessary to rely on small animal experiments The advantage of the mouse experiments is that the determination of loss of stem cell populations, or their ability to respond to stress could be done as a function of age and radiation exposure history Furthermore, correlations between the functional capacity of the marrow proliferative cells and disease incidence could be tested Some preliminary data suggested that there was a marked diminution (30-60%) in the number of CFU's in the femoral marrow of old mice that had been exposed to midlethal doses at 100 days of age While there is considerable information about recovery of marrow stem cell population over a relatively short time span after irradiation, little is known of the very late effects on the number of stem cells in proliferative populations The possible relationships of such changes to life shortening and tumor incidence are not known The effects of several other environmental factors may, particularly, influence the bone marrow cell population and will have to be known for interpretation of results of low-level irradiation studies The question was posed whether an understanding of differences in organ and species sensitivity for the induction of tumors could be derived from experiments in which whole-body exposures were given, even with the additional information from local irradiation, or will it be necessary also to carry out in vitro experiments to determine an index of transformation for the appropriate cells? No answers were offered References were made, both in this and other sections, to the immune system and its relation to tumor incidence but no data on the changes in the immune competent cell system as a late effect were presented

Genetics and Cellular Radiobiology

GENETICS

Seymour Abrahamson

University of Wisconsin

Dr Crow spoke on the problem of assessing spontaneous detrimental mutations rates in Drosophila These mutations are measured in a statistical manner by their action of decreasing viability They may represent single gene mutations with a large effect, or a large number of mutations, each with a small effect These mutations arise spontaneously on a given test chromosome at between 0 2% and 0 3% frequency At equilibrium they are at 10% frequency Thus the average detrimental mutation will persist for approximately 40 generations Recessive lethal mutations for the same chromosome arise spontaneously at a 0 5% frequency and at equilibrium exist at about 25% frequency and likewise persist for about as many generations as the detrimentals Therefore, both the recessive lethals and the recessive detrimentals exert their effects in heterozygous condition, and the elimination of both classes results from the slight dominant action of these recessive mutants It follows that a recessive detrimental exerts as much heterozygous effect as a recessive lethal The difficulty of obtaining equivalent data in man was stressed

Data were presented on the induction of chromosome aberrations in Drosophila oocytes by low doses Aberrations increased linearly between 10 and 50 R of X rays, and quadratically between 50 and 500 R In the study of sex-linked recessive lethals in oogonia at 0, 20, 100, and 500 R doses, with some 77,000 chromosomes analyzed, none of the treatments was significantly increased above the control rate In reviewing other workers' results on spermatogonia in Drosophila at doses below 500 R, it again becomes evident that there are few if any data which demonstrate any significant increase in the induction of mutations Thus, even in systems which optimize the

detection of mutations, the difficulty of demonstrating their induction at low doses in the important cell stages for estimating hazards becomes very evident.

F2 data were presented on the induction of detrimental mutations in the mouse when spermatogonia are irradiated. The detrimental effect was measured as an incremental component of mortality within the first 21 days after birth. Grahn described this effect as being induced at a rate of 1.7×10^{-6}/R day. This is the first demonstration of transmitted detrimental mutations in irradiated mammalian systems. Subsequently the discussion centered upon the proposal (see his position paper) to monitor master samples of the U. S. with well-determined genetic and somatic endpoints. A large segment of mammalian radiation genetics was unfortunately unreviewed because of the unexpected absence of one of the panelists.

CYTOGENETICS

A. B. Reiskin

The University of Connecticut

The position papers on cytogenetic effects 1) explained the great difficulty in obtaining statistically significant cytological differences at low levels of radiation, and 2) pointed out the relations between chromosomal effects and other effects in radiobiology, and possible synergisms with other agents.

