ANL-94/26

Studies of Acute and Chronic Radiation Injury at the Biological and Medical Research Division, Argonne National Laboratory, 1953–1970: Description of Individual Studies, Data Files, Codes, and Summaries of Significant Findings

by D. Grahn

with the technical assistance of
C. Fox, B.J. Wright, and B.A. Carnes

Center for Mechanistic Biology and Biotechnology
Argonne National Laboratory, 9700 South Cass Avenue, Argonne, Illinois 60439

May 1994

MASTER

This report is printed on recycled paper.

CONTENTS

CONTENTS (Cont.)

FIGURE

TABLES

FOREWORD

In late 1990, the Office of Health and Environmental Research (OHER) of the U.S. Department of Energy (DOE) became interested in creating a central archive of data from long-term studies of the effects of radiation on laboratory animals. This interest prompted us at the Center for Mechanistic Biology and Biotechnology (CMB; formerly the Biological and Medical Research Division) of Argonne National Laboratory to reevaluate the status of our existing data archive. While we focused on the data from the JANUS program and from our studies with the beagle, there was also an extensive archive of magnetic tapes containing the card-image data from studies with mice between 1953 and 1969, before the JANUS program assumed a dominant position. (All early data management used IBM data cards and data manipulation on IBM accounting machines; the availability of a mainframe computer for division use was a distant dream.)

We decided to print out the tape files and evaluate them for completeness, accuracy, readability, and scientific utility. This decision served two purposes. First, it could lead to the creation of an easily accessible database of the pre-JANUS studies, thus extending the record of Argonne's contribution to external radiation toxicology from 1953 to 1993. Second, a serviceable data archive of the early studies with mice could materially contribute to the developing DOE program on interspecies extrapolation, which is to develop models by which response parameters could be transposed from mouse to dog to man. The availability of a long-term participant in the early program, Dr. Douglas Grahn, Senior Biologist (Retired), made possible the archive's creation. Dr. Grahn had supervised the original establishment of the data-record system and the codification of survivorship data, having previously been trained in such procedures at the Statistics Laboratory, Iowa State College, before joining the Biological and Medical Research Division staff in 1953.

The evaluation, correction, and refiling of the data on laser-read hard disks, as well as the preparation of this document explaining the recreated archive, have been tedious and time-consuming. The data tapes presented, collectively, over 110,000 lines of 60+ digits, depicting codes for strain, sex, cage, dose, age, survival time, pathology at death, and other characteristics that enabled every line to be unique. The archived data files are now secure and readily accessible for analysis.

The stable funding provided by the U.S. Atomic Energy Commission was essential to the successful completion of the experiments described in this document. Quality long-term animal studies are difficult to conduct and, today, are nearly impossible to initiate. It was, therefore, important to capture the information derived from these studies in a form that will be both intelligible and accessible to future investigators. We thank the U.S. Department of Energy, Office of Health and Environmental Research, for the funding that has permitted the preservation, continued analysis, and documentation of these studies. This support has ensured that these data will remain a valuable resource for future insights into acute and chronic radiation injury, carcinogenesis, and aging.

Eliezer Huberman
Director, Center for Mechanistic Biology and Biotechnology

ACKNOWLEDGMENTS

NOTATION

Abbreviations

AEC	U.S. Atomic Energy Commission
ANL	Argonne National Laboratory
BIM	Biological and Medical Research Division
CMB	Center for Mechanistic Biology and Biotechnology
Co	cobalt
DOE	U.S. Department of Energy
ISU	Iowa State University
LD_{50}	median lethal dose, at which 50% of test subjects die
$LD_{50/30}$	median lethal dose, at which 50% of test subjects die within 30 days
ln	natural logarithm
MAS	mean after-survival
MPD	maximum permissible dose
NCI	National Cancer Institute
OHER	Office of Health and Environmental Research

Units

Ci	curie
cGy	centigray
cm	centimeter
d	day
ft	feet
Gy	gray
h	hour
in.	inch
kVp	kilovolt (potential)
L	liter
mA	milliampere
min	minute
mm	millimeter
qt	quart
R	roentgen
rad	rad
rem	rem
wk	week
yr	year

Studies of Acute and Chronic Radiation Injury at the Biological and Medical Research Division, Argonne National Laboratory, 1953–1970: Description of Individual Studies, Data Files, Codes, and Summaries of Significant Findings

by

D. Grahn
with the technical assistance of C. Fox, B.J. Wright, and B.A. Carnes

ABSTRACT

Between 1953 and 1970, studies on the long-term effects of external x-ray and γ irradiation on inbred and hybrid mouse stocks were carried out at the Biological and Medical Research Division, Argonne National Laboratory. The results of these studies, plus the mating, litter, and pre-experimental stock records, were routinely coded on IBM cards for statistical analysis and record maintenance. Also retained were the survival data from studies performed in the period 1943–1953 at the National Cancer Institute, National Institutes of Health, Bethesda, Maryland. The card-image data files have been corrected where necessary and refiled on hard disks for long-term storage and ease of accessibility. In this report, the individual studies and data files are described, and pertinent factors regarding caging, husbandry, radiation procedures, choice of animals, and other logistical details are summarized. Some of the findings are also presented. Descriptions of the different mouse stocks and hybrids are included in an appendix; more than three dozen stocks were involved in these studies. Two other appendices detail the data files in their original card-image format and the numerical codes used to describe the animal's exit from an experiment and, for some studies, any associated pathologic findings. Tabular summaries of sample sizes, dose levels, and other variables are also given to assist investigators in their selection of data for analysis. The archive is open to any investigator with legitimate interests and a willingness to collaborate and acknowledge the source of the data and to recognize appropriate conditions or caveats.

1 HISTORICAL BACKGROUND

The long-term studies initiated in 1953 had their scientific genesis during World War II. Investigations of the biological effects of radiation exposure were initiated early in the Atomic Energy Program (the Manhattan Project). Strict control measures were going to be needed to prevent excess exposure of laboratory and industrial personnel and of the

general public to radiation sources expected to be of greater magnitude and complexity than any previously experienced. An important concern was the applicability of the then-existing tolerance dose (or maximum permissible dose, MPD) of 0.1 R/d of x-rays or γ rays. The tolerance dose and the general concept thereof had evolved from clinical radiology experiences, a vastly different environment from that anticipated in the production of large quantities of fissionable materials.

Many studies with animals were initiated in the 1940s under the auspices of the Manhattan Project, Corps of Engineers. These studies were principally done at Columbia University, the University of Rochester, the University of Chicago (Metallurgical Laboratory), the University of California, the Clinton Laboratory (now Oak Ridge National Laboratory), and the National Cancer Institute (NCI). Studies at NCI were under the direction of E. Lorenz and were funded through the Metallurgical Laboratory (now Argonne National Laboratory [ANL]). The Lorenz studies addressed the question of tolerance dose by exposing mice and guinea pigs to doses of radium γ rays in the tolerance range of 0.11–8.8 R/d (8-h day). The survival time data are included in this archive. These studies and those done at the University of Chicago raised questions about the applicability of the tolerance dose or MPD for the two sexes and for both somatic and genetic measures of injury.

At the University of Chicago, theoretical studies of the response to the MPD and of the use of animal data for the evaluation of possible human responses were being developed by G.A. Sacher, A.M. Brues, and others. The need for more extensive exposure facilities became evident from the early studies. In addition, the MPD was lowered from 0.1 R/d to 0.3 rem/wk in 1949 and lowered again in 1956 to 5 rem/yr (approximately 0.1 rem/wk). The direct evaluation of the MPD thus became nearly impossible because of logistical and statistical limitations.

In this early period, laboratory animal husbandry was not a well-developed science, so testing at low doses was often confounded by high rates of intercurrent mortality from infectious diseases. One of the confusing outcomes of inadequate animal husbandry was the observation that groups irradiated at low doses sometimes outlived their controls, a phenomenon classified some years later as *hormesis*. It became imperative, therefore, to generate dose-response data adequate for regression analysis and to employ sample sizes sufficient for actuarial (life-table) analysis.

As a consequence, in the late 1940s, the construction plans for Building 202, for the Biological and Medical Research Division (BIM) at ANL, incorporated two large walk-in, live-in radiation rooms designed for ^{60}Co γ irradiation of large numbers of small mammals. The low-level γ-ray room, designed for the remote operation of an approximately 10-Ci source, became the principal experimental facility. The high-level γ-ray room, designed for kilocurie sources, was used for short-term (acute) and fractionated exposures. These two rooms became available for experimental exposures in mid-1954.

The importance of life-table statistics for the analysis of long-term injury was established in the early theoretical approaches developed by G.A. Sacher. The principles and expectations are presented in simple terms by Brues and Sacher (1952). In essence, they

note that the Gompertz function (life table) of an exposed group would be displaced from the normal or control life table in a predictable manner in response to acute or chronic injury and that the induced injury (displacement) would be substantially additive to the normal processes of aging.

Building 202 was occupied in November 1952. From January 1, 1953 (the arrival of D. Grahn), to November 1954, G.A. Sacher D. Grahn, other members of the BIM staff, and personnel from the Remote Control Engineering Division of ANL pursued the logistical issues and preliminary experiments needed to start a major series of animal studies. These issues included choice of animals, design of cages and cage racks, dosimetry, animal husbandry, installation and debugging of source control mechanisms, data management and codification, selection of daily dose levels, and preparation of program plans and their presentation to U.S. Atomic Energy Commission (AEC) headquarters. The ^{60}Co sources were assembled in February 1953, and trial runs in the low-level γ-ray room were initiated in July 1954. The first major long-term study (GCM-4) was initiated on November 18, 1954.

A decision was made in mid-1953 to have all experimental data codified and stored on standard IBM punch cards. Appendix A presents the format and contents for each file. A codified record was made for all major experiments and for most mating records.

In the following documentation, the individual experiments will be explained and the specific logistical details such as animal supply, caging, exposure parameters, animal care, animal entry and exit, pathologic findings, and data management will be presented. The experiments will be discussed in the general chronological order of their initiation. The duration of individual experiments varied. Some were performed simultaneously and used a common control (GCM-4, GCM-9, GAM-2, and GFM-1). Others were carried out in overlapping periods. Before the JANUS reactor experiments began in 1971 (Grahn et al. 1972b), a continuous series of acute and chronic injury experiments was being performed. Not all are in these files, as some were probing studies of limited scope or limited tests of a genetic variable.

1.1 DESCRIPTION OF APPENDICES

Three appendices provide details on the data files, radiation exposure levels, mouse strains, and numerical codes used to identify the fate of each animal. The contents of the appendices are described below.

1.1.1 Appendix A: File Formats

Appendix A (Tables A.1 to A.14) contains the format for the original IBM card-image file for each experiment or data file. In those instances where several files have been merged, the format has been modified to describe the actual file available. The original file numbers have been maintained so records can be related to other data archives.

All information is in numerical form and is constrained to the 80-column IBM card. The same columns were used for the same type of data in most files to facilitate comparisons among separate experiments and to reduce errors in data entry and readout. Between 60 and 75 columns were usually required. The first six columns were for housekeeping or program identification. In some files, several columns are deliberately left blank to preserve the consistency of column use.

1.1.2 Appendix B: Strain Codes, Strain Designations, and Brief Notes on Characteristics

The numerical code for each strain, hybrid, or genetic or mutant marker stock is given in Appendix B. A brief description or genetic identification is also presented. The mouse colony was established originally with well-known and commercially available inbred strains. Background documentation on such strains is widely available (Staats 1968, 1980; Green, E.L. 1966). Standard nomenclature was used for all strains or stocks or is given for identification. The inbred strains obtained from the Department of Genetics, Iowa State University (ISU) at Ames, Iowa, in 1963 were less well known, so some background is presented for these in the appendix. The mutant stocks all carry one or more known mutations that are described in the document by M.C. Green (1966).

For the record here, note that full-sib matings were used to maintain all inbred strains, and all matings were registered in a single sequence of mating numbers. Each litter within a mating was separately recorded in a pedigree book for the given strain. The mating number and litter sequence (parity) number are unique identifiers within and across the strain and are used in many of the data files.

The mice weaned in each litter were numbered in a unique sequence for each strain and listed in a pedigree book. The individual animal was marked by toe clipping to accommodate numbers from 00 to 99. The repetition of numbers with each advancing hundred in the pedigree presented no unavoidable problems. In segregating generations, the coat color or other characteristics were also recorded for each mouse.

1.1.3 Appendix C: Data Codes and Radiation Protocols

Appendix C consists of six tables.

Table C.1. Pre-JANUS Data Codes. The original numerical codes used to identify sex, mode of exit from an experiment (death, discard, etc.), whether an autopsy was performed, and, for selected experiments, the individual's coat color are given in this section.

Table C.2. Equivalence of Pre-JANUS and JANUS Codes. The equivalence of autopsy and exit codes for the two series of experiments is presented, as is a conversion of pre-JANUS experiment codes to a JANUS-format code.

Table C.3. Pathology Codes. The original numerical pre-JANUS codes are presented and are matched to the JANUS-equivalent three-letter and four-letter gross pathologic diagnosis codes. The equivalent JANUS Combined Pathology File codes and definitions are also stated. Because of the limited diagnostic information given in the pre-JANUS histopathologic records, code equivalence has been constrained to the JANUS gross pathologic diagnoses.

Table C.4. Pre-JANUS Pathology Codes with SNOMED Codes Assigned. In this section, the appropriate Systematized Nomenclature of Medicine (SNOMED) codes are assigned to the pre-JANUS codes.

