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Founded 1947

Hi Sherm —

Paul said to send this on to you. Everyone asks for you — what are you doing ?!!! we all miss you —

Regards,

MJ

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December 10, 1979

TO: Consultants

FROM: Jeanne Seferovich
Conference Manager

SUBJECT: November 7th Conference on Radiation

As Dr. Nygaard stated in his December 7th letter, enclosed are copies of the draft agendas that were prepared by each cluster.

Cluster: A - Diagnostic Procedures

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A - Diagnostic Procedures

Outline for Research Topics

I. Do Diagnostic exposures produce biologic effects? If so, what type and frequency

A. Epidemiological studies of fetal exposure
Endpoint more than cancer.

B. Epidemiological studies in adults not attractive at 1 rad level

C. Above 10 rads - epidemiological studies in select groups.

D. Potential effects of contrast medium and other drugs including radioactive carriers.

1. Importamce of having an "acceptable" dose descriptiom for external dose. NO AGREEMENT

2. Nuclear medicine - distribution retention macro to micro dosimetry
   a. How the measurements are made
   b. Need to make measurements in patient

3. Need comparative studies of biological effects; external and internal exposure. (ex: thyroid -external x ray vs INV)

E. Benefit vs Risk: linear hypothisis is general expression of risk... is the public conception; increase risk between benefit and risk

any radiation is dangerous; lowest radiation/denominator

F. Adopt hypothesis: There is risk.
1. essential to qualtify
2. if you have exposure you have risk...linear
3. Are we practing overkill?(On benefit side)

G. Research to improve benefits to maximum degree in dose radiation.
1. reduction
2. necessity
3. utilization review
4. delay factor (there is no such thing as 0 yeild factor)

Comparison of I diagnostic modality with another yeilds more information.
What is effect on health itself
What are outcomes of feeling of well-being of public(non-biological)

Ultimate end point: put risk over procedure; information needed for benefit - risk diagnostic radiology.
Definition: diagnostic radiology - index of reliability

Conclusion: Are we endorsing method of dose reduction to cut dose radiation

or epidemeological studies?

H. High priority: improve known knowledge. How do we manage in high atmosphere of information?

1. Retention of information of dose.
2. Replacement of x-ray, radioactive diagnostic methods..
3. Ionizing effects of radiation: information and treatment have no reliable records.

I. Technology Advance Exploring new Techniques

1. Promote approproate techniques to see if too much information has been acquired.

2. What constitutes Radiographic Information?

II. Recommend:

A. Hardware Research

phantom
quantitative imagery
charged pariicals
detectors
scatter rejection

Imagery enhancement

B. Information Research

Perceptual evaluation
Thresholding
Resolution
Contrast

film
noise
phonton density
alternate diognostic techniques

C. Chemistry

Radiopharmicology
Contrast agents
Radiation modifiers

D. Population Distribution
dose containment in cancer patients

E. Shall Consider: maximum dose flexibility be designed

F. Outcome Analysis
Health benefits
Psychological benefits

Every administrative x-ray program to be re-examined; only those in the public to be continued.

Strategic Projection Papers -

Assigned authors were not submitted

Cross-Cutting Questions -

Were not submitted

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B - Technology Development

Outline for Research Topics

A. SOURCES, PATHWAYS, ETC.

1. Natural Radiation

a. Radon & Thoron

Survey measurements in homes, buildings, workplaces (as a function of time, and estimate doses).

Measurement techniques for Thoron and Daughters

b. External Gamma Rays from Building Materials

Further identification of sources of radiation in building materials (marble in Boston's South Station).

c. Airplane Travel

Measurement of doses to passengers and crew.

d. Radioactivity in Drinking Water (Surveys - realistic standards)

2. OCCUPATIONAL EXPOSURE

a. Improved personnel measurement techniques, especially neutrons (cf. limit of detector at 10mR or less).

b. Relationship between surface dose measurement and estimated dose to organs of individual.

c. Metabolism of radionuclides in worker, es pecially after inhalation of Put Th (form is very important).

d. Special study of the "high dose" group of workers.

e. Identification of purpose of personnel monitoring system in relation to retrospective epidemiological studies.

3. RELEASES TO THE ENVIRONMENT

a. Is monitoring adequate for accidental releases from all sources?

b. Waste Management: ~~a~~ 1) incineration, and ~~b~~ 2) accelerated life testing for solid high-level waste disposal.

4. EXPOSURE IN HOME FROM CONSUMER PRODUCTS

a. Radon

b. Important area to monitor technology developments - (especially NARM materials); also tritium in watches.

5. TRANSPORTATION OF MATERIALS INCLUDING ACCIDENTAL RELEASES

   a. Monitoring methods intrinsically sound, but monitors not always available where needed (also shielding).

   b. Models for accident situation - adequate?

   c. Emergency plans.

6. EFFECTIVE ENERGY STRATEGIES

   a. Effects of improved insulation-ventilation.

   b. Effects of increased coal burning; releasing more radioactivity (?geothermal).

   c. Underground home

   d. Radioactive products from fusion (Tritium released to space?).

B. REDUCTION OF EXPOSURE

1. Occupational

   a. Other Modality Research (structure testing, etc.)

   b. Better shielding of radiographers and radiologists.

   c. Identification of occupations with poor protection practices (e.g., industrial radiographers) and taking appropriate action.

2. Improvement of Medical Techniques

   a. Dose optimization in treatment planning.

   b. Quality Assurance: Investigate systems analysis and apply to individual clinical situations.

   c. Development of dose reduction technology

      1) Improve Contrast Agents
      2) " Detector Efficiency
      3) " Image-Processing Procedures
      4) " Source Spectra
      5) " Scatter Rejection
      6) " Resolution (System MTF)
      7) " Low Attenuation Materials

   d. Early detection of cancer

   e. Other modalities (ultrasound, NMR, thermography, microwaves)

   f. Medical cyclotron development for short-lived isotopes

3. Improvement of Waste Management Procedures

C. MEASUREMENT AND DOSIMETRY

1. Measurement and Instrumentation

   a. Improve low-dose high-LET measurement procedures (low dose-high dose rate)

   b. Application of measurement techniques to retrospective exposure estimation

   c. Dosimetry applicable to biological significance (fundamental considerations)

2. Measurement and Prediction of Dose Distribution

   a. Improved modeling for dose distribution situations

   b. Assessment of whole-body dose in partial-body exposures (tinia capitis ankylosing spondylitis)

3. Internal Emitters Dosimetry

   a. Hot particle dose specification

   b. Organ dose distribution and metabolism

TECHNOLOGY DEVELOPMENT

Additions and Deletions to original outline that was included in packet

Under A.1: Add "d" - Exposure and consumer products (radon). (More important than other 3.)

Under A.2: Add 4) Organ distribution

5) Identification of tissues at risk

6) Improved measurements of dose distribution

Under A.3: Add a) Measurements of populations exposed

b) Improved personnel measurement techniques, especially to neutrons (10 milliroentgens or less)
c) Relations between surface-dose measurements and dose to organs
d) Metabolism of radium nucleites in workers
e) Isolate high-dose group and make special studies
f) Clear identification of personnel monitoring systems and appropriateness re retrospective studies

To A.4a: Add Is monitoring adequate for accidental releases? What don't we know about waste management? Ex.: incineration. Accelerated testing for waste disposal.

To B.2a: Add "--i.e., research to improve tissue-exposure ratio

To A.4, b, c, d: Improvement to technology development, but identification of problem areas would require collaboration of at least other ecosystems (biology, chemistry, physics experts)

Change item 5 to: Exposure in the Home and Consumer Products
Add a) Radon (see A.1d)
b) Improvement to future population exposure--e.g., release of tritium.

To A.1 add: e) External gamma radiation from building materials
f) " " " " plane travel
g) Thorium

Add: A.6. Transportation of materials, including accidents.

To A.1d add 1) Survey measurements in homes and buildings as a function of time, including dose information.
2) Exposure reduction.
3) Disposal of radon-emitting wastes.