One of the main points discussed concerned the use of automated chromosome scoring to increase the resolution of the analysis. In general, radiobiologists are hopeful that such techniques will aid in the evaluation of low level effects. It was pointed out, however, that the biophysicists who are involved in the development of such automated machines are often less sanguine. Their projections for the cost of analysing each cell seem to preclude the use of machines for scoring chromosome aberrations after irradiation of multicellular organisms. At this meeting, however, several people expressed the opinion that the cost estimates will prove to be wrong and the the cost per cell will reflect the state of the art and become infinitesimal.

The central role of chromosomes as sensitive targets whose damage underlies many radiobiological phenomena was illustrated in that two separate models were presented relating the kinetics of tumor induction and/or cell killing to the kinetics of aberration formation.

Among other intriguing notions briefly mentioned was the possible implication of radiation chromosome breakage in virus-induced tumorigenesis. It has been proposed that breaks in DNA are necessary for incorporation of the viruses. The curves for the induction of multibreak chromosomal aberrations are linear at very low doses. Data were presented showing that this is true for other multitarget radiobiological phenomena, such as cell survival. The mechanisms involved in these low-dose linear components of chromosome rearrangement and cell killing are not adequately known, and further work is needed.

CELLULAR RADIATION BIOLOGY

G. F. Whitmore

Ontario Cancer Institute

It is likely that some of the information required to evaluate the hazards of low doses can only be obtained from studies involving humans or laboratory mammals, but considerations of cost and convenience suggest that where possible such information be derived from studies on mammalian cells in vitro. It has been suggested that our ability to predict effects at low doses will ultimately depend upon our ability to understand the mechanisms whereby certain phenomena arise. It is probable that the major contribution of in vitro studies will be in developing an understanding of mechanisms.

The three major effects of radiation which concerned this conference were: (1) loss of cell viability, (2) mutagenesis and (3) carcinogenesis. In each of these areas in vitro assays or endpoints are available, and it is likely that these will be improved as the degree of knowledge obtained and required is increased.

To date the major emphasis of in vitro studies has been on the loss of cell viability, usually after doses from one hundred to several thousand rads. As a result, a great deal of information has been obtained on the

effects of radiation type, cell age, dose fractionation, sensitizing and protective agents, etc. The variations in survival response which result from changing any of the listed parameters make it possible to use correlation studies in the search for underlying mechanisms.

Since the subject of the conference was effects at low dose, it was natural that the question of survival at low doses should be discussed. There is now little doubt, especially from studies with synchronized populations, that X-ray survival curves have a negative slope at low doses, and not the zero slope which is predicted by a simple application of the multitarget model of inactivation. The magnitude of this slope may, however, be extremely difficult to determine.

To date, in vitro studies with mammalian cells have not greatly advanced our knowledge of either radiation-induced mutagenesis or carcinogenesis. However, as a result of recent technical advances it now seems possible to use in vitro studies to investigate a variety of subjects concerned with both processes. Amongst these are:

(1) The nature of acute dose response curves
(2) The effects of varying dose rate and fractionation
(3) The effects of agents which might alter response
(4) Species, cell type and locus variations in sensitivity
(5) The possible synergistic roles of virus and radiation in carcinogenesis.

In vitro techniques are now available to investigate mutations involving drug resistance, auxotrophy and conditional lethality, both in the forward and backward direction. The data available are extremely limited and apparently variable, and suggest that in addition to the variables, such as cell number at risk, expression time and drug levels, which have been tested, other factors play a major role in determining apparent mutation frequency. In addition, the nature of the apparent mutations produced has not been adequately investigated.

With respect to radiation-induced carcinogenesis, the possibility has been raised that this may require or be greatly facilitated by co-factors, with viruses being the most likely candidates.

Human Epidemiology

FOLLOW-UP OF EXPOSED POPULATIONS

G. W. Beebe, M. L. Griem, and E. L. Saenger

National Academy of Sciences, The University of Chicago, and University of Cincinnati College of Medicine

Epidemiology will continue to be one of the most useful sources of information concerning effects of low doses in human beings. We outline the various steps to be taken to generate further information on contributions from this approach.