Table C.5. Pre-JANUS Radiation Protocols. The radiation protocols are converted to the JANUS format in this section. The original γ-ray or x–ray exposure levels that were given as "roentgens in air" (R) are converted to midline tissue doses in rads or centigray (cGy) to be in equivalent terms to the doses given in the JANUS series. Both the original doses in roentgens and the converted doses in centigrays are given. The conversion factor for 200-kVp x-rays is 0.8714 cGy = 1 R; and for ^{60}Co γ rays, it is 0.8966 cGy = 1 R.

Table C.6. JANUS Radiation Protocols. For the record here, the radiation protocols for all the JANUS experiments are presented.

2 NATIONAL CANCER INSTITUTE STUDIES, 1943-1953

The NCI studies, performed under the general supervision of E. Lorenz and W.E. Heston, were reported in detail by Lorenz et al. (1954). Several less comprehensive reports were also published (Lorenz 1950; Lorenz et al. 1947, 1951, 1955). The Lorenz data file held at ANL is not all-inclusive for these early studies, but what is available has some noteworthy scientific interest and is therefore included in the data archive (Appendix A, Table A.1).

The file contains the survival data from the initial low-dose study started between February and April 1943, with the LAF_1 mouse. That study employed exposures of 0, 0.11, 1.1, 2.2, 4.4, and 8.8 R/d (8-h day) of γ rays from encapsulated radium sulfate sources. The file also includes the data from a low-dose follow-up study that employed the two exposure levels of 0 R and 0.11 R/d; this study was carried out from 1949 to 1953. Other data in the file involve the female C3Hf mouse that was used to study the induction of mammary tumors. Portions of these data were reported (Lorenz et al. 1951), but some of the data in this file have apparently never been analyzed or discussed. Summaries of the survival data are presented here with some comment and caveats. No pathology data are available, but the pertinent published reports do present tumor occurrences by age interval so that pathology-specific life tables could be generated.

2.1 LOW-DOSE STUDIES

The initial low-dose study employed 302 LAF_1 mice, in equal numbers for the two sexes. The six daily exposure levels were 0, 0.11, 1.1, 2.2, 4.4, and 8.8 R/d (8-h day). Two radium sources were used, one for 0.11 R/d and the other for the four levels from 1.1 to 8.8 R/d. The mice were exposed at night. Three separate rooms were therefore involved: a room for controls, a room for the 0.11-R/d group, and a room for all other exposure levels. Thus, the microenvironment was confounded at the outset. Mean age at entry was 60 d for controls, 52 d at 0.11 R/d, and progressed from 62, 70, 74, and 85 d for the levels of 1.1, 2.2, 4.4, and 8.8 R/d, respectively; age at entry was, therefore, also confounded. The original reports did not give survival time separately for the sexes, and there were some errors in the values given. The present file gives a set of mean after-survival (MAS) values, as shown in Table 1 (tables begin on p. 42). The oversurvival at 0.11 R/d was troublesome but not statistically significant for either sex or for the combined sexes. The regression of ln(MAS) on R/d was -0.0450 for all data and -0.0426 with the 0.11 group deleted. The correlation coefficient was -0.996, and the estimated intercept of 709 d (compared with the observed value of 714 d) suggested the data at 0.11 R/d might have been a minor aberration.

The comparison of 0 R with 0.11 R/d was redone in the low-dose follow-up study, with larger samples, in 1949 to 1953. These values are summarized in Table 2 (the survival data are in the file). The oversurvival at 0.11 R/d for the combined sexes was 58.1 ± 16.2 d ($p < 0.01$), and that for the males alone was 100.2 ± 20.1 d, also highly significant. The excess for females was not significant.

The data from these two studies have become almost legendary for those who wish to believe that extremely low doses of radiation may be harmless, let alone possibly beneficial. Some cautionary notes are in order. Table 1 in the article by Lorenz et al. (1955) gives mean survival times that are actually ages at death. This is an error in the published report and served to exaggerate the differences seen in the original study. A more serious concern, in addition to the use of different holding rooms for the two dose groups, is the note by Lorenz et al. (1955) that the original controls developed dermatitis and had to be replaced about a year after the experiment began. This type of experimental heterogeneity cannot be rationalized retrospectively in the absence of information on pathologic findings at death. This file does not contain any pathology data. The published report does note that reticular tissue tumors increased in frequency at 0.11 R/d for both sexes, lung tumors increased in males, and more mammary and ovarian tumors were observed. Otherwise, there was little or no difference between the two dose groups.

2.2 FEMALE C3Hf MOUSE STUDIES

The balance of the file contains survival data on normal and "castrate" C3Hf female mice. One group of 96 mice exposed to 8.8 R/d was studied and reported in detail (Lorenz et al. 1951), with emphasis on mammary tumor induction. Controls referenced in that report are not in this file, except for 16 control mice that were held until the last irradiated mouse died; then the controls were sacrificed. A group of 100 mice exposed to 4.4 R/d were apparently not reported. Control and 8.8-R/d groups of castrate females (96 and 144 animals, respectively) also seem to have been forgotten. Life shortening in these data was on the high side (−0.057/R·d), but the data are internally consistent. These studies with the C3Hf mouse were initiated in 1946, 1948, and 1950–1951. No pathology data are available in the file, but detailed time-interval data on mammary, lymphoid, and ovarian tumors are in the Lorenz et al. (1951) article for 91 autopsied mice exposed to 8.8 R/d.

3 ARGONNE EXPERIMENTS

3.1 EXPERIMENT XAM-3

3.1.1 Background

D. Grahn joined the BIM staff at Argonne on January 1, 1953, to work with G.A. Sacher in developing the long-term γ-irradiation studies and to introduce the genetic variable into the experimental plans. The results of experiments conducted during the 1940s indicated that considerable genetic variation existed in the acute and chronic responses to radiation exposure, but this variation in response lacked quantitation and an adequate genetic analysis. The selection of inbred strains with which to carry out the genetic studies also served to broaden the basis for selection of strains or hybrids for the major long-term studies. The background of the principal investigator (D.G.; animal genetics, statistics, veterinary pathology) also meshed well with the planned program.

Breeding colonies of six diverse, well-characterized, and widely available inbred strains were established in 1953–1954. These strains were the A/Jax, BALB/c, and C57BL/6 from the Jackson Laboratory, Bar Harbor, Maine, and the A/He, C3Hf/He, and C57L from W.E. Heston, NCI. Characterization of the strains for three primary variables — reproductive performance, radiation resistance, and life expectancy — was begun in September to October 1953, and the activity became identified as the XAM-3 experiment.

Exposure levels were established iteratively to determine the acute lethal dose ($LD_{50/30}$) values for the 200-kVp x-rays chosen as the radiation source for this experiment. The XAM-3 experiment continued with only brief interruptions for nearly 20 years. The last control died in mid-1972. Overall, the experiment provided a codifiable and consistent manner for studying the three primary variables noted above plus the major pathologic findings at death for 15 inbred strains, 4 genetic marker stocks, and 14 outcross/backcross generations from the BALB/c and C57BL/6 inbred lines. The experiment was a means of continuously evaluating genetic aspects of radiosensitivity and life expectancy. Although XAM-3 lacked the formal design parameters of a set piece, it served as a concurrent baseline study and source of information for the design of subsequent experiments (Appendix A, Table A.2).

3.1.2 Experimental Design

3.1.2.1 Radiation Variables

All exposures were done with a GE Maximar x-ray therapy unit. Operational settings were 200 kVp, 15 mA; a half-value layer of 1.1 mm of copper; a dose rate of 21–23 R/min in air at a target distance of 27 in. (68.6 cm). Approximately 18 mice could be irradiated at once on a rotating Bakelite disk that was 0.5 in. (1.3 cm) thick and about

24 in. (61 cm) in diameter. The mice were restrained in 1-in.-diameter, perforated, celluloid centrifuge tubes, which were capped with a standard cork and held down on the turntable with an elastic tie. Exposure times were 20–40 min. The tabletop was about 2 ft (61 cm) above the floor, and the dosimetric readings included backscatter from walls, floor, and the tabletop. All measurements were done with a 1-cm^3 Victoreen thimble-chamber dosimeter. Table 3 presents the exposure levels used for each strain or hybrid.

3.1.2.2 Animals

Although the XAM-3 study continued for nearly 20 years, it subdivided into three major parts to study genetic variation in radiation resistance. The first part involved the six principal inbred strains (A/He, A/Jax, BALB/c, C3Hf/He, C57BL/6, and C57L), and the F_1, F_2, and F_3 hybrids of strains C57BL/6 and BALB/c. The second part focused on the outcross/backcross generations from the two parent strains noted above (Figure 1). The third part involved the inbred and genetic marker stocks that were brought to ANL from the ISU Department of Genetics in September 1963. In terms of the ANL strain codes (Appendix B), the three studies involved codes 02–14, 15–44, and 47–62, respectively.

Generally, the mice were between 60 and 120 d of age at exposure. As the animals were all bred at ANL, it was not possible to predict the availability of adequate samples for a given replication; therefore, age could not be rigorously controlled. Table 4 presents, for each strain, the total number of animals involved and the number held for the study of chronic injury and survival time for both irradiated and control groups. In Table 4, these latter numbers are for mice dying of natural causes at 61 or more days after exposure. The difference between these numbers and the total numbers would be accounted for by acute (1–30 d) and subacute (31–60 d) deaths plus accidental losses and discards. Not all strains and/or dose groups were part of the long-term studies.

For ease of presentation, the tabulated data in Table 4 were summed across the two sexes and all exposure levels within each strain, although the file contains the data separately by strain, sex, dose, and survival time. The two sexes are about equally represented, but the sample size for irradiated survivors is largest at low doses and declines with increasing dose. Because the range of doses was generally from about 0.8 to 1.2 times the LD_{50}, the data can be pooled for comparison of controls versus exposed by using a weighted mean exposure level.

3.1.2.3 Animal Husbandry

The mice were housed in plastic "shoe-box" cages designed to hold 12–15 mice. Stainless-steel cage tops contained a bin for pelleted food and a water bottle. Bedding was usually sterilized wood shavings, although the exact bedding material changed from time to time over the years. Food and water were always available. Cages were changed at least once a week. They were kept on racks or shelves along the walls of rooms in the BIM animal facilities.
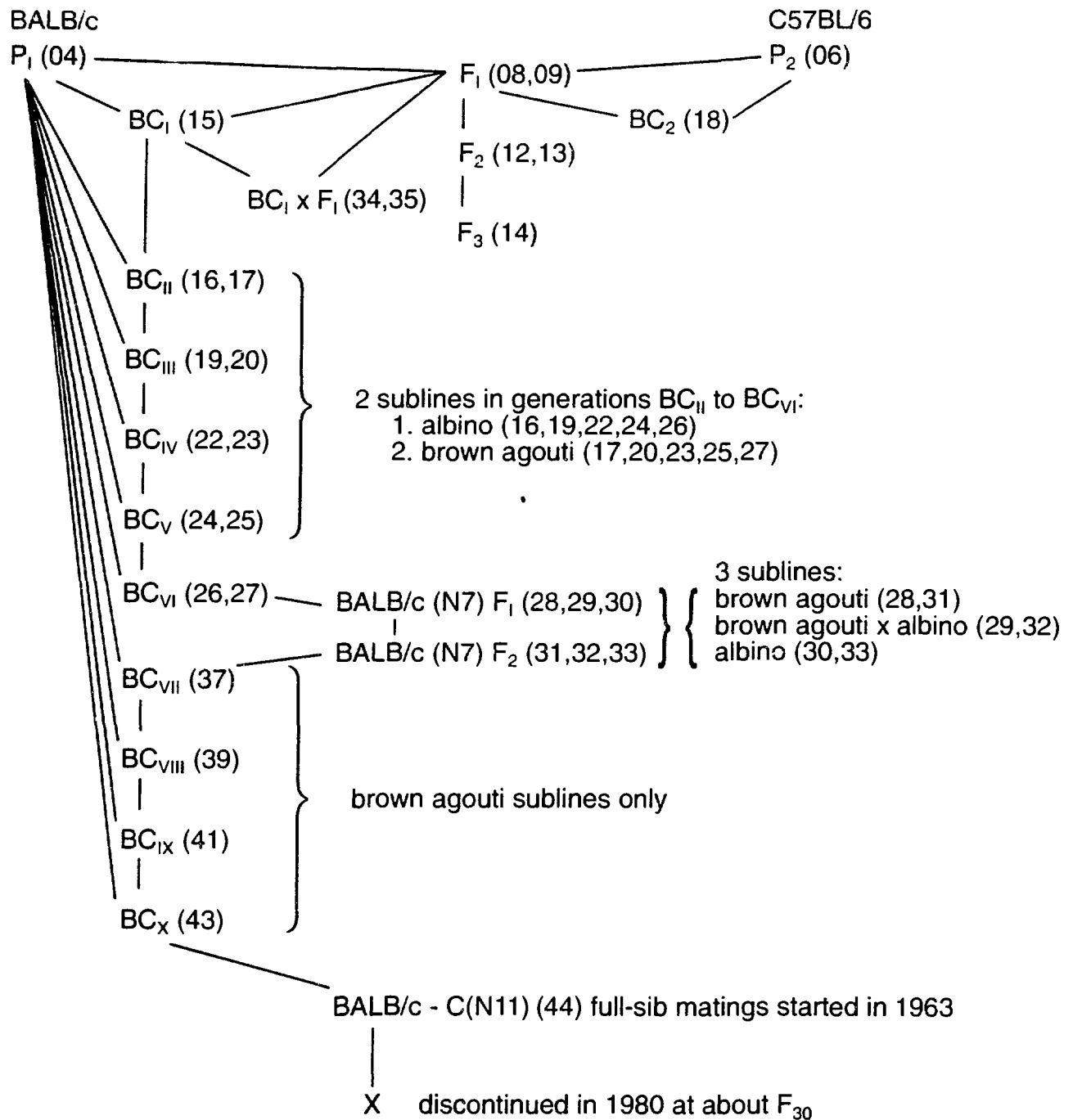
FIGURE 1 Diagram of Outcross and Recurrent Backcross Matings Used to Study the Inheritance of Radiation Resistance and Mean Life Expectancy and the Potential Genetic Linkage of These Traits with the Albino Locus (strain codes in parentheses)

In early stages of the study (1953–1960), bacteremias would periodically occur and cause the death of all mice in a cage within a matter of days, without any relationship to dose or known dose-time mortality expectations. Such cages were discarded from the study. A precautionary statistical measure involved the exposure of mice from a single cage to two to four different dose levels, thus distributing the impact of infection more randomly across doses. If mice were to be held for lifetime observation, they normally remained in the original cage, though some recaging occurred because of the demand for space.