Add: A.1.e. Furtheridentification of gamma ray radiation from building materials.
f.1) More definitive measurements of external gamma ray radiation from airplane travel. (Check this.)
2) Quantitative constituents of dose.

A.

~~Add A.7:~~ Effective energy strategy

Cross-cutting question: Consider question of personnel dosimetry for everyone in population to integrate all sources of radiation exposure.

Add A.1.6.a: Monitoring methods are intrinsically sound but not always available as needed.

b: Models for accident situations--how they act.

c: Emergency plans.

Add A.1.7: Effects of Energy Strategies

a. Effects of improved insulation
b. Effects of coal burning (see A.1.d and e). Geothermal?
c. Underground homes
d. Tritium--released to space?

B.1:
a. Research on other modalities
b. Radiation protection of radiographers and radiologists
c. Identification of occupational areas with poor protection--e.g., industrial radiography (see A.3, high-dose group).

B.2: (Concentrate on c, d, e; drop b, not technological.)

B.2.c:
1) Restrict definition of Q/A to mean "maintaining process of of control."
2) Investigate systems analysis and its application to individual situations.

B.1.d:
1) Improve contrast agents
2) " detectors efficiency
3) " image processing
4) " source spectra
5) " scatter-rejection techniques
6) " image resolution
7) Reduction in attenuation material between source & detector,

(Citation: Wagner & Jennings, q.v.)

B.2.a. Add --i.e., research to improve tissue-exposure ratio
d, Change to read: Dose reduction technology

B.3. Amelioration? Or radiation protection procedures?
B.4. Accelerated testing for waste disposal

B.2. NOTE: Early detection.

B.2.e. Alternative modalities--ultrasound and NMR microwaves.

B.2.f. Consider early detecti

B~~x~~3~~xxxxxxxxxxxxx~~3~~xxxxxxxxxxxxx~~.

B~~x~~4~~.~~

C.1.a. Improve low does, high LET

b. Better characterization of inadequately identified radiation fields such as accelerator.

c. Applicationof measurement techniques to retrospective exposures.

d. Biological significance of physical dosimetry techniques at low doses.

NOTE: high dose rate, low dose exposures (e.g., accelerators)

C.2.a. Improve modeling for dose distribution situations

2.b. Assessment of whole body dose in partial body situations

C.3. Hot prticle dosimetry
Improve assessment of organ distribution, better knowledge of metabolism in man.

D.3. Deletewords after microdosimetry.

Add D.4.: Theoretical models. (Physical dosimetry?)

E.1.e. Add after "models," (relative vs. absolute risks).

E.2.e. Add after "factors," (synergism).

Add new E.2.h. ?Sensitive populations

5.c. Add "and physical factors."

Add new 6.f.: Pharmacological considerations

Strategic Projection Papers -

Assignments:

A - 1 Natural Radiation: J. Rundo
A - 2 Occupational Exposure: E. Webster
A - 3 Releases to the Environment: Bjarngard
A - 4 Exposure in Home from Consumer Products: Bjarngard
A - 6 Effective Energy Strategies: Gregg

B - 1 Occupational: Webster
B - 2 Improvements of Medical Techniques: Schneider
B - 3 Improvements of Waste Management Procedures: Gregg

C - 1,2,3 - Measurement and Dosimetry: Loevinger & Schneider

Cross-Cutting Questions - They were not submitted

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Outline for Research Topics

I. Beneficial Aspects of Radiation

Overview and Collation

Medical exposure to ionizing radiation is responsible for curing orders of magnitude more cancers than it produces. Such cancer cures come from diagnostic radiology and from radiation therapy. For example it has been estimated that radiotherapy is responsible, either totally or in part, for curing approximately 100,000 cancer patients in the United States per year. There are approximately 3/4 million former cancer patients who have been cured of their disease due to radiotherapy. Improvements in radiotherapy resulting from the research efforts listed below will lead to an additional significant reduction of the 100,000 cancer deaths due to lack of local control by current treatment methods in the United States. Improved diagnostic techniques combined with the optimum use of radiotherapy plus a systemic agent (eg. chemotherapy or immunotherapy) could lead to a further significant increase in cure rate. Against this beneficial use of radiotherapy the deleterious effects in terms of cancer production are very small, less than one in one thousand cured patients.

The following outline addresses the broad research areas identified as ways to improve our ability to achieve improved cure of cancer, improved quality of life, and decreased cancer care costs.

A. Studies into biological mechanisms relevant to radiation response in tumors and in normal cells and tissues.

Design of optimum treatment and consequent improvement in cure rates will depend largely on our understanding of the interactions of ionizing radiation with biological materials at the sub cellular, cellular and tissue levels. Of special importance are the various repair processes. Improvement will also depend on better understanding of tumor biology, including the mechanisms of metastatic spread, tumor cell kinetics and differentiation, the relationship between stroma and the vascular system and the development of cells that are hypoxic, acidic and at low pH etc.

B. Conventional irradiation used alone for cancer therapy: time, dose, dose-rate, and volume effects on tumors and normal tissues.

1. Experimental

What determines biological responses to fractionated irradiation of tumor and normal tissues (eg reoxygenation, repair, repopulation, recruitment, etc.; what are target cells; new models for normal tissue injury).

2. Clinical

Evaluation of various fractionation schedules or dose-rate on tumor and normal tissue response.

a. tumor response

b. acute effects on normal tissues

c. late effects including carcinogenesis and teratogenesis

C. Heavy particles and other non-conventional radiation.

These may have advantageous physical and/or biologic properties.

1. Physical properties

   a. Improved dose distribution yielding higher tumor dose with decreased dose in normal tissue.

2. Biological properties

   a. Circumventing the protective effects of hypoxia in tumors

   b. Repair mechanisms

   c. Optimum fractionation schedules

   d. Late effects on normal tissues, including fibrosis, vascular changes, carcinogenesis, etc.

   e. Other

D. Modification of radiation response in tumors and normal tissues:

1. Chemical radiation sensitizers of tumors

2. Radiation protectors of normal tissues

3. Hyperthermia

4. Other physical modifiers

Increasing the tumor response with a radiosensitizer eg. Misonidazole, and/or decreasing the normal tissue response with a radioprotector eg. WR 2721 would increase the tumor cure rate. Similarly, localization of heat treatment to tumors would increase local control rates.

E. Combining treatment by ionizing radiation with other anti-tumor modalities:

1. Surgery
2. Chemotherapy
3. Hyperthermia
4. Immunotherapy
5. Other

For each of the above we need to understand the basic biology of the independent actions and interactions, the effect of sequencing and dose, possible effects on distant metastases and other factors. The goal of these adjuvant treatments (eg radiation + chemotherapy, and radiation + immunotherapy) is often to treat distant metastases, and therefore the need for a differential effect on normal and malignant tissues is not essential. However, interactions at the local site do occur, need to be understood, and may be used to enhance local control rates.

F. Tumor localization techniques in radiation therapy (cross cut with diagnosis)

1. External imaging systems
   a. Conventional X-ray
   b. CT scanning
   c. Ultrasound
   d. Microwave
   e. Nuclear magnetic resonance
   f. Heavy particles
2. Internal and external imaging systems
   a. Radionuclides, tumor seeking nuclides or complexes
3. Invasive localization procedures
   a. Intravascular catheterization and imaging
   b. Endoscopy, visual, ultrasound

Strategic Projection Papers -

Assignments:

A and B: J. Denekamp and S. Field
C: R. Parker and D. Hussey
D: J. M. Brown, M. A. Bagshaw and J. Yuhas
E: T. Phillips and/or R. Kallman
F: D. Bragg or R. Castellino

Note: Phillips, Kallman, Bragg and Castellino were recommended by cluster to write paper. We did not receive their titles nor addresses from cluster group.

Cross-Cutting Questions - they were not submitted

Cluster: D - Pathways to Man

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D - Pathways to Man

Outline for Research Topics

GENERAL RESEARCH OBJECTIVE

Identify and quantify those processes and parameters that have a significant effect on the type and degree of human exposure to ionizing radiation.

Notes:

1. Physiology to determine distribution and deposition in humans should receive more emphasis than the cluster group assignments would signify.