I. Exposed populations possibly available for study.
   A. Those in high background regions
   B. Occupational workers including military personnel
   C. Individuals irradiated for medical purposes
   D. Atomic bomb survivors including Marshallese

Of the exposed populations, the radiation workers, physicians, war veterans exposed to medical radiation, atomic bomb survivors and patients in prepaid medical programs would seem to be groups amenable to simple follow-up.

II. Specific groups to be considered. These would include all groups in whom such studies are already under way.
   A. Populations, for alteration in sex ratio
   B. Fetuses irradiated during early pregnancy, for birth defects
   C. Abnormalities in children receiving high gonadal doses, along with consideration of follow-up in their offspring
   D. Further consideration of correlation of cytogenetic abnormalities and subsequent development of disease. Improvement in automation of cytogenetic scoring is strongly urged.

III. Factors which must be considered in obtaining maximum usefulness and economy in above and similar studies.
   A. It is essential that the hypotheses to be tested and the research design be clearly stated prior to the start of

data collections
B. Sizes of samples need be specified
C. Good dosimetry is important. Qualitative studies (i.e. radiation vs. no radiation) should be considered less desirable
D. Quality of controls. Consideration of their appropriateness in regard to eligibility and similar criteria is important
E. Reasonable cost estimates are required
F. Estimate of time to assure successful completion is important, especially for long term observation
G. Access to Social Security records should be improved
H. Development of a National Death Index would be highly desirable.

IV. Theoretical and practical considerations relating human and animal investigation
A. Mathematical treatment of dose-effect relations extrapolated to low doses should be intensified
B. Experimental studies of the shape of the dose-response curve at low dose and dose rates, and of mechanisms of cancer induction should be continued actively
C. Animal experiments comparing effects of same doses of ^{131}I and X rays, such as have been done for cell killing and oncogenesis in the rat, should be continued.

EPIDEMIOLOGY OF ENVIRONMENTAL EFFECTS

P. E. Sartwell

Johns Hopkins School of Hygiene and Public Health

The first speaker, Dr. Arthur Tamplin, offered the opinion that there is an immediate problem of setting radiation exposure limits; that there is increasing evidence of a linear dose-effect relationship at low dose levels; and that the weighing of risks against benefits was not an acceptable method of procedure in determining health practices. He cited immunization against poliomyelitis, in which he thought the principle was to minimize all risks. In the discussion it became clear that there was disagreement by a substantial number of participants with these views. It was pointed out that in the first large-scale use of poliovaccine a considerable risk of adverse effects was taken, in recognition of the large anticipated benefit; and that unanticipated hazards did, in fact, appear. Another example of the weighing of risks against benefits was the decision, in the face of evidence that oral contraceptives produce thromboembolism, to continue to sanction their use, in view of their superior efficacy, and the probability that adverse effects associated with pregnancy, delivery and illegal abortions would outweigh their hazards.

The question as to what epidemiological approaches are promising was raised. Exposed groups on which longitudinal studies can be made are of two chief sorts: occupationally exposed, and those who have received therapeutic or diagnostic radiation. Examples of the former are physicians, radium workers and uranium miners. Among the second class, it was suggested that tuberculosis patients who had received pneumothorax treatments (in connection with which fluoroscopy was practiced) should be followed up. The case-control method of epidemiologic study was recommended as wholly satisfactory in appropriate circumstances. Further attempts to study populations living in certain areas of high background radiation were advised. Situations in which a group accidentally sustains an excessive exposure should be so dealt with that any consequences can be assured of detection over a sufficiently long period. They should be under the cognizance of a governmental or quasi-governmental agency, although the observations might be made by some other team under contract. Creation of a "National Environmental Effects Surveillance Center" was proposed.

An initial report was made on the pooled data from two groups of radium-exposed persons. Although the exposures occurred forty-odd years ago, it was surprising to learn that a large majority of the subjects are still alive, despite the heavy exposures which many of them sustained. Malignancies have been divided into those believed to be caused by radiation (osteosarcomas and carcinomas of the cranial sinuses and mastoid), and those not judged to be so caused. While estimation of accumulated dose from this type of exposure is difficult, no radium-caused malignancies have been observed at estimated doses below 1000 rads. Approximately eight central nervous system tumors have been identified. Investigation of the children of exposed subjects will now be initiated.