3.1.3 Data Recorded

The animals were checked twice daily on weekdays and once daily on weekends. Date and post-exposure day of death were recorded. For long-term survivors, a modest amount of information on the pathologic findings at death was recorded on a standard autopsy record sheet. Tissues were taken from some animals, but only a limited histopathologic examination was actually done. Unfortunately, the original autopsy record sheets were inadvertently discarded; however, some useful data are in the original data books from which the data cards were keypunched.

The acute period of response was limited to the usual 30-d interval following exposure. If the survivors were to be discarded, that would generally be done before 50 d. Early analyses of the data for all strains showed that acute mortality actually ceased before the 30th day. A few subacute deaths occurred sporadically over the next 30 d, and by 60–90 d after irradiation, the first evidence of chronic injury would appear, usually as a localized thymic lymphoma large enough to cause terminal respiratory distress. The rather limited pathology codes used indicate the limitations of the data (Appendix C, Table C.3). Nevertheless, the major observations were adequate to differentiate the strains and hybrids by their innate or genetic propensities to succumb to different causes of death.

Because the animals were all bred at Argonne, the mating and/or litter record of each mouse was available and became part of the permanent record. The original intentions were to seek any correlations that might exist among such basic variables as maternal age, parity, litter size, age at entry, weight at entry, and, if possible, early mortality in the given litter or in other parities of the given dam. Analytical capabilities at the time were not adequate to carry out these plans except for an analysis of the influence of age at entry, parity, and litter size on $LD_{50/30}$ values for four inbred strains (Grahn and Hamilton 1957).

3.1.4 General Findings

The XAM-3 study consisted of three semi-independent efforts that partially overlapped in their execution. The results of these efforts were never completely reported, although extensive statistical analyses were carried out. The unpublished findings are on file, and a brief summary is given here. Many analyses should probably be redone in light of the present computational capabilities of handling more complex survival analyses.

Part I: The Primary Inbreds and the F_1, F_2, and F_3 Hybrids of Strains BALB/c and C57BL/6

The results of the first part of XAM-3 were published by Grahn and Hamilton (1957) and Grahn (1958a, 1958b, 1960). Significant differences in acute $LD_{50/30}$ values for 200-kVp x-rays were observed, with a maximum difference among inbreds of 500 R (BALB/c) versus 630 R (C57BL/6). The F_1 generation showed significant hybrid vigor with an LD_{50} of 660 R, and there was no difference between the two reciprocal crosses (B6C vs. CB6 F_1 generations). The LD_{50} values for the F_2 (628 R) and F_3 (613 R) generations regressed to that of the C57BL/6, the resistant parent. The dose-response slope dropped sharply in these two genetically segregating generations, reflecting significant increases in genetic variance. Heritability of radiation sensitivity was estimated to be about 0.55. The F_2 mice also showed a significant relationship between radiosensitivity and the segregation of the albino gene. $LD_{50/30}$ values were 602 ± 9 R for albinos and 639 ± 8 R for all non-albinos.

With regard to long-term effects, LD_{50} values were positively correlated with the normal control life expectancies — that is, the higher the acute LD_{50}, the greater the life expectancy. There was some variation among strains in the life-shortening effect per roentgen, but much of this variance could be reduced by removing the specific effect of lymphoreticular tumor deaths and ovarian tumor incidence. Life shortening was estimated to be 28 d/100 R for all strains and both sexes as a basic parameter to which the effects of tumor incidence would be added. At the LD_{50}, life expectancy was reduced by 19% for all strains after appropriate adjustments for strain differences in their pathologic affinities (Grahn 1960).

Part II: The BALB/c:C57BL/6 Outcross and Backcross Generations

This portion of the XAM-3 study involved a rather classic recurrent backcross series, as diagrammed in Figure 1. A primary goal was to define the genetic behavior or transmissibility of radiation response and its corollary of life expectancy. It also endeavored to prove and quantitate the linkage between the qualitative coat-color trait at the albino locus and the quantitative trait of radiosensitivity. Recurrent backcrosses to the sensitive parent (P_1; BALB/c) were carried out to the sixth backcross, where less than 1% residual genotype from the resistant parent (P_2; C57BL/6) would be expected. Starting with the second backcross ($BC_I \times P_1$), two family lines were established (an albino family and a brown agouti family) to better isolate the genetic factors controlling sensitivity. LD_{50} values were derived for all generations, and control survival values were attained for the BC_I, BC_{II}, BC_{III}, and BC_{VI} generations.

The first backcross to the resistant parent ($F_1 \times$ C57BL/6) was also done, along with the cross of the BC_I back to the F_1. The latter cross was done to test a prediction model, and both LD_{50} and long-term survival values were collected.

Analyses of the above data were performed, and several summaries were presented (Grahn et al. 1962, 1964). The linkage analysis was mathematically and genetically complex

and required assumptions that were only testable by the analysis of residual variances. The endpoints (LD_{50} values by coat-color family and survival data) are, characteristically, statistically noisy, making for large uncertainties. In addition, the baseline LD_{50} values for the parent strains changed during the course of the study because of improved animal care procedures. The LD_{50} value increased by 10% for the sensitive parent, from 500 to 545 R, and increased from 660 to 700 R for the BCF_1. Nevertheless, an estimate of the linkage relationship was derived along with an estimate of the portion of the difference between the P_1 and the F_1 that was linked to the albino locus. These estimates were 0.21 for the recombination frequency that involved 31% of the F_1-P_1 difference (Grahn et al. 1962).

LD_{50} values and control life expectancies were also positively correlated, as was previously seen among the inbred strains. Life expectancies and LD_{50} values for the sequence of backcrosses steadily and conjointly declined as the proportion of BALB/c genotype increased (Grahn 1972). Mean life expectancy from birth dropped from 850 d (F_1) to 570 d (BC_{III}), while LD_{50} values dropped from 700 to 560 R.

Although this portion of the XAM-3 study was never fully reported, a detailed summary is available in Grahn et al. (1964). The backcross series was extended to the tenth generation with the brown agouti family, whence full-sib inbreeding was begun to establish a congenic BALB/c line that was a brown agouti non-albino. The standard BALB/c line is also brown agouti, but it is covered by the albino trait. By 1968, four or five years after the line was established, LD_{50} values were 567 R for the original BALB/c and 581 R for the BALB/c-(N11) (Appendix B, strain code 44).

Part III: The ISU Strains and Mutant Stocks

In September 1963, nine inbred strains and four mutant marker stocks were brought to Argonne from the Department of Genetics, ISU. These had been maintained at ISU by J.W. Gowen (D. Grahn's major professor) for many years; some had been at the Department of Genetics since the early 1930s and others had come from the Rockefeller Institute in 1938 when Gowen took the position at Iowa State. The principal background of the strains was their known resistance or susceptibility to the infectious disease known as mouse typhoid, caused by *Salmonella typhimurium*. When Gowen moved to Colorado State University, he took the stocks and some ongoing experiments that were funded by the AEC. Moving the stocks to ANL in 1963 was a "safekeeping" maneuver agreed to by all parties, including the AEC. D. Grahn agreed to characterize the stocks in a manner similar to that used for the regular inbreds and hybrids (see Parts I and II above) and, thus, extend the range of known genetic variation available for radiation studies.

Four strains (C, K, Q, and N) originated at the Rockefeller Institute for Medical Research (Webster 1937); strain S at ISU (Schott 1932); strain Z at the Rockefeller Institute Yellow Fever Laboratory in the early 1930s; strain E from a dealer in Pennsylvania; and the Bab and BaB lines were originally BALB/c mice given to J.W. Gowen in 1932. The marker stocks were obtained from various sources during the 1950s and include several mutants

originally detected at ISU. Appendix B contains more details on these strains and stocks (codes 47 through 58 and code 61).

Data were collected on the LD_{50} for x-rays, long-term survival of mice exposed to single midlethal doses, control life expectancy, major pathologic findings at death, reproductive performance, and, for selected stocks, survival under daily γ irradiation. The data have never been fully assembled, analyzed, or interpreted because of Dr. Gowen's death in September 1967 and because of major changes in program priorities, which included the programmatic justifications and reviews for critical modifications of the JANUS reactor and the proposed JANUS research program. LD_{50} estimates are available, as are control survival values and some reproductive performance data. Pathology data are in data books but not in the computer files. The following are some of the observations.

1. LD_{50} values ranged from about 475 to 750 R. The lowest value was for mice carrying the W^a (Ames dominant white spotting) gene, which causes a deficiency in hematopoietic response to radiation injury. The Rockefeller strains (C, K, Q, and N) did not have LD_{50} values that correlated positively with their known differences in response to bacterial infection, as was seen among the other ISU inbreds. Control mean life expectancy also had very little relationship to the LD_{50} value, in contrast to the high positive correlation seen among the regular inbreds (see Part I, p. 12).

2. Control mean life expectancies from approximately 100 d of age ranged from 200 d to over 700 d, with females generally outliving males. The lowest expectancies (<350 d) were mostly in the mutant tester stocks (strains 56, 57, and 58), but several inbred lines also had poor survival times. Pneumonia was a common cause of death in these cases. Among the 13 stocks, however, the spectrum of major pathologic findings was quite varied, and some hand tallies are on file. The usual array of neoplastic diseases was seen (lymphoreticular, lung, liver, ovarian, mammary, and connective tissue), as were some heart thrombi and cases of the liver herniating through the diaphragm. The pathology records are not complete because the detailed autopsy records were among those inadvertently discarded. Major differences among stocks could be validated by tabulation of existing handwritten records in data books and files and by entering the data as they exist into the computer files.

3. Reproductive performance among the stocks was generally within the customary range for inbred mice. Between 5% and 25% of the matings were sterile, average litter sizes at birth were between 5 and 9, and preweaning losses were between 15% and 35% (though several stocks were as high as 50–60%). Most stocks had females in single-pair matings that were in production for 5–6 months and

produced four to six litters. One uniquely resistant strain, S, produced an average of only two large litters per dam that then suffered 50% preweaning losses. The whole mix of characteristics have not been fully analyzed for these strains and stocks from ISU.

3.2 EXPERIMENTS GCM-4, GCM-8, AND GCM-12

3.2.1 Background

These three studies are documented conjointly because GCM-4 (Appendix A, Table A.3) established the basic experimental parameters. GCM-4 and GCM-8 (Appendix A, Table A.4) were done simultaneously, and GCM-12 (Appendix A, Table A.5) was an extension of GCM-4 and GCM-8 to lower doses. The best discussion of the history and background is in the introductory sections of Sacher and Grahn (1964).

Briefly, the duration-of-life irradiation procedure evolved from the studies by Lorenz (1950) and Lorenz et al. (1947, 1954) carried out at the NCI from 1943 to 1945, and by Sacher (1956b) at the University of Chicago Metallurgical Laboratory from 1944 to 1946. Daily irradiation was initiated at an age generally considered equivalent to the young adult human (i.e., 50–90 d of age in the NCI studies and 40–60 d in the Sacher study). The procedure tested the concept of tolerance dose (or MPD), provided data on responses to protracted exposure as compared with short-term (or acute) exposures, and gave data on all of the typical radiation syndromes but without the abruptness and incompleteness associated with responses to single doses. The resulting continuum of responses provided a complete picture of radiation injury that lent itself to good statistical analysis and to the development of more sophisticated hypotheses on the mechanisms of chronic radiation injury (Brues and Sacher 1952).

At the outset of these studies, there was no consensus on the biological basis of long-term injury, how to model it, or how best to study it experimentally. The ANL approach had its detractors; however, our daily irradiation paradigm brought out, in proper sequence, all known and some previously unknown radiation syndromes. This was the strength of our approach, which was based on an analytical and theoretical model (Brues and Sacher 1952) that we believed to be superior to competing models that we considered simplistic and incomplete.

The duration-of-life irradiation procedure did generate two problems, neither of which has been fully explained or rationalized, though a reanalysis of the full database now available might provide some answers. These problems are hormesis and wasted radiation. Hormesis (survival of low-dose groups beyond their controls) is probably primarily induced early in the exposure history, and wasted radiation is a terminal issue (does the individual respond to exposures occurring in the last part of its lifetime?).

3.2.2 Experimental Design

3.2.2.1 Radiation Variables

The same basic exposure procedures were employed in all three studies, and these are presented in detail in Sacher and Grahn (1964). A 12-in. (30.5-cm), linear, 6- to 8-Ci ^{60}Co source was located in the center of the low-level γ-ray room. The room's dimensions were 24 × 24 × 12 ft high (7.3 × 7.3 × 3.65 m high). It was a ground-level concrete bunker with walls 2 ft 8 in. (81 cm) thick with an L-shaped entrance maze. The source was operated remotely by an electromechanical timer. The animals were irradiated during the night hours (the usual period of activity for most small mammals). Exposure periods varied between about 8 and 12 h, depending on source strength. The period was increased by 5-min increments at intervals calculated to compensate for source decay.