2. Since all radioactive materials in the environment contribute at least some dose that may be perceived as a health risk, there can be no end to the need for research until a judgement is made on what is significant and what of no concern. In order to bound the type and scope of research there is a pressing need for a national consensus on what constitutes an acceptable "risk".

A. ~~NATURAL~~ BACKGROUND ENHANCEMENT

1. Indoors - gaseous, particulate
2. Drinking water
3. Coal Emissions
4. Weapons fallout

B. SOURCES

1. Types
   a. Atmosphere
   b. Surface water / sediments
   c. Ground water / soils
   d. Food
   e. Structural materials
2. Variables
   a. Particle size
   b. Physical, chemical form
   c. Aerosol interaction

C. TRANSPORT AND TRANSFORMATION

1. Physical dispersion and transport by:

a. Atmosphere

b. Surface water - streams, lakes, oceans

c. Ground water

Note: includes deposition and resuspension

2. Chemical transformation and metamorphosis (physical weathering, geochemical weathering, microfloral)
3. Resuspension
4. Depletion

a. Deposition - air

b. Sedimentation - water

c. Soil binding

5. Biological processes

a. Mobile fractions

b. Folial deposition

c. Soil, root, plant

d. Adsorption and absorption

e. Organism to organism (food chains)

D. EXPOSURE AND UPTAKE

1. Extent of contact by people with sources

a. Demography

b. Living habits

1) Work and recreation

2) Food and drink

c. Other modifying factors

1) age

2) sex

E. Human Physiology
1. Variables Influencing Uptake
a. Inhalation
b. Ingestion
c. Topical absorption and wounds
2. Metabolism
a. Partitioning
b. Retention - biological half-life
c. Concentration
d. Other modifying factors
1) age
2) sex

F. RESEARCH ACTIVITIES

1. Models - development and validation

2. Measurement of parameters

3. Physiological studies

a) Animal - interspecies scaling

b) Human

c) Other

4. Assesment of variability

5. Assessment of uncertainty

PATHWAYS TO MAN

NEEDS

A. Background sources
   1. Authoritative review of extant data - concise.
   2. Operational needs for certain surveys.

B. Mill tailings and Mines
   1. More adequate characterization of effluents (including aerosol interactions)
   2. Improved concepts for ground stabilization
   3. Better understanding of releases in accident situations (chemical and physical form)

C. 1 a 1) Improve atmospheric dispersal models (complex terrain, "instantaneous", validation)

C. 1 b 1) Information on ocean transport of buried (high level) wastes (ocean circulation)

2) Additional information on leach rates of buried radioactivity.

C. 2 Improved understanding (quantification) of geochemical and physical weathering processes and microbial transformation.

C. 3 Better quantification of resuspension fractions under specific geographic / topographic / soil structure conditions.

C. 4 Upgrade model parameters.

C. 5 Upgrade model parameters and improved understanding of critical food chain pathways.

D. 1 1) Validate data being used in exposure models.

2) Assess parametric variability and modifying factors vs. current simplifying assumptions, e.g.

3) Consider agricultural, subsistence, and recreational food chains.

D. 1 b. Determine need to account for food and living habits of exceptional individuals.

E. 1 a 1) Measured data on size distribution of respirable particles

2) Improved understanding of behavior of ultrafine (e.g. oil micron) particles.

E. 1 b. Quantification of gastro intestinal uptake factors for different chemical forms of radionuclides (e.g. organic complexes, valence state, etc.)

E. 2 1) Information on metabolism as a function of age.

2) Need to account for exceptional individual

3) Variations in metabolism caused by differences in the form of the material.

F. 1. Models currently being used for dose estimation require validation.

F. 2. Experiments should be designed to provide the data required to to develop model parameters. This requires cooperation between modellers and experimentalists.

F. 4, 5 Assessments of variability and uncertainty and desireable and models should take these into account.

Research on methods for including these quantities is also needed.

PROJECTION PAPERS AND AUTHORS

A - John Harley	Background Enhancement
B - Lynn Anspaugh	Sources
C - Burt Vaughn	Transport and Transformation
D - Dick Foster	Exposure
E - Bruce Boecker & Steve Book	Human Physiology
F - John Harley	Research Activities

Cross-Cutting Questions - they were not submitted

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E. Ecosystems and Environment
OUTLINE OF RECOMMENDATIONS AND EXPANSIONS

I. There is a need for increased capabilities for radioecological research, because of the multiple concerns perceived by the public.
   - A. Information needs
     1. Summarization of literature
     2. Translation of foreign literature
   - B. Training of radiation ecologists
     1. Programs
     2. Promotion
     3. Summer institutes
     4. Short courses
   - C. Critical past experiments
     1. Reevaluation
     2. Confirmation
   - D. Enhancement of international scientific interchange

II. Execute continuing studies of ecological systems at selected nuclear facilities, using careful dosimetry and radionuclide analysis as related to specific site attributes.
   - A. Environmental releases
     1. Bioaccumulation
     2. Consequences
   - B. Waste disposal
     1. Bioaccumulation
     2. Consequences

III. Systematic determination of uptake and transfer coefficients for specific radionuclides, organisms, and media, under steady-state conditions.
   - A. Within food webs
   - B. Dosimetry assessment models
     1. Improvement
     2. Validation

IV. Evaluate the relationships between doses due to both external radiation exposure and deposition of radionuclides and their consequences on selected organisms and on populations of organisms.
   - A. Field
   - B. Laboratory
   - C. Comparisons of field and laboratory studies

V. In the event of a buildup of radionuclides in the environment, there will be a need to evaluate the evolutionary consequences and the effects on behavior

of individual organisms and populations.

A. Radiation as a selective force in evolution

B. Comparative studies

VI. Investigate the effects of the interaction of radiation with other environmental pollutants (synergy) on natural and laboratory populations in relevant media.

VII. There is a need to understand the ecological and related environmental factors which affect the spatial and geographic distribution of radionuclides.

VIII. Ecological evaluation of reclamation and stabilization procedures for reduction of exposure from uranium mining and milling.

IX. There is a need to study the ecological problems associated with the decommissioning and decontamination of various nuclear facilities.

A. Reactors and related facilities

B. Low-level waste disposal sites

C. High-level storage facilities

E. Ecosystems and Environment

Writers for Projection Paper

The chapter numbers correspond to the numbers of the subjects on the outline.

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C Charles Osterberg

II. Stanley I. Auerbach

III. Stanley I. Auerbach

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VIII. Philip Gustafson

IX. Philip Gustafson

Coordinator: Stanley I. Auerbach – No deadline as far as we know

Cross-Cutting Question

Should we be directing more of our radiobiologic research effort to questions related to standards and standard setting?

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Outline for Research Topics

I Fundamental Scientific Questions.

A. Multidisciplinary in nature-require mathematics, physics, chemistry, and biology together at most basic level.

1. Radiation effects are a perturbation of the normal biological system-one must study normal and perturbed systems.

2. To understand complex biological systems one needs to understand the much simpler atomic and molecular processes both normal and perturbed.

3. One of the roles of physics, after understanding and quantitating simple systems, is to synthesize logical models which describe behavior of more and more complex biological systems.

B. Physics research essential to progress in biological effects of radiation.

1. Primary energy transfer from radiation to matter, especially condensed matter.

2. Time sequence and spatial distribution of secondary radiation-induced events.

3. The progression of these radiation-induced events into the molecular damage, reflected biologically.

4. Effects on the above process due to physical differences between various kinds of radiation.

5. Complete understanding of these phenomena will require input from diverse fields of physics, atomic physics, molecular physics, nuclear physics, thermodynamics and statistical physics, kinetics, physics of condensed matter,...

C. Physical characterization of radiation exposure

1. Conceptual translation of above fundamental information to biologically relevant parameters. Present dosimetry system, based on absorbed dose and LET, needs improvement or replacement.

2. Improvement of dose distribution information, including radiation quality, inhomogeneities, tissue variations, and size of domain including micron and submicron levels.