Several equations representing dose-response relationships for the cancers judged radiation-related were tested for fit. The linear equation did not fit all the data sets; a dose-squared exponential provided

a better fit to one set of data.

It was observed that incidence of lung cancer bears a roughly linear relation to number of cigarettes smoked, while skin cancer does not show this simple relationship to beta radiation. When there are relatively few subjects at low doses, it is difficult either to demonstrate, or rule out, linearity. The question of how differences in susceptibility in a nonhomogeneous population might affect the dose response curve was discussed.

The meaning of "doubling dose" was considered in terms of the stability of the base-line incidence of mutations or, as in this instance, of malignant disease. Two models were suggested: one which is linear throughout, and one which approaches linearity at low doses but becomes exponential above the doubling dose. According to the latter model, the estimate of the low-dose slope differs, depending on the dose range within which the estimates are made.

Physics and Models

J. J. Broerse

Radiobiological Institute, TNO

The results of Bond, Shellabarger and Vogel on the incidence of breast carcinoma in the rat after irradiation with X rays and fission neutrons were discussed. It had been proposed originally that both types of radiation yield linear dose-effect relationships. It was shown, however, that plotting the results on a log-log scale clearly indicates that the dose-effect curves are nonlinear. From microdosimetry considerations, it can be inferred that the development of a tumor originates from more than one cell. The paper of Kellerer and Rossi on RBE and the primary mechanism of action was reported. The data in this paper indicate that the X-ray cell survival curve has an initial non-zero slope, as was found earlier in the experiments of Barendsen, and Sinclair and Morton. The consequence of this initial slope for X-ray survival curves is that the RBE for high-LET radiation, e.g., fast neutrons, will not grow to infinity at low doses, but will have a maximum value. The importance of microdosimetry for an understanding of low-level effects has been clearly demonstrated.

The need for cooperation in late effects research was stressed, since these studies require large-scale experiments and long-term commitments. The preliminary results of a dosimetry intercomparison within a group of European laboratories were presented.

The concept of the dose effectiveness function (DEF) was introduced. This sometimes can be approximated as the inverse of the RBE. A number of properties of the DEF over a large dose range were described. A cytogenetic model is under development, which seems able to account for the DEF. The properties of the DEF for various endpoints have to be studied in more detail, since they promise to provide a basis for evaluating the parameters of low-dose effects on man.

THIS PAGE
WAS INTENTIONALLY
LEFT BLANK

MEETING AS A COMMITTEE OF THE WHOLE

A steering committee had been appointed by the Conference conveners to meet on the second evening and produce an agenda for the plenary committee session. The chairman was M. Elkind, the secretary was S. Abrahamson, and members were M. Fry, C. Hollander, G. Silini, C. Edington, L. Hempelman, C. Mays, H. Rossi, G. Beebe and A. Tamplin. The committee reported back with the following recommendations:

1. the Proceedings of the Conference should be issued as an Argonne National Laboratory Report;
2. an account of the Conference should be prepared for publication in an appropriate journal;
3. there should be no attempt at this time to formalize the organization of this group, but instead,
4. the North American Late Effects Group should be asked to establish a continuing committee to have cognizance of research on low dose effects, and to recommend conferences or other actions as needed.

The group approved issuance of the Proceedings as an Argonne report, with the stipulation that it should include a summary of the Conference focused on identifying the important unresolved problems. It was agreed that this should be done by a team consisting of G. A. Sacher, W. K. Sinclair, and R. E. Rowland. The same team was instructed to produce the account of the Conference for publication in a scientific journal.

The group accepted the steering committee's recommendation about continuity and adopted a resolution recommending to the North American Late Effects Group that it accept a specific responsibility to form a subcommittee on the subject of low dose and low dose rate effects, which would keep informed of work in those areas and convene workshops on the subject when appropriate.