Dosimetry was initially done with a Victoreen thimble-chamber dosim...er inserted into an animal cage at the normal location of the animals. Ultimately, a measure of "cage-average" absorbed dose was derived with a phantom designed by W.K. Sinclair (Sacher and Grahn 1964; Sinclair 1963). Backscatter was high close to the walls and floor, so these areas were not used. All structural materials in the room were plastic or aluminum, except for the stainless-steel cage tops and glass water bottles. The absorbed dose for mice under normal conditions and room loadings was 0.9 rad per roentgen in air (researchers should note that all original records are in terms of roentgens in air).

Experiments GCM-4 and GCM-8 were carried out simultaneously, and the above dosimetric remarks pertain to both. To obtain two or three dose rates lower than those available for GCM-4 (daily doses less than 5 R/d), several modifications were made in 1958. A 1-in. (2.5-cm), 120° lead shield was mounted on a steel tripod next to the source-up position, and a 4-in. (10-cm) bulk lead shield was mounted in the southeast corner of the room. The source shield produced large areas where daily doses were below 3 R/d, and the bulk shield produced a limited area with a daily dose of 0.3 R. The dose levels of 0.3, 1.3, and 2.6 R/d were thus available for the GCM-12 study.

Absorbed dose measures were not made in the shielded areas, but pulse-height dosimetry was done by P.F. Gustafson. While the characteristic [60]Co γ-ray energy of about 1.2 MeV prevailed, there was a considerable increase in the size of the degraded energy spectrum. The absorbed dose of 0.9 rad/R in air given in Sacher and Grahn (1964) could therefore be a high estimate. The fully loaded room (racks, cages, mice, food, water) also degrades the spectrum, so the presence of additional lead shielding may not have altered the absorbed dose substantially.

Table 5 presents the daily exposure levels used in GCM-4, GCM-8, and GCM-12 and indicates which levels were incorporated in each study. Levels of 270 R/d and above, used only in GCM-4, were carried out in the high-level γ-ray room under conditions comparable to those used in the low-level γ-ray room.

3.2.2.2 Animals

GCM-4. The LAF_1 mouse was chosen for this study after an evaluation by Sacher and Grahn of a number of candidate strains and hybrids with regard to availability and known characteristics about disease susceptibility, tumor propensities, and life expectancy. The LAF_1 was selected for reasons of cost, commercial availability, and its known favorable attributes for long-term study. It was the mouse of choice for the NCI studies in the 1940s and for the studies on the effects of weapons-quality radiations performed at Eniwetok (Operation Greenhouse) in April to May 1951 (Upton et al. 1960). The LAF_1 mice were bred at the Jackson Laboratory and shipped to Argonne (on a biweekly basis) when about seven weeks of age. Entry was nominally at 14 weeks or 100 d of age. Both sexes were used in equal numbers, and sample sizes per exposure level are given in Table 6. Replication 1 was entered November 18, 1954.

GCM-8. Although GCM-4 took precedence, it was possible to introduce adequate samples of four inbred strains (A/Jax, BALB/c, C3Hf/He, C57BL/6) and the B6C/CB6 F_1 and F_2 generations from the reciprocal crosses of BALB/c and C57BL/6. These were chosen as parent strains, as they represented the available extremes in radiation sensitivity, as judged by $LD_{50/30}$ values. BALB/c was sensitive ($LD_{50} = 500 \pm 7$ R); C57BL/6 was resistant ($LD_{50} = 630 \pm 4$ R). Less regular samples were entered for strains A/He and C57L. The latter started late and continued into the GCM-12 study period. Age at entry was about 100 ± 15 d, and equal numbers of both sexes were used (Table 6).

All of the entrants for GCM-8 were bred at ANL. Because of space and sampling limitations, the GCM-8 study did not fully duplicate GCM-4. The GCM-4 experiment included 15 daily dose levels between 5 and 220 R/d in the low-level γ-ray room (the limiting doses in the facility in 1954–1958); GCM-8 regularly used only 10 levels between 12 and 220 R/d (Table 6).

GCM-12. Three inbred strains and an F_1 hybrid were used in this study, which was initiated in the summer of 1958. The strains were the A/Jax, BALB/c, C57BL/6, and the C57BL/6 × BALB/c F_1 ($B6CF_1$). Age at entry was approximately 100 ± 15 d, and both sexes were used in approximately equal numbers. All mice were bred at Argonne. Strain C57L was originally included in the records of GCM-12 but was not a part of the experimental design. These data on the C57L can be considered an extension of GCM-8. The data for the C57L have been transferred from the GCM-12 file to the GCM-8 file (Table A.4). Changes in the format were made to accommodate the transfer. Data from the GCM-12 file can be identified by their project and experiment codes, which differ from those of GCM-8. Cage positions in the gamma room were renumbered for GCM-12, so inconsistencies exist within dose levels for such data. The numbers of mice employed for each exposure level and sex are given in Table 7.

3.2.2.3 Animal Husbandry

With a few exceptions (to be noted), the mice in all three studies were housed in cylindrical cages modeled after a 2-qt (1.9-L) liquid container. The cages were made of a transparent Bakelite, 5 in. (12.7 cm) in internal diameter and 6.25 in. (15.9 cm) deep. A perforated stainless-steel cage top held a 5-oz (0.15-L) water bottle and pelleted food retained by a steel screen. The cage top was 2.5 in. (6.4 cm) deep, approximately half of which was inside the cage. The remaining space for the mice was approximately 100 in.^{3} (1600 cm^3). Three inches of sterile wood shavings were usually used for bedding, into which the mice always burrowed. Three mice were placed in each cage at entry into the exposure field.

The cage top was slightly modified for the GCM-12 study by inserting a barrier in the food-bin portion to maintain an open section (approximately 4 in.^{2} [25.8 cm^2]) to improve ventilation. The exceptions to the use of the cylindrical cage were for the one-third of the GCM-4 controls that were held in a shoe-box plastic cage (nine per cage) in a regular animal room, and the mice exposed to 0.3 R/d in the GCM-12 study, which were also kept in a shoe-box cage (12 per cage). Controls were held in the maze/corridor of the γ-ray room where the environment was nearly identical to that in the exposure room itself. Death checks were made routinely — twice daily during the week and once daily on weekends.

At high daily doses, where survival was less than 14 d, irradiations were performed in the high-level room by using a kilocurie source. Exposure conditions and housing were the same as those used in the low-level room. Death checks were more frequent at high doses. With survival times of 7 d or less, checks were performed at 12-, 4-, or 1-h intervals, depending on mean survival time (Sacher and Grahn 1964).

Cages were changed at least once weekly, more often if conditions required. Intercurrent infection was not a consistent problem in GCM-4 and GCM-8, but it was not entirely absent. Not all strains adapted well to the small cylindrical cage. Strain C3Hf did poorly, largely because of poor ventilation. Strains more sensitive to bacterial infection (A strains and BALB/c) may have suffered shorter survival times at the higher dose levels that severely damaged the hematopoietic system. Although cage conditions for GCM-4 and GCM-8 were not ideal for all strains of mice, they were much improved for the GCM-12 experiment because of the increased ventilation.

As noted previously, daily exposure levels, sample sizes, and mouse strains or hybrids employed are all given in Tables 5, 6, and 7. The C57L strain was entered late into the GCM-8 study and was included only in replications 72–90 (the last replication). Strain A/He was also entered later than the main body of entries and involved replications 40–90. All other strains were entered in replications 1–89.

3.2.3 Data Recorded

In all of these studies, the primary observation was survival time or day of death measured from the start of irradiation. While some mice were sacrificed in a clearly

moribund state, the majority died of "natural causes." Gross pathologic findings at death were recorded for most animals, and uncertainties were checked by histologic evaluation. Lesions present at death were coded and are part of the permanent record. For GCM-4 and GCM-8, the record is limited to 21 pathology codes: nine for the most common neoplastic diseases and six each for the most prevalent acute or chronic infectious and degenerative diseases. The GCM-12 pathology record was more complete, and eight additional codes were added. These codes have all been translated into equivalent JANUS MACRO codes to permit full intercomparisons (Table C.3).

Though limited, the pathology data accommodated the majority of lesions then considered of primary value for differentiating "cause of death" or "major contributors" to an animal's death. For GCM-4 and GCM-8, the pathology record is "complete" for all doses between 0 and 56 R/d. No file record is available at the higher doses where acute and subacute hematopoietic system damage prevailed, though some autopsies were performed to confirm the presence of acute and subacute marrow damage. A pathology record is available at all dose levels in GCM-12.

For all three studies, there are additional data in the file. Appendix A contains the complete format for all files. For GCM-4, age at entry was always 100 d, and body weight data were taken at four weeks and two weeks before entry and on the day of entry. Cage, replication, and cage position (rack, shelf, and position on shelf) in the room are in the data file. There were three control groups: A (rack 20), in the corridor of the γ-ray room; B (rack 21), in a nearby standard mouse room (A and B mice were caged in the cylindrical γ-ray room cage, three per unit); and C (rack 22), in a mouse room with B but in shoe-box cages, nine per cage. Investigators are cautioned that the different cage environments led to marked differences in survival time and life-table parameters.

The GCM-8 file contains the same basic data as in GCM-4 with regard to body weights, cage position, and replication. Age at entry is entered as the exact age (varying between about 80 and 120 d). In addition, the mating number and parity for the specific mouse are in the data file, as is a coat-color code for the F_2 generation where five coat colors segregated out. Since most entries were a pair of cages (one of each sex at a given dose), the paired cage number is also given.

For GCM-12, the file format changes slightly because the animals moved from stock-cage holding status to experimental status in a manner that ties the pre-irradiation history to the exposure history by use of a common stock cage number. Cages of 12 were held under routine observation from weaning (at about 30 d) to time of entry (approximately 100 d), and the data are recorded in File No. 94 (Appendix A, Table A.11). Stock cages were divided into four γ-ray-room cages of three mice, keeping the same stock cage number and adding a subcage number (1–4). There was only one body weight taken at entry. Age at entry, mating number and parity, and cage position are in the file as in GCM-8.

We did not integrate the files for GCM-12 (Table A.5) and for pre-experimental stock cage history (Table A.11), but this can easily be done by use of the common cage number and

then the mouse number, mating number, and parity. Table A.11 also has the exact birth date (month, day, and year).

Control cages for GCM-8 did not have a fixed cage position, as they generally were held in the corridor/maze along with other controls and mice being held for studies of age dependence (GCM-9A), on a space-available basis. GCM-12 controls were assigned a specific cage position, however.

Lastly, although GCM-4 and GCM-8 were concurrent, GCM-4 was the primary study and had more exposure levels than the GCM-8 study. Dose levels of 49, 64, 85, and 145 R/d were added about a year after the start, to provide more detail in the responses to acute and subacute injury and to the initial occurrence of deaths from neoplastic disease, principally lethal thymic lymphoma. The availability of cage positions at these doses was limited, but the two A strains were exposed to 64 and 85 R/d in GCM-8, with adequate sample sizes of 24 mice per sex, dose, and strain. A few (three per sex) BALB/c mice were entered at these two levels, but the data can be ignored.

3.2.4 General Findings

The results of these three studies were used in a number of articles and formed the basis for some new concepts and considerations in radiation toxicology. Data from the GCM-4 study were reported more concisely than those from the other two studies and addressed the then-existing controversies in the field of chronic radiation injury. The following paragraphs present some of the findings and principal references.

GCM-4. The two principal references are Sacher and Grahn (1964), for the lethality data, and Lesher et al. (1965), for the pathology data. The Sacher and Grahn article was largely prepared by Sacher and is a tour de force on chronic radiation injury theory and modeling. Users of any of the GCM data must read this report. It destroys the simplistic Blair theory of irreparable injury, lays out basic principles of interspecies extrapolation, discusses both the hormesis and wasted radiation issues sensibly, and offers hypotheses. The article emphasizes the need for good mathematical modeling that can be related to physiologic and cellular parameters. It notes that injury is not instantaneous and urges that more attention be given to the rise time of injury, as well as to the recovery time (injury and repair conform to an algebraic parabolic function). At least four ways of expressing the life-shortening constant are also offered. The data brought out the presence of a half-dozen syndromes, including several not previously seen.

The pathology article (Lesher et al. 1965) was undistinguished. The dose-time distribution of the principal tumors and degenerative lesions was given in terms of the number of events per 50- or 100-d intervals. Life-table analyses were not used. A first effort was made to examine tumor multiplicity and the presence or absence of associations. For males, the major tumors were lymphoid, pulmonary, and liver; for females, notable frequencies of ovarian and mammary tumors also occurred. Amyloidosis was common at

lower doses (≤24 R/d), as was degenerative kidney disease. The absence of life-table analyses makes interpretation difficult. These data need reanalysis.

GCM-8. Unfortunately, the data from the GCM-8 study were never completely reported. The major findings on life shortening were incorporated into several reports on the influence of genetic variables in radiation toxicity (Grahn 1958b, 1960), and on the analytical approaches to interspecies modeling (Grahn 1970; Grahn et al. 1978). A number of other analyses were performed, including an effort at data transformation to enhance the extraction of both phenotypic and genetic variances.