3. Special problems of internal radionuclide dosimetry.

II Applied Physics and Technology

A. Radiation Sources.
New radiation sources are becoming important, e.g. heavy ions, synchrotron radiation, pi mesons, exotic particles, space radiations.

1. New protection problems
2. New research opportunities
3. New therapeutic and diagnostic applications

B. Dosimetry.

1. Improved dosimetry methods and instrumentation.

a. Solid state dosimetry, passive and active
b. Chemical systems.
c. Improvement of traditional systems, e.g., calorimetry, ionization.
d. Search for new systems, e.g., lyoluminescence, liquid xenon.
e. Biological dosimetry methods.
f. Biophysical; analysis of exposed biological systems.
g. Indirect methods of dosimetry, e.g., spectroscopy.
h. High time resolution dosimetry methods.
i. Systems with similar response to biological systems.
j. Instrumentation for dose pattern measurement.
k. Technology of dose distribution calculations.

2. Problems where improved dosimetry is needed.

a. Personnel Monitoring-low energy neutrons, beta rays, low energy photons.
b. Dosimetry of radionuclides incorporated in the human body, location and quantification, e.g., plutonium particles in the lung.
c. Methods for population dosimetry-background levels, nuclear accident, medical exposures, civil defense.
d. Environmental dynamics of dose or activity distribution patterns-local and global.
e. Dosimetry of other environmental agents which may synergize with radiation.
f. Dosimetry for epidemiological studies retrospective and prospective.
g. Incorporation of dosimetry information into decisionmaking in various fields-radiation emergencies, risk estimation, medical patient management.
h. Improved radiation treatment planning.
i. Standardization and quality control of dosimetry measurements.

C. Physics Contributions to Radiation Applications

1. Diagnostic radiology

   a. CT scanning and imaging.

   b. Reduction of population dose through advanced imaging technology.

   c. Source improvements such as magnification radiography, heavy ion radiography.

2. Nuclear Medicine

   a. Three dimensional scanning.

   b. Time-dependent dynamic imaging.

   c. Use of radioactive beams.

   d. Use of fluorescent x-rays.

   e. Neutron activation methods.

   f. New in-vitro assay methods.

3. Radiation Therapy

   a. New Radiations-neutrons, heavy ions, pi mesons.

   b. Improvements in radiation treatment planning, e.g., 3-dimensional inhomogeneities, CT scanning, interactive therapy.

   c. Mixed modalities-high and low LET, chemical sensitizers, chemotherapy, surgery, hyperthermia.

   d. Modeling of biological data for radiation therapy.

4. Analysis of molecular and cellular structure

   a. Soft x-ray, electron and heavy ion microscopy.

   b. EXAFS-Extended X-ray Absorption Fine Structure.

   c. X-ray and particle fluorescence microanalysis.

   d. Auger and photoelectron spectroscopy.

   e. Small angle fast neutron scattering.

   f. Cytofluorinetry.

   g. Channeling and blocking of charged particles.

III Problems in the implementation of research of BEIR

a. Need for interdisciplinary approach-physical scientists should participate in planning, execution, and analysis of biological experiments.

b. Education of highly-qualified scientists for radiation physics and related multi-disciplinary fields should be stimulated by fellowships, postdoctoral appointments, etc.

Strategic Projection Papers

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IB. Turner and Inokuti

IC. Roesch

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IIB.1 Caswell

IIB.2 Auxier

IIC.1 Roesch

IIC.2 Tobias

IIC.3 Roesch

IIC.4 Inokuti

III Caswell

First draft to Inokuti (1)	December 1
Combined draft to members	December 20
Comments to Inokuti	January 10
Documents due	February 1

(1) Send also to group members

Comments on Cross-Cutting Questions

1. Important. Question as phrased is too general. We need more information about low levels.

2. Important. Poorly worded question semantically.

3. Some say important, some say not. Quantifying benefit will be very difficult. A more important question is how to minimize dose from diagnostic procedures.

4. This is two difficult questions. First question is important, but it is important to specify that results come from a model, and are not facts. The "de minimus" level is a public policy question. The decision will probably not be a scientific one.

5. Very important question which merits further research. Answer to second part of the question is "yes".

6. This is two separate questions. Both questions are interesting questions meriting further research.

7. This is a fundamental public policy question. We must understand the phenomena occurring in order to understand model systems for extrapolation.

8. Important. Good dosimetry as a basis for decisionmaking, early and accurate communication, shielding, decontamination, and chemical blocking agents are of much interest.

9. Very important. This is a key question for this meeting. Exploration of cell transformation for this purpose is highly merited.

10. This question should be rewritten to include multivariate studies of radiation and other agents.

11. Scientifically interesting but of low priority for population radiation protection. New dosimetry will be needed-it is desirable to plan ahead. There may be late effects on neurological systems.

12. First question is important. Can best be attacked through public education and experience. Answer to second question is that this is acceptable in order to have a common denominator for comparison to other risks, but should not be done for semantic obfuscation.

Disciplinary Omissions

1. Medical physics is underrepresented in Physics, Therapy and Diagnostic Procedures clusters.

2. Mathematics is not represented in the disciplines.

3. Developmental biology is not represented in the disciplines.

4. Neuroradiobiology is not represented in the disciplines.

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Outline for Research Topics

IDENTIFICATION OF AREAS OF RESEARCH IN RADIATION CHEMISTRY FUNDAMENTAL TO RADIATION BIOLOGY

Among all the environmental hazards that man is exposed to, ionizing radiation is the most thoroughly investigated and the most responsibly monitored and controlled. Nevertheless, much more information concerning the biological effects induced and their modifications and reversal is required. Together with radiation physics, an understanding of radiation chemistry is necessary for full appreciation of biological effects of high and low energy radiations and for the development of prophylactic, therapeutic, and potentiating methods and techniques in biological organisms. This group has identified the following general areas of radiation chemistry for which extensive support should be considered to realize these goals.

I. Very Early Time-Scale Events Preceding Chemistry

Relative importance of ionization, excitation, and charge recombination in model systems. Some of these processes can be studied only at the theoretical level; but attempts should be made to correlate with experimental studies. Such experimental studies will involve very early time-scale measurements.

II. Kinetics and Mechanisms of Free Radical and Excited State Reactions

A. Experimental approaches
   1. Steady state radiolysis and product analysis
   2. ESR techniques for radical studies
   3. Pulse radiolysis for characterization of properties of transients (absorption and emission spectroscopy, conductivity, fast ESR, light scatter, etc.)
   4. Chemistry of excited states as related to ionization processes and photo ionization (involving low and high energy protons).

B. Physico-chemical parameters
   1. Concentration of solutes in solvent ("direct" vs. "indirect" effects) and organization
   2. State of aggregation (micelles, membranes, liposomes, solid state systems)
   3. Oxygen effects (peroxy radicals, super oxide radical, peroxides, etc.)
   4. Electron transfer between and within biomolecules and model systems.

III. Modifiers of Radiation Biological Effects

A. Enhancement
   1. Radiation sensitizers in, and relation to, radiation therapy (redox sensitizers, anti-cancer drugs, cyanide release, synergisms)
   2. Metal ions.

B. Protection
   1. Chemical restitution (electron, charge and H atom transfer)
   2. Effects of antioxidants and nutrients.

IV. Problems in Applying Radiation Chemistry to Radiation Biology That Must Be Resolved

A. Very high dose rates within pulses not normally encountered in radiation biology
B. Single pulses usually used in pulse radiolysis--perhaps not applicable to radiation biology (repetitive pulse studies required)
C. Application of knowledge from nonpolar systems required.

V. Large Instruments for Study That Should Be Generally Available to Scientific Public

A. Lasers (high power and various wave length)
B. Electron pulse accelerators
C. High energy particle pulse accelerators
D. Synchrotron orbital radiation.

At present, laboratories known to Cluster G that welcome outisde users are:

1. BEVALAC, Lawrence Berkeley Laboratory, Berkeley (particle pulses)

2. Center for Fast Kinetics Research, Austin (electron and laser photon pulses)

3. Synchrotron Orbital Radiation, Cornell.

Strategic Projection Papers

Assignments:

AUTHORS:	Section I	Chatterjee
	Section II	Burr
	Section III	Simic
	Sections IV and V	Powers

Final draft will be Powers and Simic.