There was a brief discussion of the North American Late Effects Group and the European Late Effects Group as informal interest groups. The present role of NALEG is primarily communication, whereas ELEG is responding to a need in Europe for better international and interinstitutional cooperation on research programs, facilities and standards. The two groups are in close contact, and other regions of the world (e.g., Japan) are moving toward a similar pattern of organization.

THIS PAGE
WAS INTENTIONALLY
LEFT BLANK

OVERVIEW AND CRITIQUE OF THE CONFERENCE

W K. Sinclair, R. E. Rowland, and G A Sacher

One of the recurrent themes in the commentaries on both systemic and cellular effects is the suggestion that in vitro models and assay systems are potentially powerful tools for investigating mechanisms of late and low-level radiation effects. Until a year or so ago this would have been little more than a pious hope, but recent advances in the development of in vitro assays for carcinogenesis give grounds for confidence that these methods will usher in a period of rapid progress in the study of cancer induction, just as the Puck cloning technique did for the assay of lethal effects in mammalian cells

Although these in vitro systems deserve to be investigated with all deliberate speed, our planning should take account of the possibility that the induction of a neoplastic transformation by ionizing radiations in vitro will be more difficult than induction by chemical agents Accelerated research on promoting factors and the role of viruses may, therefore, have to precede and accompany investigation of the role of radiations per se We can anticipate that research on ionizing radiations in cancer induction will need to break new ground, because most of our knowledge of radiation effects in mammalian cells is based on cell killing as the endpoint and may not apply to more subtle transitions in surviving cells. An important additional problem is that the tumorigenic efficacy of high-LET fast neutrons and alpha rays is not satisfactorily explained by presently accepted models, in view of the absence of repair of damage by high-LET radiations, and of evidence that the whole chromosome complement is the geometrical target for cell killing

The inference that more than one cell is involved in the induction of mammary cancer in rats, which was drawn from an analysis of the dose dependence for induction of mammary tumors by gamma rays and fast neutrons, deserves to be followed up, because it is critically important in relation to the estimation of tumor yields at very low doses However, evidence was also presented that the life shortening in mice given lifetime gamma ray exposure changes from a multiple-event (square of daily dose) to a single-event (first power) trend at low doses A similar transition to first-power dose dependence is observed in the killing of mammalian cells in vitro by X or gamma rays These findings make it important to investigate the relation between the radiation-induced precancerous molecular lesions and the "spontaneous" lesions The extent to which they interact is important for cancer and aging research as well as for the study of low-level radiation effects

There was a consensus that increased understanding of mechanisms is perhaps the most effective way in which laboratory research can contribute to the determination of the effects of very low doses This does not diminish the importance or necessity of large epidemiological studies, involving small or large animals, or retrospective studies in humans since these will continue to have an invaluable role in providing guidance, limited though it may be, for the setting of exposure guidelines for a number of critically important occupational and medical exposure situations. The importance of these studies in the present state of our knowledge, while we await a more definitive understanding of mechanisms is obvious However, such large experiments should also be designed and performed, so far as possible, to decide between hypotheses about mechanisms or to provide valid estimates of the basic biological and physical parameters concerned with dose-effect relationships

An important unanswered question in the modeling of human radiation effects which can be settled by experimental epidemiology is whether the doubling dose assumption emphasized by Gofman and Tamplin is the best first approximation for the estimation of expected tumor incidence This question is still moot after decades of animal research, but it could probably be decided to an acceptable level of precision by a critical reanalysis of the accumulated experimental data, published and unpublished, and, failing that, by a well-conceived experiment

The validation of models and estimation of parameters for the low-dose domain can become excessively costly, and even fail completely, if there is an injudicious choice of test system The laboratory mouse was a fortunate first choice for epidemiological studies and continues to play a vital role in many late effects studies, but there is a growing awareness that some questions about low-dose effects can best be answered with longer-lived animals An experiment with a relatively small number of dogs may perhaps be more cost-effective than a large mouse experiment