Some of the findings are summarized here. As a preface, we note again that the different strains did not thrive with equal success in the small cylindrical cage. Intercurrent infection and higher-than-desirable humidity levels reduced life expectancies in disease-susceptible strains. Animal husbandry was the same at all dose levels, so any specific detrimental factor probably influenced survival values consistently within a strain. Although GCM-8 and GCM-12 are to a degree a continuous study, they cannot be compared or combined without careful examination of the GCM-8 life tables for inconsistencies or perturbations possibly induced by infectious disease. For example, control MAS values in GCM-8 were similar to those in GCM-12 for the A/Jax and BCF_1 but were 60–70 d shorter in GCM-8 for C57BL and 170–190 d shorter for the BALB/c. These represent 10% and 42% losses in mean life expectancy for the two strains, respectively. The differences are highly significant ($p < 0.001$) for BALB/c and borderline ($p = 0.06–0.13$) for the C57BL/6 strain.

The basic life-shortening coefficient expressed as a fraction of the control MAS days lost per roentgen per day is 0.037, which equals 0.037 d/R, or approximately 0.04 d/rad. This value is consistent for all strains and hybrids throughout GCM-8 and GCM-12 (Grahn et al. 1978). The genetic variance is principally in the control life expectancy and in the pattern of specific causes of death, not in the life-shortening coefficient. Heritability of life expectancy, as derived from the estimated environmental and phenotypic variances of the two parent strains and their F_1 and F_2 hybrids in GCM-8, varied from 0.1 to 0.9 among 10 dose levels between 12 and 220 R/d. There was no correlation between dose level and the heritability estimate, which averaged 0.625 across all doses.

Control MAS values for the radioresistant strain C3Hf were 36% shorter in GCM-8 than XAM-3, probably attributable to the difference in caging. C3Hf mice did not thrive in the small cylindrical cage as compared with their behavior in the larger shoe-box cage used in XAM-3. Nevertheless, the radiation-induced life-shortening coefficient was 0.035, similar to that seen for other strains and hybrids. This suggested that the intrinsic life-shortening parameter will prevail even under poor environmental conditions.

The pathology data are in the record, but no full analysis was done. Strains like C57BL/6 with high frequencies of induced thymic lymphoma showed predictable perturbations from otherwise monotonic responses. Decrementation of the life tables for lymphoreticular tumor mortality would enhance the analysis of the residual causes of death or comparison with other strains. High frequencies of amyloidosis in some strains (A and

C57L) compete with tumor mortality late in life and may obscure the occurrence of tumors at low doses. At the higher dose levels ($\geq$74 R/d), where hematopoietic factors are paramount, substantial genetic variance is apparent in MAS values, suggesting an important genetic control of bone marrow injury and repair processes.

GCM-12. The data from this study, the last major long-term study that preceded the JANUS program, were used in many articles that dealt with issues as diverse as gerontology and radiation safety standards in space flight. The major results are in Grahn (1970), Grahn et al. (1972a, 1978), and Sacher et al. (1970). Portions of the data are selectively used in Grahn (1969), Sacher (1970, 1976, 1977), and Norris et al. (1976). The study also provided an experimental baseline and methodological standards for the JANUS program.

Two findings from the GCM-12 data are of some importance in the field of occupational and population radiation safety. First, the data demonstrated unequivocally that most (>85%) radiation-induced excess risk of mortality at low doses could be attributed to neoplastic disease. In general terms, for the mouse, this would be for doses that induced less than 15% life shortening, or less than 6 R/d in this study. For humans, this would roughly extrapolate to less than 0.2 R/d.

Second, induced life shortening in days per roentgen is linearly and additively a function of accumulated dose and is independent of instantaneous dose rate up to daily doses of 12 R/d. Above this level, life shortening per roentgen begins to rise rapidly as increasing dose rate becomes a more dominant factor. For the mouse (and again independent of genotype), the parameter is 3.1 d lost per 100 R (90 rad, 0.9 Gy) of accumulated dose delivered at 12 R/d or less (Grahn et al. 1978). We conclude that this constant rate of loss of life is also almost entirely a function of excess deaths from neoplastic disease. This pattern should logically extrapolate down to the zero dose intercept.

The pathologic findings from the GCM-12 experiment permitted a more extensive analytical treatment than done for previous studies. Results of some of these analyses can be found in the previously cited reports. In brief terms, the following interpretations were developed.

1. Integrated lifetime lung tumor risk rises exponentially with daily dose level, but very little excess risk was seen at 0.3 R/d.

2. Ovarian tumors and cysts do not appear in excess of control before about 500 d of exposure. The response saturates at the same level for doses of 6 R/d and below, with an exception at 0.3 R/d where there may be a threshold (no excess) until nearly 1000 d of exposure.

3. A negative relationship exists between lymphoreticular tumors and renal lesions. The latter reflect the incidence of amyloid degeneration, and this lesion appears to suppress the appearance of reticular tissue neoplasms.

4. Lymphoreticular tumors involving the thymus are expressed rapidly (within the first several hundred days of exposure) at the high daily doses of 24, 32, and 43 R/d. The response is transitional at 12 R/d. From 6 R/d and below, non-thymic tumors are the general rule, and they increase in a total-dose and daily-dose dependent manner beyond the first year of exposure.

5. Liver tumors were not a major finding, though some excess was seen at doses below 6 R/d. The strains involved in the GCM-12 study are not characterized by a marked frequency of liver tumors.

6. Because of the high nonlinear excess of lymphoreticular tumors, much analysis was done on leukemia-decremented data. This procedure permitted more orderly analysis of lifetime risks and a more compatible baseline for interspecies extrapolation models.

7. Life-table analyses of all deaths with one or more tumors for the three inbreds and the BCF_1 supported the interpretation that the relative risk model is the better approach to long-term risk analysis. In these data, excess deaths with tumor varied by a factor of 4 to 5 among the four stocks, but differences in relative risk at low daily doses (≤ 12 R/d) averaged less than 1.0–1.5.

3.2.5 Adjunct Studies to GCM-4

The GCM-4 study was the centerpiece for a series of related studies. These other studies, all principally employing the LAF_1, the same caging and husbandry, and comparable radiation procedures, were identified as follows.

GCM-5. This was a sacrifice series. Mice were exposed to selected GCM-4 dose levels and were removed from the field at predetermined post-irradiation times and sacrificed for detailed hematologic and cell turnover studies. The data are not available in a card-image file.

GCM-9. This was the primary study of the dependence of response (MAS) on age at exposure to selected daily-dose levels. See Section 3.3 for further details.

GAM-2. This was a single-dose study employing 13 doses between 150 and 1100 R of γ rays. The study was integrated with GFM-1, which included, in addition to five single doses common to GAM-2, the use of the split-dose procedure with eight different intervals between the two doses. See Section 3.4 for further details.

3.3 EXPERIMENT GCM-9

3.3.1 Background

The possibility that the level of response could be influenced by age at exposure had not been extensively considered in the early studies. Most of the concern focused on the young adult as the individual to be protected in occupational situations. The Manhattan Project changed that viewpoint. The GCM-9 study addressed the question, "Does radiosensitivity vary significantly as a function of age at exposure or at initiation of protracted or periodic exposures?"

The file has been divided into two separate components identified as GCM-9A (Appendix A, Table A.6) and GCM-9B (Appendix A, Table A.7). GCM-9A contains the data for the pre-irradiation period for only LAF_1 mice. Component 9B contains the post-irradiation survival data for the LAF_1 plus the limited data from seven additional strains or hybrids.

3.3.2 Experimental Design

3.3.2.1 Radiation Variables

All exposure conditions were the same as those used in GCM-4. Dose levels of 170, 125, 97, 74, 43, and 12 R/d were used for exposures of the LAF_1, though the lowest dose was only employed at two age levels: 550 and 650 d. Table 8 presents the sample sizes by sex and dose for the LAF_1. Table 9 gives the sample sizes and exposure levels for the other mouse stocks employed and the general range of ages at entry. Locations in the radiation field were shared with animals in the GCM-4 and GCM-8 studies.

3.3.2.2 Animals

As noted, the LAF_1 hybrid was the principal animal employed (Table 8). Several of the regular inbred strains and the BCF_1 hybrid also were entered into the study, and these are identified in Table 9. The study continued sporadically into the early 1960s.

3.3.2.3 Animal Husbandry

Caging and other husbandry factors were identical to those in the GCM-4 and GCM-8 studies. After 1958, the regular inbreds and the BCF_1 were maintained, before irradiation, as in the GCM-12 experiment.

3.3.3 Data Recorded

Survival time and major pathologic findings at death were routinely recorded; however, the pathology data were never entered into the original card-image file and are now unavailable. All of the survival data are available in this file. The ages at entry for the LAF_1 are given in Table 8. A complete set of survival data is available for the six age groups between 250 and 800 d and the five daily doses between 43 and 170 R/d. The baseline responses at 100 d of age are the data from experiments GCM-4 and GCM-8. Change in MAS from start of irradiation, relative to the MAS for the 100-d age group, was used as the measure of change in radioresistance.

3.3.4 General Findings

One summary report was published by Sacher et al. (1958). With the 100-d GCM-4 values as the starting point, resistance (post-irradiation MAS) increased up to the 400-d age level for all dose groups except at 43 R/d. Beyond 400 d of age, resistance tended to diminish steadily, though the MAS remained above or at the 100-d value until 650–725 d of age. At 43 R/d, resistance tended to diminish for all age groups, though this was irregular at 250 and 400 d of age. Note that the baseline MAS at 43 R/d was 150 d, so an increased age at first exposure substantially increased the probability of the MAS being reduced simply by the normal dying-out process.

These data require complete reanalysis, and the nearly 1500 LAF_1 mice under observation before exposure (GCM-9A) should be considered as a control population supplementary to that from GCM-4. The data derived from the several inbreds and the BCF_1 are limited in terms of sample size and age range, but they may provide some added support to the general findings from the LAF_1 data.

3.4 EXPERIMENTS GAM-2 AND GFM-1

3.4.1 Background

The single-dose test (the exposure of young adult animals to brief high-dose-rate exposures in the acute lethal dose range) was the ultimate baseline study in the 1940s and 1950s. The derived $LD_{50/30}$ dose was an accepted standard for laboratory animal studies. It tested hematopoietic system response to acute injury in clear and unequivocal terms. The response was self-limiting (30 d in most mammals and 60 d in humans), and survivors moved into a chronic injury mode within 60 d (at least in the mouse), when lymphoreticular neoplasms began to appear. The similarities between man and mouse were abundant.

Magnitude of injury and time to recovery of the hematopoietic system were critical parameters for therapeutic intervention and protection procedures. The use of paired-dose, split-dose, or protracted-dose procedures to estimate the injury and repair parameters was

common. We chose the split-dose method (i.e., a given single dose would be divided into two equal portions, and the time between the two exposures would be varied so as to provide a basis for estimating recovery rates).

3.4.2 Experimental Design

3.4.2.1 Radiation Variables

The same basic radiation procedures were used for these two studies as for GCM-4. Single doses of ^{60}Co γ rays were delivered over a period of approximately 1 h in the high-level γ-ray room. Dose was controlled by varying the distance from a nominally 1200-Ci source. Animals were exposed in their cylindrical home cages. GAM-2 (Appendix A, Table A.8) used 13 single doses: 150, 300, 450, 600, 700, 750, 800, 850, 900, 950, 1000, 1050, and 1100 R (in air). GFM-1 (Table A.8) used five doses: 150, 300, 450, 600, and 750 R. The doses of 450 and 750 were used for the split-dose test, which employed nine intervals between the two half-doses of 225 and 375 R. The intervals, in d, were 0 (a single dose), 0.125 (3 h), 0.4 (about 10 h), 1, 3, 5, 7, 14, and 28. To randomize any potential influence of age differences at time of exposure for the longer intervals, three different starting times were used: day 0 (100 d of age), day 14, and day 28. Table 10 gives the number of animals exposed at each single-dose and split-dose interval.

3.4.2.2 Animals

These two conjoint studies were restricted to the LAF_1, and entries into the experiment were drawn from the regular shipments on a generally random basis. GAM-2 required 6 replications, and GFM-1 was done in 10 replications. Entry age was the nominal 100 d.

3.4.2.3 Animal Husbandry

Animal care procedures were the same as for GCM-4; and after irradiation, the animals were held for long-term observation in one of the regular animal holding rooms.

3.4.3 Data Recorded

As in the other concurrent studies, survival time and major pathologic findings at death were routinely recorded. All of the pathology data are in the file. Thus, complete survival and pathology data are available on the LAF_1 for GCM-4, GAM-2, and GFM-1, which were done concurrently. A common control (that for GCM-4) was employed for these three studies plus that portion of the GCM-9 (component 9B) study that used the LAF_1.

3.4.4 General Findings

The $LD_{50/30}$ value for the two sexes combined was about 975 R, compared with 630 R for 200-kVp x-rays. Life shortening induced by the single γ-ray exposures was about 18 d/100 R for males and 25 d/100 R for females. These values reflect a relative biological effectiveness for ^{60}Co γ rays of about 0.6–0.7 compared with 200-kVp x-rays. The XAM-3 experiment showed a 28-d life shortening for males exposed to midlethal single doses.

The split-dose procedure had no significant influence on either overall life shortening or on the incidence of lymphoreticular tumors, principally thymic lymphomas. The two dose levels (450 and 750 R) were differentiated and dose dependent in their responses; but within each dose level, the nine different intervals between dose increments did not influence the two noted endpoints. The two dose increments acted additively (Grahn and Sacher 1968). Portions of these data were used by Grahn et al. (1972a) in a comparative analysis of the effects of single versus protracted exposures. An important finding was that for exposure levels at or below the LD_{50}, excess mortality among survivors of the acute syndrome was attributable to neoplastic disease, as was seen for mice exposed to low daily doses of γ rays. For the LAF_1 exposed to single doses when compared with those exposed to low daily doses, a protraction factor of about 5 was seen for both life shortening and excess mortality from lymphoreticular tumors. No specific results have been reported for other neoplastic or degenerative diseases.