CROSS-CURRENT QUESTIONS

1. Can metal pollution of the environment conceivably affect MPL's because low concentrations of metals do increase radiation sensitivity?
2. How can radiation chemistry contribute to the improvement of clinically used radiation sensitizers of tumors?
3. Can improvements in human nutrition alter radiation sensitivity?
4. How can interaction and cooperation between Radiation Chemists and Radiation Biologists, which has been sadly lacking in the U.S., be specifically encouraged?
5. How is existence of a threshhold for radiation damage consistent with conclusions from Radiation Chemistry that such a threshhold should not exist?
6. How can the relationship between radiation chemical changes in a biological molecule and the biological expression of this change be better understood?
7. How in general can we use cellular systems with biological end-points in the application of radiation chemical knowledge to biology?
8. How can any of the biological effects of radiation (mutagenesis, carcinogenesis, cell death, transformation, and many others) be better understood by involving radiation chemists and their chemistry directly in the experiments?

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Outline for Research Topics

A. Spectrum of Damage Produced in Crucial Biological Molecules (high priority)

1. DNA, chromatin, (e.g. protein-DNA interaction), other cellular structures, (e.g., membranes)
2. Improved methodology for recognition and quantification of specific lesions (e.g., immunochemical methods)
3. Dependence on radiation quality

B. Cellular Processing of Lesions

1. Unmodified, Persistent Lesions
2. Repaired (e.g., removed) lesions
3. Modified lesions

C. Correlation of Specific Lesions with Biological End Points

1. Comparisons with chemicals or UV-producing similar lesions,
2. Use of cell systems deficient in processing of damage (e.g., repair deficient cell lines)

D. Repair Processes (Reversal or Removal of Lesion)

1. Molecular mechanisms (integrated approach combining enzymology with genetics)

   Viral and bacterial systems

   Lower eukaryotes - yeast, drosophila, etc.

   Mammalian systems (more repair deficient mutants needed)
2. Viral probes
3. Role of chromatin structure
4. Effificacy and Fidelity

E. Effects of Physiological State on Recovery Responses

1. Growth state in relation to biological end points and repair.
2. Comparisons of different cell types (e.g., differentiated, transformed)

F. Conditioned Responses

1. Models and mechanisms for inducible responses
2. Modifiers

G. Function of Damaged Templates in Replication and Transcription, (e.g., in vitro studies using defined, sequenced DNA containing specific lesions)

H. Cellular Effects

1. Amplify the range of end points
2. Increase the range of differentiated and mutant cell systems
3. Studies on heterozygotes - gene dosage effects

I. Cell Transformation as Altered Differentiation?

1. Testing of non-mutagenic mechanisms

J. Viral Interactions

1. Activation of Viral Gene Expression
2. Enhanced viral transformation
3. Interactions with DNA Repair Systems
4. Altered cellular response to radiation
5. Are there other intracellular nucleic acid interactants?

K. Chemical and Physical Interactions

1. Tumor promoters
2. Synergism with chemical carcinogens
3. " " radiomimetic chemicals

4. Synergism with radiation sensitizers and protectant

5. Hyperthermia

L. Genetic Alterations of Cellular Radiation Response

Strategic Projection Papers

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Cross-Cutting Questions - they were not submitted

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MUTAGENESIS, TRANSFORMATION, CELL-KILLING

I. Mutagenesis In Vitro

A. Studies using existing systems

1. Dose-response relations. Is there a threshold?

2. Mechanism: frame-shift? substitution? deletion? also spontaneous mutation mechanisms

3. Effects of fractionation, dose-rate, LET

4. Cell cycle dependence

5. Effects of chemical modifiers and hyperthermia

B. Development of new systems

1. Loci in rodent and human cells other than HGPRT (hypoxanthine-guanine-phosphoribosyl-transferase)

2. Use CHO-single human chromosome hybrid to measure small deletion and total chromosome loss in mutagenesis independently of single-locus mutation

3. Host-mediated somatic cell mutation assay

C. Mechanistic Studies

1. Use of human cells from patients genetically pre-disposed to spontaneous or radiation induced cancer to study control of mutagenesis

2. Use of specific repair-defective mutant cell lines to determine rolls of specific repair processes in radiation mutagenesis

3. Determine locus-specific of radiation mutagenesis

4. Seek further correlations among gene mutations, cytogenetic effects (including sister chromatid exchange), and oncogenic transformation in vitro

D. In Vivo Relevance

1. In vivo/In vitro approach: determination of expression in vitro by somatic cells irradiated in vivo

2. Prediction of somatic mutation in vivo

3. Correlation of somatic and germinal in vivo mutagenesis

II. Cell Transformation In Vitro

A. Studies using existing systems (e.g. Syrian hamster embryo, mouse balb/3T3, and C3H/T10 1/2)

1. Dose response relations; is there a threshold? Shape at low doses

2. Effects of chemical modifiers and hyperthermia

3. Cell-cycle dependence

4. Required promotional events

5. High LET and dose rate and fractionation dependence

6. Relationship between mutagenesis and oncogenic transformation

B. Development of new systems

1. Human cells that transform in vitro

2. Epithelioid cells

3. Earlier identification of transformed state (new experimental procedures)

C. Studies with modulation of transformation expression

1. Factors that facilitate phenotypic expression of transformation (e.g. phorbol esters)

2. Factors that suppress expression (e.g. protease inhibitors, retinoids)

D. Mechanistic studies

1. Systematic assessment of essential events between irradiation and expression of transformation. Use recent techniques (extended chromosome banding, "haplicon" concept).

2. Use of human cells from patients genetically predisposed to cancer

3. Use of specific repair-defective mutant cell lines to determine the roles of specific repair processes in suppressing and enhancing transformation

4. Relationship between cytogenetic damage including sister chromotid exchange and transformation

E. In vivo relevance

1. Effects of in vivo environment on transformation assessed in vitro

2. Correlate in vitro transformation with animal carcinogenesis by using agents that modulate both

3. Role of cell proliferation in the expression of transformation in relation to cell killing

III. Cell Killing

A. Mechanistic Studies

1. Correlation of cell-cycle, LET, chemical modifications of cell-killing and molecular events to identify molecular processes leading to cell death

2. Why chromosome aberrations and lethality correlate; is the molecular basis for both the same?

3. Relation of cell killing to gene mutation and in vitro transformation

4. Use of specific repair-defective mutant cells to determine roles of specific molecular repair processes in cell survival

5. Characterization of sequence of events between radiation insult and cell death

6. Mechanism of post irradiation progression perturbations (e.g. DNA synthesis inhibitions and G2 block) and their relation to cell killing

7. Control of events that regulate cell cycle and progression and its relation to cell killing mutation and transformation

8. Sublethal damage interaction

B. In vivo relevance

1. Radio sensitivity of human cells derived from fresh explants of tumors and normal tissues

2. Differential radiation sensitivity among cell types and the role of cycle-age distribution in vivo

Strategic Projection Papers

Assignments:

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Transformation: John B. Little
Cell-Killing: William C. Dewey

Pre-Amble, Coordination, and Editing will be done by
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Outline for Research Topics

I BASIC MECHANISM OF CARCINOGENESIS

A. MOLECULAR

1. What are the molecular events following the absorption of ironzing radiation essential to the carcinogenic process.
   a) Investigate the role of DNA injury, repair and integrity.
   b) What is the role of direct and indirect events in the carcinogenic process.

B.Cellular & Sub-cellular

2. What are the cellular and sub-cellular events that are essential to the carcinogenic process.
   a) What is the synicicance of invetro cell transformation in understanding the carcinogenic process.
   b) What sequence of cellular events render a cell neoplastic, eg. cell cycle, cell differention, cell function etc.
   c) What other factors influence a cell in the production of a carcinogenic cell.
   d) Can a single neoplastic cell be identified?