These considerations apply to the choice of radiation doses and qualities as well One necessary step for the validation of a mechanism deduced from an in vitro model is the demonstration that the cellular and whole-animal responses agree in absolute sensitivity, and in DEF and RBE over a significant dose range

The survivors of a cell population exposed to a dose of high-LET fast neutrons consist mostly of cells that sustained no damage in the target for lethality, whereas the survivors of a comparably effective gamma-ray

dose are made up preponderantly of cells that sustained damage and underwent repair Wider exploitation of fast neutrons is, therefore, justified by the possibility of separating repair mechanisms from population recovery mechanisms and for providing a more reliable extrapolation to effects at low doses.

The paramount problem in the domain of low-level effects is that of linear versus nonlinear response Evidence was heard on both sides of this question, in respect to diverse endpoints. The fact of nonlinear response is not in question, for all systems studied thus far yield nonlinear responses in some part of the dose range, but it was reported that life shortening and tumor incidence in the mouse make a transition to a linear dose relationship at low doses The question is whether other, and perhaps all, endpoints have linear dose dependence in a finite dose interval above no dose This question can best be answered by the sequential formulation and testing of hypotheses about the conditions under which a linear trend arises, and the formulation of these hypotheses will be favored by fruitful interaction between systemic, cellular-molecular and microdosimetric research

The discussion of dose dependence during the Conference was in fact two separate discussions, with little effort to achieve a unified viewpoint One discussion developed around external radiations and endpoints such as life shortening, tumors, microcataracts and chromosome aberrations, while the other centered on internal emitters, with emphasis on tumor incidence This lack of interchange is not a recent development, for the two areas have already developed divergent modes of analysis and mathematical models There are practical reasons for these differences, stemming from the great differences in sample size between mouse and dog experiments, and from the special problems of dosimetry for internal emitters, but we nevertheless must not risk losing sight of the fact that all the work on external exposure and internal emitters must finally converge to a single consistent model. Some small fraction of the effort that goes into modeling these two domains of radiation effect should, therefore, be devoted to quantitative reconciliation of these models

The discussion of human epidemiology dealt mostly with the follow up of defined exposed populations and with the problems of monitoring health, morbidity and genetic parameters in the civil population These were covered in the position papers and rapporteur accounts Another important approach, not adequately represented in the discussion, is the epidemiological analysis of morbidity and mortality experience in the large population of industrial radiation workers in AEC or contractor installations These people receive exposures within limits allowed by FRC guidelines, and their radiation exposure histories are on record The stable employment pattern in the nuclear industry for a period of a quarter century presents a favorable opportunity to evaluate the health status of this population relative to the general population, and perhaps to test the predictions of some contending models of low-level radiation effects A follow-up study on the employees of some large AEC installations, entitled the AEC Health and Mortality Study, is now being conducted

There were two distinct kinds of proposals for monitoring the status of the entire civil population One was for systematic sampling of morbidity and mortality variables together with a number of environmental and socioeconomic variables The other was for a mass screening of newborns for selected biochemical mutations These approaches should be examined further as two aspects of a single program, for the two kinds of measures are much more valuable if examined jointly

There was agreement among most of the conferees that risk-benefit analysis is an essential feature in the evaluation of hazards and the formulation of guidelines, and that the methodology of this process needs to be investigated and developed This view was coupled with an equally broad agreement that discussion of this profound problem should be deferred until a more competent panel can be assembled The convening of such a conference will be a challenging problem because of the wide span of biological, behavioral, ethical and political matters it must deal with

In overall evaluation, it can be said that the Conference achieved its objective of bringing together for the first time representatives of the several disciplines that can contribute to solving the problem of low-level effects It can also be recognized, however, that the brief initial discussions did not get beyond general consideration of some problems, and that certain aspects were not considered at all The subject is so many-faceted that there is need for continued examination of developments in the several important areas and discussion of their implications for the evolution of rational biological and social bases for guidelines Means should be found to foster this kind of multidisciplinary interchange, under whatever sponsorship is deemed to be appropriate