3.5 EXPERIMENT XAM-6

3.5.1 Background

This was a follow-on experiment to XAM-3, which had studied acute and chronic mortality following single doses of 200-kVp x-rays limited to the acute lethal dose range (about 0.8–1.2 of an LD_{50} dose). XAM-6 (Appendix A, Table A.9) studied the response to sublethal single doses, to bring the dose-response curve for life shortening into the low-dose range. The purpose was to improve the estimation of the regression coefficient at sublethal doses and to provide a broad, multistrain database for extrapolation to exposures below 100 R.

3.5.2 Experimental Design

3.5.2.1 Radiation Variables

All exposure procedures, the dosimetry, and the radiation source were the same as those used in experiment XAM-3. Exposure levels were 0, 100 R, and a level equal to 0.6 of the LD_{50} for each of four inbred strains and the BCF_1. The specific levels for the different strains were BALB/c, 300 R; A/He, 335 R; C3Hf/He, 355 R; C57BL/6, 380 R; $B6CF_1$, 395 R.

These levels were based on LD_{50} values published in Grahn and Hamilton (1957) and Grahn (1958a).

3.5.2.2 Animals

As noted above, the mice chosen for this study were the inbred strains A/He, BALB/c, C3Hf/He, and C57BL/6, and the F_1 hybrid $B6CF_1$. Strain A/He was used in place of the A/Jax strain because the latter was committed to the GCM-12 experiment, and the A strains were not prolific breeders. The two strains were essentially identical in their responses (Grahn and Hamilton 1957). Equal numbers of both sexes were used at an entry age of approximately 85 d. Table 11 provides the strain by dose matrix and sample sizes.

3.5.2.3 Animal Husbandry

The animals were housed in the standard plastic cage used for mice (12 per cage). Food and water were always available. After irradiation, the cages were moved to a regular animal holding room in the BIM animal facilities. They were kept in the same cage into which they had been weaned at about 30 d of age. The 12 mice were randomly assigned to the three dose levels of 0, 100 R, and 0.6 LD_{50}, so there were four mice per dose per cage. No unusual husbandry methods were used.

3.5.3 Data Recorded

The mice entering the XAM-6 study were under pre-irradiation surveillance from the time of weaning, as they were part of the management procedure described in the Pre-experimental Stock Cage Records (Appendix A, Table A.11). Entries began in September 1958, and finished in June 1961. Survival time and major pathologic findings at death were routinely recorded. Pathology records are not complete, but the available record is in the file.

3.5.4 General Findings

The results of this study were never completely analyzed or reported. Between three and four dozen mice were used for each sex by strain by dose (2 × 5 × 3) subgroup, except for the BALB/c where only about 18 mice were entered per subgroup (Table 11). A disturbing feature was that, except for the BALB/c female, every control group had a shorter MAS from time of entry than that observed in the XAM-3 study. The deficit in MAS values ranged from about 20 to 180 d and averaged about 80 d, or 15% of the average control MAS. All comparisons, therefore, had to be internal and could not use the equivalent of colony controls.

All female groups showed a substantial life-shortening effect at 100 R, averaging about 0.8 d/R. This life shortening was accompanied by a twofold to tenfold increase in the frequency of ovarian tumors and cysts. Between 100 R and the 0.6 LD_{50} dose, life shortening was further increased but by only one-fifth the amount per roentgen as seen between 0 and

100 R. This abrupt increase in life shortening at 100 R and its relationship to the metabolic disruptions associated with induced ovarian dysfunction had been seen and discussed by Sacher (1956a) and Grahn (1960) in several separate experiments.

The males showed no life-shortening response at 100 R, except for a loss of 7 d for the BCF_1 (1% of the control MAS). The inbred strains all had slight increases in MAS at 100 R over their control, but the values ranged from only 9 to 19 d; none was statistically significant. The loss between 100 R and the 0.6 LD_{50} dose was more typical for males, a loss of 0.3 d/R (Grahn 1960; Grahn and Sacher 1968).

Regarding tumor frequency, there were, as noted, sharp increases in the frequency of ovarian tumors at 100 R. Depending on the specific strain sensitivities, there was some increase in frequency of lymphoreticular, pulmonary, and liver tumors. There was a generally consistent, though small, increase in the frequency of "all other" tumors (involving the mammary glands, kidneys, adrenal glands, pituitary, and connective tissues). Thus, in spite of minimal or no life shortening, some tumor occurrences were increased slightly at 100 R. The data at the 0.6 LD_{50} dose need to be analyzed with life-table statistics to correct for age variation in time of tumor occurrence as a result of the higher exposure level and greater life shortening.

3.6 EXPERIMENT XAM-7

3.6.1 Background

This study was also a follow-on to the XAM-3 experiment, and it also tied into the XAM-6 study. XAM-7 (Appendix A, Table A.10) evaluated the effect of age at time of exposure to single doses of 200-kVp x-rays. The age variable was studied in the GCM-9 experiment by using daily exposures to γ rays, but the influence of age on the response to single doses was not a part of the earlier studies. Three ages were used: 40, 300, and 500 d at time of exposure.

3.6.2 Experimental Design

3.6.2.1 Radiation Variables

Exposure procedures, dosimetry, and radiation source were identical to those used for the XAM-3 and XAM-6 studies. Two exposure levels were used, 100 and 450 R, in addition to the control. The 100-R level was also used in XAM-6 where age at exposure was approximately 85 d.

3.6.2.2 Animals

Three inbred strains were employed: A/He, C3Hf/He, and C57BL/6. Most of the data are from the A and C3Hf strains. Table 12 gives the number of animals entered into the study at each age and dose level for the three strains.

Generally, equal numbers of both sexes were used, though intervening mortality before the time of exposure made it impossible to maintain equality. Initially, the effort focused on the 0 vs. 100-R comparisons, and the 450-R exposures were entered during the second half of the period over which the 51 replications were entered. The first replication was entered in April 1960 and the last in August 1964.

Although this was not a large experiment, the numbers in Table 12 underestimate what might be considered the total entries, because every cage that ultimately entered the study can be considered as a "control" from weaning (about 30 d of age) until actual entry.

3.6.2.3 Animal Husbandry

There were no unusual husbandry procedures employed. The animals came from the stock holdings. Cages of 12 were set up at weaning and would be assigned into this or other experiments at the appropriate age. The standard plastic "mouse" cage was used, and food and water were always available. Cages were cleaned weekly. After irradiation, the cages were moved to a standard animal-holding room in the BIM animal facilities. In this study, the 12 mice per cage were always divided randomly into four controls and eight irradiated, either 100- or 450-R, but not both, exposure levels. When fewer than 12 survived to the age at entry, the survivors were assigned at the ratio of one control to two irradiated.

3.6.3 Data Recorded

As noted, the animals were under observation from the time of weaning until entry into the experiment, as a control population, and this continued into the experimental period. Survival time and major pathologic findings at death were recorded, but the pathology file record is incomplete.

3.6.4 General Findings

As for the XAM-6 study, the results of XAM-7 were never fully analyzed or published. Even now, a full analysis will require the pre-irradiation data to be merged into this file from the Pre-experimental Stock Cage Record (Appendix A, Table A.11) so the mean after-expectations of life can be calculated more precisely. Intervening mortality was about 23% in strain A/He before the 500-d time of entry. It was only 7% in the C3Hf/He.

Strain C3Hf/He provided a full matrix of ages, doses, and sexes. Life shortening averaged 34 d/100 R for both sexes exposed at 40 d and 9 d/100 R at 500 d, when measured

across the three dose levels. For both sexes at 300 d of age, the average loss of life was 31 d/100 R at 450 R; but at 100 R, the average MAS increased by 28 d. In other words, at 300 d the response was typical for the young adult.

Ovarian dysfunction may not have been an important factor in this study, as there was little difference between the two sexes. For the older females, this may have been due to the lack of a sufficient latency period when the entry ages are as late as 300 and 500 d, in contrast to responses at about 100 d (see XAM-3 and XAM-6). At 450 R, both sexes of strain A/He had mean losses of life between 9 and 19 d/100 R at 300 and 500 d of age at exposure. At 100 R, both sexes had small increases in MAS at 300 d and small losses in MAS at 500 d.

In summary, for both strains and sexes, there was no consistent response to the single dose of 100 R, but there was a consistent life-shortening response to 450 R at all ages at exposure. This again indicates the existence of a nonlinear dose-response equation over the 0 to 100 to 450 R range. This type of nonlinear response was also seen for the males in the XAM-6 study. In the absence of any summary of the pathologic findings, we hesitate to argue for the existence of a threshold dose, even for the advanced ages of exposure. As was seen in XAM-6, there can be subtle increases in the occurrence of neoplastic disease even in the absence of a clear life-shortening effect.

4 RECORDS MANAGEMENT

4.1 INTRODUCTION

The description of the XAM-3 study noted that we maintained a number of inbred mouse strains, outcross generations, and genetic marker stocks of mice in the BIM animal facilities. These are all identified in Appendix B. Procedures were established in mid 1953 for maintaining the records of the breeding colony and of the experiments in a permanent, machine-readable form. At that time, the available machine calculation capability was primarily through the use of IBM accounting equipment in the ANL Accounting Department. All records were therefore designed to conform to the requirement of easy transfer to IBM cards for storage and analysis. Cards were printed specifically to accommodate our needs, which were diverse. Some final card-image records, for example, required the collation and calculation of data from two or three basic data cards. As computers evolved, the card files were converted to magnetic tape files; these, in turn, have been transferred to laser-read hard disk files. Data tapes were regularly replicated and were stored in a controlled-temperature, fireproof vault. Thus, 40-year-old records have been well preserved.

The basic animal records in the present database consist of three files. The first two are the Mating Record (Appendix A, Table A.12) and the Litter Record (Appendix A, Table A.13). Both records run from early 1953 to late 1969, when the records were stopped because of funding constraints. The original written mating records and the pedigree books are still in the archives in Building 202, ANL. Thus, on an as-needed basis, these two files could be brought up to the date of the final dissolution of the colony in October 1987.

The third file is a more limited record of the mice from six inbred strains and the B6CF$_1$ hybrid. This is the Pre-experimental Stock Cage Record (Appendix A, Table A.11), which records the history of the mice from weaning until they were assigned to an experiment, to a mating, or were discarded. This file runs from mid 1958 to late 1969 and contains a record on over 32,000 animals.

Although the data in these three files can be easily accessed for statistical analyses, which has been done on a selective basis, the files are principally stock records and not an integral part of any specific experiment. The files are described in statements that are not in the format of preceding descriptions of individual experiments. Some indication of the results of analyses that have been or could be done will be presented, however.

4.2 RECORD DESCRIPTIONS

4.2.1 Mating Record

The Mating Record contains the identification data for all matings that maintained the inbred strains, outcrosses, and genetic marker stocks. The record gives the strain of both

the sire and the dam separately to accommodate outcross matings. Other pertinent features of the record are in Table A.12. It is important to note that the dates of mating and of discard are both given, along with the reason for discard. These items could be critical in any study of reproductive performance.

The Mating Record can be cross-referenced to the Litter Record, which contains data on litters born between May 1953 and October 1969. Since a mating will appear in the litter record only if it has produced at least one litter, the frequency of sterile or otherwise nonproductive matings must be obtained by collating the mating and litter records for the strains of interest. A full match of the two records appears to exist for all pertinent mating numbers through 5331 (all matings set up through April 1969). The litter record is incomplete for the balance of the mating record. The handwritten mating record continues to mating number 8396, which was discarded in October 1987.

4.2.2 Litter Record

This Litter Record (Appendix A, Table A.13) may well be unique in the history and annals of mouse genetics. The uniqueness rests on the fact that all newborn mice were sexed at birth, or within several days of birth, and daily monitoring created a record of deaths by sex and age. This record was then summarized for the permanent card-image record into three age intervals: 0–5, 6–15, and 16 d to weaning (which was generally at 25–30 d of age). The record includes data on over 21,000 litters.

The information in this file includes basic information on the litter (strain, dam, sire, mating number, and parity), the number born and date born, and the number weaned and date weaned. The number born and weaned by sex and the survival record by age and sex are also included, along with the age of the dam on the date of birth of the litter. Some gross pathologic examinations would have been done as required to maintain proper surveillance for infectious or nutritional problems. Such information is not in the file, however.

We note here that the existence of this record was principally due to the interest, diligence, and skill of K.F. Hamilton (later, K.F.H. Allen), who worked with the colony and the principal investigator, D. Grahn, from 1953 until 1974, and with the JANUS Program from 1971 until her retirement in 1980. She came to Argonne from the Jackson Laboratory in 1949, where she had been employed since graduation from Mt. Holyoke College in 1945.

To facilitate the use of the mating record and litter record files, we have combined the two files into an additional file for the archive — Combined Mating and Litter Records 1953–1969 (Appendix A, Table A.14). The Mating Record has been entered into the Litter Record, and the two have been made compatible with regard to the strain designation for both sire and dam. The Mating Record is entered at the beginning of the specific mating's Litter Record, if any litters were produced, and is listed with a parity of 00. The three dates in the Mating Record (dam's birth date, mating date, and discard date) and reason for discard are added to the Litter Record in additional columns so that this file goes beyond the usual 80-column card-image format.