C. Tissue

3. What are the microenvironmental factors within tissues and organs that are important to the carcinogenic process;

   e.g. vascularity
   gasious exchange (anoxia)
   nutrition
   humanoral
   preneoplasia
   cell interaction
   tissue damage and scarring
   cell mix and cell kinetics
   inducibility--succeptibility at tissue level

D. Host

4. What host factors are essential to the understanding of radiation carcinogenesis?

   e.g. age
   sex
   other desease state
   nutrition
   environment -- cigarette smoking
   immune competence
   genetics
   natural cancer incidence
   endocrine function

II DOSIMETRIC CONSIDERATIONS (DOSE RATE, QUALITY ETC.)

A. How do the spatial, temperal and quality factors of dose affect carcinogenesis?

e.g.-biological significance of dose factors

-internal emitters, including mini and micro distribution and dose

-external sources (geometry)

-LET

-rate

-fractionation including split dose recovery

III DOSE EFFECT RELATIONSHIPS (INCEDENCE, TEMPORAL)

A. What are the dose effect relationships for the incidence and time patterns of radiation induced cancer?

1. Can quantitative models of dose effect relationships contribute to our understanding of radiation carcinogenesis?
2. How can basic biological information contribute to choice of mathematical models of dose effect relations-especially for extrapolation to the low dose region?
3. What additional biological information is needed?

e.g.-dose rate and fractionation

-latency period

-duration of exposure

-RBE and LET

-duration of expression

4. What is the measure of the effect-absolute vs. relative risk?
5. Comparative dose effect relations e.g. experimental data vis-a-vis human experience.
6. What is the predictive value of other biologic indicators in radiation carcinogenesis

e.g.-chromosome aberrations

-neutropemia

DNA strand breaks

IV INTERACTION OF CHEMICAL AND PHYSICAL AGENTS, INCLUDING MODIFIERS, WITH IONIZING RADIATION.

A. How do chemical, physical and biological agents, including modifiers, interact qualitatively and quantitatively with ionizing radiation?

-what are the mechanisims of interation
-interaction of chemical carcinogens and ionizing radiation carcinogenesis
-interaction of chemical cofactors and ionizing radiation carcinogenesis e.g. Tinea cases
-amelioration of effect e.g. chelation (pharmaceuticals)

B. How does the magnitude of the dose affect the nature of the interaction?

V HUMAN-ANIMAL COMPARATIVE RESPONSES (EXTRAPOLATION FROM ANIMALS TO HUMANS)

A. How do we use the data derived from laboratory experiments?

1. to predict human risks
2. to derive common parameters
3. to choose proper biolobical models to resolve the question
4. Lifespan vs latency and the influence of competing risks

B. What is the biologic basis of interspecies differential response?

C. What is the role of species specific factors that alter dosimetry i.e. comparative dosimetry?

J.- Somatic Effects I - Cancer

Strategic Projection Papers

Assignments:

I BASIC MECHANISM OF CARCINOGENESIS
- A. Molecular --Burns and molecular biologist to be identified
- B. Cellular and sub-cellular--Burns and Clifton
- C. Tissues and Organs--Clifton and Ullrich
- D. Host--Clifton, Ullrich and Schuman

II DOSIMETRIC CONSIDERATIONS (DOSE RATE, QUALITY ETC)

Burns (external) Wrenn(Internal)

III DOSE EFFECT RELATIONSHIPS (INCIDENCE, TEMPORAL)
Albert, Goldman & Beebe

IV INTERACTION OF CHEMICAL AND PHYSICAL AGENTS, INCLUDING MODIFIERS, WITH IONIZING RADIATION.

Schuman, Ullrick and Wrenn

V HUMAN-ANIMAL COMPARATIVE RESPONSES (EXTRAPOLATION FROM ANIMALS TO HUMANS)

Lundin, Thompson and Goldman

Each of the authors to send not more than 10 pages

Underlined names are those of the lead author of each group.

Cross-Cutting Questions - they were not submitted

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Introduction

Somatic effects of radiation other than cancer can be considered in two categories; low and high level effects. In the low level region (defined here arbitrarily as single dosage the order of 10 rads or less, or higher doses at very low dose rates), the only effects known definately at present to have health significance are those on fertility and on the developing individual from conception to near birth. These are considered to be of great importance and a ~~detailed~~ outline of the types of investigations required are given below. Although the outline focuses on radiation effects, it is evident that narrowly-oriented studies around such effects are insufficient. What is needed is a better knowledge and hence advances in the understanding of the fundamental biology involved. As an example, only through an improved appreciation of the development of the ova in different species will it be possible to understand in adequate detail the effects of radiation in a single species such as the mouse, and to translate that understanding into predicting effects in the human being.

In addition to the fundamental approaches described above, additional emphasis on quantitative dose-effect relationships for the various effects described below are required. These are necessary for radiations of different quality, and attention must be given to internal as well as external radiations. Because of the ~~intense~~ strong difficulty or impossibility of observing some effects at low doses and dose rates, it is necessary to rely on dose-effect relationships to make at least upper-limit estimates of what might be expected at lower doses and for dose rates.

With respect to non-cancer somatic effects of radiation at intermediate & high doses and dose rates, enough is known to describe in general the course of early (over the first days to perhaps six weeks) effects, following

Introduction

different doses of external radiation. A large number of gaps in knowledge remain, however, and some of these are outlined below. In particular, the non-cancer late effects of intermediate to high doses of internal and external radiation need better definition.

The distinction between non-cancer and cancer-related somatic effects is blurred. For instance, hormonal imbalance resulting from irradiation can be of major importance in the overall carcinogenic ~~re~~expression. Additional interactions requiring study include the immune status, other homeostatic factors, and stem cell dynamics.

Outline for Research Topics

I. Fertility

A. Male Fertility

The relationship between dose to the testes and sterility, fertility, and effects on offspring require further study. For such a study volunteer cancer patients with diseases such as seminoma, Hodgkins disease and lymphosarcoma, who have a good prognosis and are generally in the child siring age group could be included. These patients generally receive pelvic field radiation and preliminary studies indicate that in spite of gonadal shields, the testes receive through unavoidable incidental backscatter doses of radiation in the range of 30 to 200 rads; dependent on treatment and disease.

B. Female Fertility

Comparative studies of germ-cell and ovarian development in different species including man

1. Relation to differences in oocyte sensitivity and induction ~~or~~ of sterility or reduced fertility.
2. Mechanisms responsible for failure to recover genetic effects from early oocytes e.g. repair, selection, failure of induction.

II. Embryo

It has long been known that radiosensitivity is particularly high during intrauterine life, and that the types of effects produced are related to the developmental stage irradiated. The stages may be grouped into three broad periods:

A. Pre implantation (early cleavage, morula, blastocyst.)

B. Major organogenesis (from early post implantation through laying down of organ systems.)

C. Fetus (detailed elaboration of organs and tissues, growth)

There are still major gaps in our knowledge about intrauterine radiosensitivity.

B & C

1. Effects of low doses, especially below 25 rad

   Dose-effect curves should be constructed utilizing sensitive indicators at sensitive stages, ~~e.g.~~,

   a. Killing of primordial germ cells or oocytes

   b. Cell-division delay in the C.N.S.

   c. Homeotic shifts in the skeleton

   d. Other sensitive indicators to be developed.

A, B & C

2. Nature of the cellular mechanisms that lead to various morphological or functional abnormalities, or to death

   a. Cell death

   b. Division delay

   c. Cell-cell interactions

d. Change in differentiation

These mechanisms can be studied

a. In vivo

b. By the use of model systems

B,C 3. The role of genotype in determing intrauterine radiation sensitivity

a. Strain comparisons within a species

b. Species comparisons

B 4. Interaction between radiations and other agents, such as foods, drugs, pollutants (B). Special emphasis should be placed on possible repair inhibitors or enhancers.

B,C 5. Long-term effects of intrauterine irradiation

a. longevity
b. behavior
c. disease resistance
d. radiation resistance

A 6. Effect of chromosomal damages, especially sex-chromosome loss

III. Chromosomal Aberrations

A. Chromosomal preparations are easily available from various species, they provide a biological dosemeter and are useful for studies on clonal evolution, interactions with other agents, relationships to DNA repair defects, and the evolution of various disease states, e.g. leukemia.