The combined file simplifies the assessment of the reproductive performance of a strain because all nonproductive matings are listed with productive matings. The availability of the discard date and reason for discard provides a definitive duration for each productive mating. The separate files are kept in the archive for basic record keeping and for easy use when the larger combined file would not be needed.

The litter record has been used periodically to evaluate the breeding performance of the different strains and hybrids and to measure whether there had been any inadvertent outcrossing or spontaneous genetic change that might have altered the characteristics of a strain. Outcrossing is easy to detect simply by evaluating litter size and other variables such as preweaning mortality. According to analyses done through the late 1960s, there had been no changes in the reproductive characteristics of the primary inbred strains.

Some of the results of these analyses were published in a National Institutes of Health document that summarized discussions at a workshop on model systems for the study of aging (Grahn 1972). Previously, a comparison of one inbred (BALB/c), one outcross (BC/CBF$_2$), and the U.S. population demonstrated the similarity of neonatal, infant, and childhood death rates for the two species (Grahn 1963). A few general findings can be presented here.

1. Most of the early mortality occurs in the first five days after birth (generally equivalent to neonatal deaths in humans). There is little sex difference in mortality, but there is significant variation among strains. The neonatal death rate increases with maternal age (and parity), but death rates between 6 and 30 d seem to be less influenced by age of dam or strain. Neonatal mortality is highest in small litters (less than the mean for the strain) and drops to its minimum values at litter sizes greater than the mean.

2. Mean litter size, which varies significantly among strains, rises in some strains to a peak value at maternal ages of 100 to 200 d. Thereafter, litter size drops rapidly with age. In some strains, the A strains for example, the maximum mean litter size occurs in first litters and drops steadily with increasing age and parity.

3. Interval between litters doubles from a mean value of about 25 to 50 d, as maternal age rises from 50 to 400 d. Between 100 and 300 d, the interval remains quite steady; however, this record is for single-pair matings with the sire left in the cage at all times (all matings for production purposes and for maintenance of the strains were single-pair, full-sib matings).

4. There was a remarkable degree of uniformity or invariance within strains for such measures as neonatal mortality and mean litter size when viewed across calendar time from 1953 to 1967. Strain

differences persist but with little variance related to calendar time or season of the year.

5. By summarizing across 14 inbred strains and four genetic marker stocks, the average mortality rate from birth to day 5 varies between 0.033 and 0.175/d. The factor of 5 (0.175/0.033) has a large genetic component, but a proper analysis would have to control the influence of parity, litter size, maternal age, and possibly litter interval. These are, unfortunately, concomitant and confounded variables. The mortality rates per day between 6 and 15 d continue to show a range among the genotypes of about 5 to 1, but the observed rates drop to 0.002–0.009/d. Between 16 and 30 d, the rates vary from 0.001 to 0.004/d. By about 100 d of age, the mortality rate for most strains has dropped to 2×10^{-4}/d or less. Hybrid and outcross generations have much lower death rates from birth and on. They may start at about 0.02/d between birth and five days and drop to 1×10^{-5}/d at 100 d. An inventory of the number of litters in this file for each of the inbred strains, marker stocks, and hybrid generations is given in Table 13. Of the nearly 22,000 individual litter records, most (64%) involve the six principal inbreds and the $B6CF_1$. Thirteen percent concern the nine ISU strains, 8% involve the four ISU marker stocks, 7% concern the backcross series from the $B6CF_1$ to the BALB/c parent, and the remainder involve a range of outcross or mutant stocks.

4.3 PRE-EXPERIMENTAL STOCK CAGE RECORD

As experiments GCM-4 and GCM-8 neared completion, a decision was made in 1957, on the basis of the accruing data, to discontinue the use of the LAF_1 as the principal mouse for the long-term studies. It was less expensive at that time to produce our own animals, and the data on the $B6CF_1$ showed it to be a favorable replacement for the LAF_1. We also agreed to supplement the future studies by using additional inbred strains with the two parent lines BALB/c and C57BL/6 being obvious first choices.

It was decided that the six primary inbreds (A/He, A/Jax, BALB/c, C3Hf/He, C57BL/6, C57L) and the F_1 hybrid from the cross of the C57BL/6 female with the BALB/c male (the $B6CF_1$) would make up a standardized pre-experimental stock colony. This accumulation of stock mice began in June 1958. It continued until November 1969, when preparations for the JANUS Program precluded the need. Only $B6CF_1$ mice were used for the JANUS studies, and they were all produced at the BIM animal facilities from caesarean-derived, barrier-sustained BALB/c and C57BL/6 inbred stocks that were obtained from D. Grahn's holdings in BIM. Continuity of animal backgrounds was thus assured. No experimental work was done in the JANUS program with the two inbred parent lines, however.

Beginning in mid-1958, the six inbred strains and the B6CF$_1$ were routinely weaned into stock cages. These were the standard plastic cages used for housing mice. The cage dimensions (outside) were 8 × 18 × 5.5 in. (20.3 × 45.7 × 14 cm) (width, depth, height). The inside (floor) dimensions were 7 × 16 × 5 in. (17.8 × 40.6 × 12.7 cm). A stainless-steel top contained a food bin and held an 8-oz (0.24-L) water bottle. The stock cage provided ample space for 12 mice. This number was chosen to simplify the transfer of animals from their stock status to any experimental status that employed the small, cylindrical γ-ray-room cage holding three mice each. To ensure continuity of record, the stock cage number was carried into any experimental protocol. If four small cages of three were to be used, a single digit subcage number was added.

The contents of this file are given in Appendix A, Table A.11. The usual basic identifiers are present (strain, sex, animal number, mating number, and parity) plus the birth date and the exit date. The exit date is the actual date the animal was entered into an experiment, was placed in mating, was discarded, died, or turned up missing (see exit codes). A survival time is given, which in this record is the actual age of the mouse on the day it left the stock-cage status for any of the reasons noted above.

If a mouse died before exiting to another use, pathology codes may be in the record, though the record is incomplete.

As time passed, there were fewer demands for animals. By 1965 and on, the majority were being discarded. Nevertheless, the record was completed to the date of discard, including the survival time (age), which was usually at 100 or more days of age.

This database has had only minimal use and that involved the estimation of life-table values for the B6CF$_1$ between 30 and 100 d of age (Grahn 1970; Sacher et al. 1970). Such estimates may have also been made for some of the inbred strains, but there is no clear record. The post-weaning life table for juvenile and young adult mice can be readily generated from this file, but the removal of mice for breeding purposes, discard, or other uses must be carefully censored.

Though pathology data are not complete, there are enough to indicate what was occurring during this age period when death rates are at or approaching their minimum. For the B6CF$_1$, this rate is about 1.3 × 10^{-5}/mouse-day at 100 d of age. The first occurrence of spontaneous lymphoreticular tumors can be identified in these data as well. A thymic lymphoma occurred in a B6CF$_1$ male at 47 d of age and at 69 d of age in a C57BL/6 male. In other strains, early tumors begin to appear by 90–100 d.

The possibilities for analysis of the juvenile and young adult life table can be judged from Table 14. Altogether, there are about 2.25 × 10^6 mouse-days at risk, though the number per sex and strain varies from a low of about 93,000 to a high of about 340,000, assuming each mouse was at risk for 70 d.

This file also can be merged or linked to the Litter Record (Appendix A, Table A.13) and/or to any experimental survival record such as GCM-12, for example. The common

identifiers are strain, mating number, and parity for all files. The Litter Record and the Pre-experimental Stock Record also have the date of birth in the file. The experimental and pre-experimental records have a common cage number as well as animal number within strain. It is thus possible to link, for example, the late-life performance of any animal or group of animals to the early post-natal history of the siblings (littermates and non-littermates).

5 REFERENCES

Brues, A.M., and G.A. Sacher, 1952, Analysis of mammalian radiation injury and lethality, in *Symposium on Radiobiology* (J.J. Nickson, editor), J. Wiley & Sons, New York, pp. 441–465.

Festing, M.F.W., 1975, *International Index of Laboratory Animals* (M.F.W. Festing, editor), Medical Research Council, Laboratory Animals Centre, Carshalton, U.K.

Gowen, J.W., 1963, Genetics of infectious diseases, in *Methodology in Mammalian Genetics* (W.J. Burdette, editor), Holden-Day, Inc., San Francisco, pp. 383–404.

Grahn, D., 1958a, Acute radiation response of mice from a cross between radiosensitive and radioresistant strains, *Genetics* 43:835–843.

Grahn, D., 1958b, The genetic factor in acute and chronic radiation toxicity, in *Proceedings of the 2nd United Nations International Conference on Peaceful Uses of Atomic Energy*, vol. 22, United Nations, New York, pp. 394–399.

Grahn, D., 1960, Genetic control of physiological processes: the genetics of radiation toxicity in animals, in *Radioisotopes in the Biosphere* (R.S. Caldecott and L.A. Snyder, editors), University of Minnesota Press, Minneapolis, pp. 181–200.

Grahn, D., 1963, Mammalian radiation genetics, in *Methodology in Mammalian Genetics* (W.J. Burdette, editor), Holden-Day, Inc., San Francisco, pp. 127–155.

Grahn, D., 1969, Late effects of external irradiations in animals and the prediction of low-dose effects, in *Biological Implications of the Nuclear Age*, U.S. Atomic Energy Commission, AEC Symposium Series 16, CONF 690303, Washington, D.C., pp. 269–281.

Grahn, D., 1970, Biological effects of protracted low dose radiation exposure of man and animals, in *Late Effects of Radiation* (R.J.M. Fry, D. Grahn, M.L. Griem, and J.H. Rust, editors), Taylor and Francis, Ltd., London, pp. 101–136.

Grahn, D., 1972, Data collection and genetic analysis in the selection and study of rodent model systems in aging, in *Development of the Rodent as a Model System of Aging* (D.C. Gibson, editor), National Institute of Child Health and Human Development, DHEW pub. no. (NIH)72-121, Bethesda, pp. 55–65.

Grahn, D., and K.F. Hamilton, 1957, Genetic variation in the acute lethal response of four inbred mouse strains to whole body x-irradiation, *Genetics* 42:189–198.

Grahn, D., and G.A. Sacher, 1968, Fractionation and protraction factors and the late effects of radiation in small mammals, in *Dose Rate in Mammalian Radiation Biology*, U.S. Atomic Energy Commission report CONF-680410, pp. 2.10–2.27.

Grahn, D., K.F. Hamilton, and W. Leslie, 1962, Analysis of linkage between qualitative and quantitative traits in mice (abstract), *Genetics* 47:955–956.

Grahn, D., K.F. Hamilton, and W. Leslie, 1964, The genetic analysis of radiation sensitivity, in *Annual Report 1964, Biological and Medical Research Division*, Argonne National Laboratory report ANL-6971, pp. 125–128.

Grahn, D., R.J.M. Fry, and R.A. Lea, 1972a, Analysis of survival and cause of death statistics for mice under single and duration-of-life gamma irradiation. *Life Sciences and Space Research* X:175–186.

Grahn, D., E.J. Ainsworth, F.S. Williamson, and R.J.M. Fry, 1972b, A program to study fission neutron-induced chronic injury in cells, tissues and animal populations, utilizing the JANUS reactor of the Argonne National Laboratory, in *Radiobiological Applications of Neutron Irradiation*, International Atomic Energy Agency, Vienna, pp. 211–228.

Grahn, D., G.A. Sacher, R.A. Lea, R.J.M. Fry, and J.H. Rust, 1978, Analytical approaches and interpretations of data on time, rate and cause of death of mice exposed to external gamma irradiation, in *Late Biological Effects of Ionizing Radiation*, International Atomic Energy Agency, Vienna, pp. 43–58.

Green, E.L., 1966, *Biology of the Laboratory Mouse*, 2nd ed. (E.L. Green, editor). McGraw-Hill Book Co., New York.

Green, M.C., 1966, Mutant genes and linkages, in *Biology of the Laboratory Mouse*, 2nd Edition (E.L. Green, editor), McGraw-Hill Book Co., New York, pp. 87–150.

Jay, G.E., Jr., 1963, Genetic strains and stocks, in *Methodology in Mammalian Genetics*, (W.J. Burdette, editor), Holden-Day, Inc., San Francisco, pp. 83–123.

Lesher, S., G.A. Sacher, D. Grahn, K. Hamilton, and A. Sallese, 1965, Survival of mice under duration-of-life exposure to gamma rays. II. Pathologic effects. *Radiation Research* 24:239–277.

Lorenz, E., 1950, Some biologic effects of long continued irradiation, *American Journal of Roentgenology and Radium Therapy* LXIII:176–185.

Lorenz, E., W.E. Heston, A.B. Eschenbrenner, and M.K. Deringer, 1947, Biological studies in the tolerance range, *Radiology* 49:274–285.

Lorenz, E., A.B. Eschenbrenner, W.E. Heston, and D. Uphoff, 1951, Mammary tumor incidence in female C3Hb mice following long-continued gamma irradiation, *Journal of the National Cancer Institute* 11:947–965.

Lorenz, E., L.O. Jacobson, W.E. Heston, M. Shimkin, A.B. Eschenbrenner, M.K. Deringer, J. Doniger, and R. Schweisthal, 1954, Effects of long-continued total-body gamma irradiation on mice, guinea pigs, and rabbits. III. Effects on life span, weight, blood picture and carcinogenesis and the role of the intensity of radiation, in *Biological Effects of External X and Gamma Radiation*, Part I (R.E. Zirkle, editor), National Nuclear Energy Series IV-22B, McGraw-Hill Book Co., New York, pp. 24–148.