B. The medical significance of radiation-induced somatic chromosome aberrations is not known and requires intense investigations. There are substantial additional reasons for their study.

IV. Intermediate and Long-Term Effects

Intermediate and long term effects resulting from high doses are poorly defined and require additional work. Some specific areas are as follows:

A. Vascular, connective tissue and related changes. ~~should be defined~~ (of importance in radiotherapy).

B. Stem cell dynamics, and their relationships to differential organ and species sensitivity.

C. Organ effects, from large amounts of radioactive isotopes gaining access to the organ.

D. Effects of high-LET radiation on the lens of the eye.

E. Effects on cell surface receptors.

F. Shortening of reproductive life span.

V. High Dose Human Exposure

A. Additional information is needed on the therapy of patients with severe marrow depression, from acute radiotherapeutic exposures and acute accidental high dose total body irradiation. For example, passive immune sera could be developed against the organisms most likely to be pathogenic.

B. Therapy can be improved if we know more about pathogenesis of total body irradiation effects, i.e., the nature of the "gastrointestinal syndrome". Patients suitable for such studies are those given total body irradiation in preparation for marrow transplantation.

There is no well established treatment for patients with

C. accidental localized irradiation to an extremity, or lung irradiation due to radiotherepy.

1. Studies of vascular lesions by nuclear medical and other techniques would be useful.

2. Animal models should be developed for diagnosis and possible therapy with anti-platelet drugs (aspirin), sympathectomy, papaverine, etc.

VI. Additional Comment: at the opening of the meeting

The general slant of the outlines provided suggest that this effort is directed primarily toward the harmful effects of irradiation. Even though radiation therapy and diagnostic tests are listed, the subheadings emphasize unwanted radiation effects. We hope that an appropriate balance will be achieved in the report to Congress, with consideration of the possibilities for government support of new nuclear medical techniques, improved radiologic diagnostic procedures, and advanced methods in radiotherapy.

The committee believes that efforts should be made to help the public evaluate the dangers of radiation with a clear perspective of the relationships with other environmental hazards. It is also important to convey the information that radiation effects are among the most extensively studied and most clearly understood of all environmental problems. An additional point is that the large investment already made in radiobiology has had a vast effect upon scientific progress in other fields and has provided methods, ~~i.e.~~ e.g. autoradiography, tracer studies, carbon-14 dating, that have benefited other fields of science.

Strategic Projection Papers: The "cluster" regards the above as a draft projection statement, and is prepared to flesh it out as necessary.

Cross-cutting questions: they were not submitted

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Outline for Research Topics

I. Experimental Studies of Spontaneous and Induced Mutations

A. Dominant mutations, e.g. skeletal, cataracts

1. Induced and spontaneous frequencies at different LETs and in both sexes, i.e. does response and doese rate effects.

2. Interstrain and interspecies comparisons

B. "Recessive" mutations, e.g. "specific locus in mouse, biochemical markers, in mouse and drosophila.

1. Dose response at low doese and dose rate in both sexes.

2. Heterozygous effects

3. Nature of mutations, e.g. deficiencies or point mutations.

C. Chromosome aberrations

1. Induced frequencies in several species at high and low dose rates. This is particularly important for LET and females

2. Numerical changes--aneuploidy.

D. Polygenic

E. Viability--vital statistical parameters.

II. Monitoring Human Populations

A. Spontaneous Incidence

1. Precise studies on certain genetic disorders

2. Screening of biochemical markers

3. Large scale screening of all genetic defects (low priority)

B. Induced Incidence

1. Study of "Worst Case" Population, e.g. Japanese A-Bomb, acute chemical exposure such as Vinyl Chloride workers, PolyChlorinated Biphenyl workers, Sevaso.

2. Identification of Sensitive Populations

3. Monitoring of occupationally exposed

a. Somatic cell biochemical markers

b. Cytogenetic

III. Germ Cell vs. Somatic Cell Studies

A. Test models, to estimate effects on human germ cells

1. Intraspecific correlation of germ vs. somatic

a. Gene mutation

b. Cytogenetics

2. Interspecific correlation of germ and/or somatic cells

a. Cytogenetic (classical)

b. Dominant lethal

c. Heritable translocation

3. In vitro comparative analysis of experimental mammals to human

a. Cytogenetic

b. Biochemical markers, e.g. recessive, sex linked, dominant

4. Risk analysis based on measured spontaneous and induced rates of all studies. Best estimate of correlation.

IV. Topics of Special Concern

A. Internal Emittors -- all LETs

1. Metabolic studies

2. Tissue dosimetry

3. Endpoints

a. Cytogenetic

b. Genetic effects. e.g. non cytogenetic

B. Dose response

1. Data needed

a. High LET low dose and/ore dose rate in male and female mammalian studies and also Drosophila

b. Interspecific comparisons, particularly for female, e.g. cytogenetic and dominant lethal

c. Reexamine current dose response data for deficiencies in our ability to generate good predictive models for estimating risk at low doses and fill in gaps.

C. Modifying Factors

1. Synergisms with non physical mutagens, e.g. chemical exposure

2. Antimutator agents

3. Age effects

a. Sensitivity in fetal and young animals

b. Parental age, e.g. nondisjunction

4. Genetically based hyper-, or hypo- sensitivities

D. Nature of nutational events

E. Multigeneration studies

1. Use of a more potent mutagen

2. Measurement of cumulative genetic damage

3. Applications to human population

a. Health care costs

b. Mitigation or repair/replacement of genetic lesion

F. Non-researchable issues

1. Large scale human studies in populations exposed to doses less than two times background (0.1 to 0.2 rem per year).

Strategic Projection Papers:
Assignments

Paul Selby:

- dominant skeletal mutation in mice--males only now, expand to females and expand to multigenerations does response in male. (no data female for dominant mutation, no dato on sex link; heterozygotic effects.

Preston:

- -- spontaneous human rates frequency (for both cytogenetic and genetic effects) for both chromasonal and mutations: larger than B.C. study--several diverse populations studied.
- --mechanisms of induction of aberrations. types of DNA damage involved thus make more use of DNA repair data.
- --identification of sensitive populations in terms of heterozygotes. relevant in terms of risk estimation.(particular diseases, differentia age susceptibility.
- --identification of potentially susceptible subgroups.
  Protective agents and enhancing agents--should we search for antimutag can we find something to stop the deleterious effects of mutagents??

Bill Russell:

- search for damage of other systems in mammals besides skeletal system which can be treated
- --damage produced on 2nd generations
- --to see if empirical studies in mice using more potent mutagen than radiation could produce similar results to public health effects on viability and fertility in 2nd generation.
- --nature of induced mutations 1) heterozygous effects
  2) mutations effects are deletions or point mutations.
- --to study mutation induction in female oocytes closer to humans than mice(ie. guinea pigs, golden hamsters)

DeSerres- -]. Aneuploidy- mechah ism and frequendy of aneuploidy. Do we know as much as we want to know. (Age effects, dose response, susceptilbe subgroups.

2. High LET radiation of low dose radiation on the induction of specific locus changes -- eukaryotic ~~xxiix~~ systems

3. modifiers of mutagenic activity--both quantitative and qualitative changes using normal and sensitive cells. (mutahable genes, virus infection

Brandow -]. genetic changes in somatic cells.

2. use of chromosome aberrrations for dosimetric purposes.

3. chromasome registry should be established for the nuclear power industry, pilotand crews of aircraft, and hospital staffs

4. study of lmphocyte function.

Neel-- I. mutant protein variants in human and animal systems.

2. above studies in sensitive populations. (even if they are thought to come out negative.)

3. Global worst case approach for populations at high risk such as A-bomb survivors, Nitrogen mustard workers, PCBs and PBBs

4. more powerful mutagens — together with radiation in highly specific mutagens

GRAHN:

--genetic effects of the internally deposited radio nuclides. need to study radionuclides with their own matabolic behavior particularly low does mutagenic effects, not done in full detail. Esp. low does, high LET radiations.

--history of induced lesion in a stem cell all the way through the next generation. survival rate of translocation??????

--Quantitative genetic measure. Should we look at another species besides mouse. Litterbearing animal may not be best species. Guinea pigs(with 1 or 2 offspring) might be better for quantitative genetic measures(ie. fertility, neonatal mortality, birth weight). small rapidly reproducing mammals with 1 or two offspring which may be more like humans. (if no answer, nonresearchable).

--Extrapolation from animal species to Man particularly in regards to the complex genetic defects(multifactorial genetic effects) to see whether effects may be cumulative.

--large area of research may be a waste of funds.

GRANT:

--Is it feasible to establish baseline data on somatic and germ cell studies on the same organism and hope that somatic cell system will be cheaper and easier??

--dose response curve for many genetic end points

--Non-linear dose response for neutron radiations.

James Crow, Chairman and Editor of Projection Paper(All consultants will submit information to Dr. Crow by early December, 1979).

Seymour Abrahamson should also be invited.

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GENETICS
Additional Cross-cutting Questions

With proper prospective studies, can observations on somatic cells cytological and point mutations be utilized as an "early warning system" with reference to risk of cancer?

What is the nature of the phenotypic damage, in terms of actual disorders and ill health, that is likely to result from radiation induced mutations?

Are there any tests(biochemical) which would allow us to predict differential sensitivity of individuals to either the somatic or genetic effects of radiation?

What are the genetic effects of internal emittors compared to the effects of external radiation?

What types of molecular damage results in such effects as mutations with severe effects in heterozygotes, or in cancer?

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M - Epidemiology

Outline for Research Topics

I. Specific Issues

A. Cancer

1. Leukemia
2. Thyroid
3. Other

a. Occupation
b. Background
c. Medical
d. Weapons
e. Nuclear Power
f. Nuclear Accidents

B. Other Somatic Effects (Late)

Interactions

C. Fertility, Genetics and Developmental

1. Chromosomal
2. Twinning
3. Duration of Risks
4. In utero exposure

II. General Issues

A. Dose Response

1. Massive Doses
2. Low Dose Acute-- High LET / Low LET
3. Variations for specific cancers
4. Host Factors
   a. Age
   b. Sex
   c. Race
   d. Health Status
4. Organ Sensitivity
5. Absolute and Relative Risk Models
6. Special & Hi-Risk Populations
7. Attributable Risk

B. Data

1. Cohorts and Controls
2. Dosimetry
   a. Cytogenetics
   b. Background
   c. Fractionation
   d. Dose Distribtuion
   e. Quality Factors

C. Dose Response Known

1. Hi-Dose (Acute) is carcinogenic
   (Est. of Dose-Response are "Good")

2. Hi-Dose (Chronic) is carcinogenic
   (Dose Response Poor for Low LET - Good for High LET)

3. These organs are sensitive for development of cancer
   a. Thyroid
   b. Bone Marrow
   c. Female Breast

4. Somewhat less sensitive
   a. Lung
   b. GI Tract
   c. Bone
   d. Skin

5. Some other organs

6. Other Somatic effects
   a. Cateracts
   b. Developmental defects
   c. Cytogenetic damage

7. Other relevant factors
   a. Age at exposure
   b. Sex
   c. Smoking (possible relations to latent period)
   d. Differing population susceptibility

D. Low level exposures

1. (Low - within current guides for occupational exposure, i.e., 5 rem per year or less)

2. Acute exposures (Single exposures)
   Suggestive - e.g., thyroid risks - less than $20/10^6$/yr/rem

3. Chronic exposures
   Suggestive - Radiologists (two-fold excess)

4. Other Somatic Effects
   None known

E. NEEDS:

1. Elucidation of dose response at low levels requiring--

   a. Large populations
   b. Doses well measured (i.e., within ±
      Rate
      LET
      Fractionation
      Distribution
   c. Range of doses
   d. Population can be followed over time--long term
      (20-25 years minimum)
   e. Multiple populations--to cover appropriate host factors

2. Legislation may be necessary to make this possible

F. CONFOUNDING FACTORS (which need to be controlled for)

1. Age--e.g., at first pregnancy
2. Race - Sex
3. Occupation
4. Other exposures--(radiation (e.g, medical)
   (chemicals (e.g., benezene)
5. Personal habits
   a. Smoking
   b. Alcohol consumption
   c. Diet
6. Medical history (other diseases)
7. Family history
8. Geography
   a. Mobility
   b. Residential history

G. POTENTIAL POPULATIONS (for exposure)

1. Now (presently under study)
   Hiroshima--Nagasaki
   Ankglosing spondylitics
   Medically exposed populations
   a. Women - cervical ca--etc.
   b. Tuberculosis patients
   c. Iodine I 131 (therapeutic and diagnostic)
   d. Thymic irradiation
   e. N-P
   f. Mastitis
   g. Thorotrast exposed
   h. Tinea capitis
   i. Ra 224 (Germany)
   j. Ra 226 (Chicago)

2. Occupationally exposed
   a. Dial painters
   b. AEC-DOE etc. Atomic workers (incl. shipyard workers)
   c. Underground miners
   d. Radiologists and technicians
   e. Military (DOD--e.g., "test" exposures)
   f. Thorium workers
   g. Phosphate ferticilizer workers (FLA.)

3. Environmentally exposed

   a. Utah (Lyons)
   b. Denver population
   c. Marshall Islanders

H. NEW POPULATIONS (Candidates)

"Badged" employees
  NRC
Utah "thyroid" cohort
Free-living populations (high background but serious dose problems)
  e.g. a. Kerala
       b. China
       c. Normany-Brittany
       d. Andes
       e. Brazil

2. Accidentally exposed populations
   Windscale workers
   Peri-Uranium tailings populations
     e.g. a. Cannonsburg, Pa.
          b. Grand Junction, Colo.
          c. Middlesex (?), New Jersey

3. High altitude flyers
   e.g. a. astronauts
   b. flight attendants--pilots, etc.

Strategic Projection Papers

Assignments:

Procedure

a. Plans are to send Genevieve Matanoski copies of scientific paper sections as written by group members

b. Sam Marcus will send copy to Warren Winkelstein to get his input for corrected report.

Cross-cutting questions (author)

Jablon--Schneiderman
Legal Issues

Science Projection--General Coordination -- Matanoski

State of the Art (known and unknown)
Matanoski

Populations--Industrial, etc. (old)
Lushbaugh

Confounding and dose response
Boice--Beebe

Populations--Medical
Boice

Natural Background
Masse'

Dosimetry--(except for cytogenetics)
Matanoski

Dosimetry--Cytogenetics
Lushbaugh

CROSS CUT ISSUES

1. Identification of studies with potential yield
   -- minimum standards
   -- credibility of studies done
2. Public perception of hazards
   -- public (and other "open") participation
   -- disinterested scientific oversight
3. Coordination of Studies
   -- NIH as science monitor?) Place of Federal Interagency
   -- Non-science issues - by whom?) Committee ?
   Identification of areas of need and priority

4. Support
   Continuity - and mechanisms (grants, contracts, "In house")
   Trained personnel
   Allocation - New vs. old
   Institutionalization (who does it? what else do they do?)
   Research Funding

5. Laboratory - Epidemiology Interactions
   Structural issues
   Joint workshops - multidisciplinary projects

   Lab to man:
   DNA repair
   Enzymology
   Immune phenomena
   Repair mechanisms

   Man to Mouse (lab)
   Dose response in "mixed" population
   Breeding "non-susceptible" animal
   (to parallel human response levels)
   Age at exposure effects
   e.g., mouse equivalent of in-utero exposure in humans
   Interaction studies
   Cardiovascular (and other measurable end points--"Behavioral toxicology")
   endothelial growth patterns

6. Legal (and other) problems in data access

   --confidentiality
   --who "owns" data collected with public funds
   --Social Security and IRS data
   --Extension of National Death Index
   --Incidence data--sources ?

Additional question:

What mechanism can be developed for evaluation of data collected as as a result of public funding with particular reference to access to raw data and an opportunity to carry out parallel analyses?