Lorenz, E., J.W. Hollcroft, E. Miller, C.C. Congdon, and R. Schweisthal, 1955, Long-term effects of acute and chronic irradiation in mice. I. Survival and tumor incidence following chronic irradiation of 0.11 R per day, *Journal of the National Cancer Institute* 15:1049–1058.

Norris, W.P., S.A. Tyler, and G.A. Sacher, 1976, An interspecies comparison of responses of mice and dogs to continuous ^{60}Co γ-irradiation, in *Proceedings of the International Symposium on Biological and Environmental Effects of Low Level Radiation*, vol. I, International Atomic Energy Agency, Vienna, pp. 147–156.

Sacher, G.A., 1956a, On the statistical nature of mortality, with special reference to chronic radiation mortality, *Radiology* 67:250–258.

Sacher, G.A., 1956b, Survival of mice under duration-of-life exposure to x-rays at various rates, in *Biological Effects of External X and Gamma Radiation*, part 2 (R.E. Zirkle, editor), National Nuclear Energy Series IV-22B, McGraw-Hill Book Co., New York, pp. 435–463 [originally issued as Manhattan District Report CH-3900, Metallurgical Laboratory, University of Chicago, April 1950).

Sacher, G.A., 1970, Models from radiation toxicity data, in *Late Effects of Radiation* (R.J.M. Fry, D. Grahn, M.L. Griem, and J.H. Rust, editors), Taylor and Francis, Ltd., London, pp. 233–244.

Sacher, G.A., 1976, Dose, dose rate, radiation quality, and host factors for radiation-induced life shortening, in *Aging, Carcinogenesis, and Radiation Biology* (K.C. Smith, editor), Plenum Press Corp., New York, pp. 493–517.

Sacher, G.A., 1977, Life table modification and life prolongation, in *Handbook of the Biology of Aging* (C.E. Finch and L. Hayflick, editors), Von Nostrand Reinhold Co., New York, pp. 582–638.

Sacher, G.A., and D. Grahn, 1964, Survival of mice under duration-of-life exposure to gamma rays. I. The dosage-survival relation and the lethality function, *Journal of the National Cancer Institute* 32:277–321.

Sacher, G.A., D. Grahn, and S. Lesher, 1958, The dependence of acute and subacute radiosensitivity on age in the LAF$_1$ mouse, *Biological and Medical Research Division Semi-Annual Report*, Argonne National Laboratory report ANL-5916, pp. 84–86.

Sacher, G.A., and D. Grahn, R.J.M. Fry, and J.H. Rust, 1970, Epidemiological and cellular effects of chronic radiation exposure: a search for relationship, in *Proceedings of the First European Symposium on Late Effects of Radiation*, Comitato Nazionale per l'Energia Nucleare, Roma, pp. 15–38.

Schott, R.G., 1932, The inheritance of resistance to *Salmonella aertrycke* in various strains of mice, *Genetics* 17:203–229.

Sinclair, W.K., 1963, Absorbed dose in biological specimens irradiated externally with cobalt-60 gamma radiation, *Radiation Research* 20:288–297.

Staats, J., 1968, Standardized nomenclature for inbred strains of mice: fourth listing, *Cancer Research* 28:391–240.

Staats, J., 1980, Standardized nomenclature for inbred strains of mice: seventh listing. *Cancer Research* 40:2083–2128.

Upton, A.C., A.W. Kimball, J. Furth, K.W. Christenberry, and W.H. Benedict, 1960, Some delayed effects of atomic-bomb radiations in mice, *Cancer Research* 20:1–60.

Webster, L.T., 1937, Inheritance of resistance of mice to enteric bacterial and neurotropic virus infections, *Journal of Experimental Medicine* 57:261–286.

TABLE 1 Mean After-Survival Values for the NCI Initial Low-Dose Study

Dose (R/d)	Sex	n	Age at Entry (d)	MAS ± SE (d)
0	♂	29	60	724.6 ± 33.8
	♀	30	61	703.6 ± 32.8
	Σ	59	60	713.9 ± 23.4
0.11	♂	24	53	738.7 ± 38.8
	♀	23	51	747.5 ± 42.3
	Σ	47	52	743.0 ± 28.3
1.1	♂	24	57	662.5 ± 31.9
	♀	24	66	705.4 ± 24.8
	Σ	48	62	684.0 ± 20.2
2.2	♂	23	65	638.7 ± 24.1
	♀	24	74	622.5 ± 32.6
	Σ	47	70	630.5 ± 20.2
4.4	♂	24	69	593.7 ± 23.1
	♀	24	78	586.0 ± 21.8
	Σ	48	74	589.9 ± 15.7
8.8	♂	21	85	469.6 ± 24.3
	♀	24	86	505.6 ± 19.4
	Σ	45	86	488.8 ± 15.4

**TABLE 2 Mean After-Survival Values for the
NCI Low-Dose Follow-Up Study**

Dose (R/d)	Sex	n	Age at Entry (d)	MAS ± SE (d)
0	♂	110	31	652.5 ± 14.3
	♀	116	31	771.9 ± 16.1
	Σ	226	31	713.8 ± 11.5
0.11	♂ '	111	31	752.6 ± 14.0
	♀	120	31	789.6 ± 17.7
	Σ	223	31	771.8 ± 11.4

TABLE 3 Distribution of Strains and Hybrids across the Single X-Ray Exposures Used in the XAM-3 Experiment

Strain code →

Dose ↓ (R)	01	02	03	04	05	06	07	08	12	14	15	16, 17, 18	19, 20	21	22, 23	24, 25	26, 27	28, 29, 30	31, 32, 33	34, 35	44	47	48	49	50	51	52	53	54	55	56	57	58	61	62
400																																		X	
420				X																															
435				X																															
450				X					X							X							X						X					X	
470				●																															
475				●																															
480			X	X					X																										
490				●																															
495		X		X							X																								
500												X	X	X	X	X	X	X					X						X			X		X	
510		X	X	X					X													X													
520																			X	X															
525		X	X	X	X								X	X			X																		
530				●																															
540		X	X	X	X				X																										
550		●	●	●		●						X			X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
555		X	X	X	X		X																												
565				O																															
570	X	X	X	X	X	X			X																										
575				O								X	X	X	X		X		X																X
580																			X	X															
585	X	X	X	X	X	X	X	X																											
590		●	●	●																				X											
600	X	X	X	X	X	X		●		X		X		X		X	X	X			X	X	X	X	X	X	X	X	X		X	X	X		
611				O																															

44

TABLE 3 (Cont.)

Dose (R)	01	02	0C	04	05	06	07	08	12	14	15	16, 17, 18	19, 20	21	22, 23	24, 25	26, 27	28, 29, 30	31, 32, 33	34, 35	44	47	48	49	50	51	52	53	54	55	56	57	58	61	62
615	X	X	X		X	X	X	X																												
625			O			●					X	X					X			X																X
630	X	X	X	●	X	X		X												X																
635						O																														
645	X	X	X	●	X	X	X	X																												
650					●	●		●			X	X	X	X	X	X						X	X	X	X	X	X	X	X	X	X	X	X	X	X
660	X	X			X	X	X																													
670				●	●	●														X																
675	X	●			X	X	X		X											X																X
690	X					X		X																												
700		●	●	●	●	●	●	●					X									X	X	X	X	X	X	X	X	X	X		X	X	X
705	X						X	X	X																											
710					●	●																														
720	X							X																												
725						●		●			X	X	X							X																
735	X	●	●			●	X	X																												
750						●	X	X							X							X		X	X	X	X	X		X	X		X	X	
770						●																														
775								●																												
800												X										X		X	X	X		X		X			X		
850																						X													
900								●																												

X = Principal tests
● = Follow-on tests
O = Preliminary tests (small samples; can be ignored or combined with nearest regular exposure level)

TABLE 4 Number of Mice in XAM-3 Experiment by Strain, Hybrid, or Genetic Stock; Sexes and Doses Combined

Strain Code	Total at All Doses	Held for Lifetime Study[a]		Other[b]
		Control	Irradiated	
01	337	2	144	191
02	875	157	206	512
03	966	150	211	605
04	1,855	155	308	1,392
05	1,389	166	426	797
06	1,470	162	382	926
07	673	115	294	264
08	1,860	116	399	1,345
12	1,014	209	0	805
14	313	98	111	104
15	1,709	189	303	1,217
16	590	57	134	399
17	925	88	227	610
18	562	0	0	562
19	399	112	45	242
20	268	41	31	196
21	98	0	0	98
22	148	0	0	148
23	175	0	0	175
24	160	0	0	160
25	189	0	0	189
26	198	50	60	88
27	260	94	106	60
28	146	0	0	146
29	145	0	0	145
30	76	0	0	76
31	32	0	0	32
32	39	0	0	39
33	49	0	0	49
34	746	132	132	482
35	710	160	130	420
44	452	61	169	222
47	496	120	127	249
48	581	104	152	325
49	552	102	267	183
50	546	129	142	275
51	543	116	165	262
52	517	104	76	337
53	497	105	138	254
54	602	175	149	278
55	588	95	260	233
56	248	122	37	89
57	319	103	91	125

TABLE 4 (Cont.)

| Strain Code | Total at All Doses | Held for Lifetime Study[a] | | Other[b] |
		Control	Irradiated	
58	531	113	109	309
61	629	139	138	352
62	63	0	0	63
Σ	25,540	3,841	5,669	16,030

[a] Number of mice surviving to 61 d or more after exposure and dying of natural causes.

[b] Number of mice dying of acute injury (0–30 d), missing, or discarded earlier than 60 d following exposure.

TABLE 5 Distribution of Experiments GCM-4, 8, and 12 across Strains and Daily Dose Levels

Dose (R/d)	LAF$_1$	A/He	A/Jax	BALB/c	C3Hf	C57BL/6	C57L	BCF$_1$	BCF$_2$
0	4	–	8,12	8,12	8	8,12	8,12	8,12	8
0.3	–	–	12	12	–	–	–	12	–
1.3	–	–	12	12	–	12	–	12	–
2.6	–	–	12	12	–	12	–	12	–
5	4	–	–	8	–	8	–	–	–
6	–	–	12	12	–	12	–	12	–
12	4	8	8,12	8,12	8	8,12	8,12	8,12	8
24	4	8	8,12	8,12	8	8,12	8,12	8,12	8
32	4	8	8,12	8,12	8	8,12	8,12	8,12	8
43	4	8	8,12	8,12	8	8,12	8,12	8,12	8
49	4	–	–	–	–	–	–	–	–
56	4	8	8,12	8,12	8	8,12	8,12	8,12	8
64	4	8	8	(8)[a]	–	–	–	–	–
74	4	8	8	8	8	8	8,12	8	8
85	4	8	8	(8)[a]	–	–	–	–	–
97	4	8	8	8	8	8	8,12	8	8
125	4	8	8	8	8	8	8,12	8	8
145	4	–	–	–	–	–	–	–	–
170	4	8	8	8	8	8	8	8	8
220	4	–	8	8	8	8	8	8	8
270	4	–	–	–	–	–	–	–	–
330	4	–	–	–	–	–	–	–	–
410	4	–	–	–	–	–	–	–	–
500	4	–	–	–	–	–	–	–	–
610	4	–	–	–	–	–	–	–	–
750	4	–	–	–	–	–	–	–	–·
1100	4	–	–	–	–	–	–	–	–
1650	4	–	–	–	–	–	–	–	–
2500	4	–	–	–	–	–	–	–	–

[a] Insufficient sample size; can be deleted.

TABLE 6 Number of Mice Entered into Studies GCM-4 and GCM-8 According to Dose and Strain; Sexes Combined

Dose (R/d)	GCM-4 Strain Code 01	GCM-8 Strain Codes 02	03	04	05	06	07	08	12
0									
A[a]	180	–	103	137	129	121	41	105	112
B[b]	180	–	–	–	–	–	–	–	–
C[c]	180	–	–	–	–	–	–	–	–
5	240	–	–	66	–	60	–	–	–
12	366	18	84	60	78	84	24	78	66
24	366	18	84	66	78	87	24	84	74
32	300	18	76	60	78	84	27	78	84
43	300	18	84	66	83	83	24	78	84
49	270	–	–	–	–	–	–	–	–
56	240	48	60	48	54	57	30	60	60
64	210	48	48	6	–	–	–	–	–
74	210	48	60	53	60	57	30	60	60
85	210	48	48	6	–	–	–	–	–
97	210	48	60	53	60	60	24	60	60
125	210	30	48	48	48	48	30	48	48
145	210	–	–	–	–	–	–	–	–
170	210	24	36	36	36	36	30	36	36
220	150	–	24	24	24	24	18	24	24
270[d]	60	–	–	–	–	–	–	–	–
330	60	–	–	–	–	–	–	–	–
410	60	–	–	–	–	–	–	–	–
500	60	–	–	–	–	–	–	–	–
610	60	–	–	–	–	–	–	–	–
750	48	–	–	–	–	–	–	–	–
1100	48	–	–	–	–	–	–	–	–
1650	48	–	–	–	–	–	–	–	–
2500	18	–	–	–	–	–	–	–	–
Totals	4704	366	815	729	728	801	302	711	708

[a] Mice housed in cylindrical cages, three per cage, in corridor of γ room.

[b] Mice housed in cylindrical cages, three per cage, in standard mouse room.

[c] Mice housed in shoe-box cages, nine per cage, in standard mouse room.

[d] Exposures of 270 R/d and above were performed in high-level γ room.

TABLE 7 Number of Mice Entered into the GCM-12 Study According to Dose, Strain, and Sex

Dose (R/d)	GCM-12 A/Jax σ	A/Jax $\female$	BALB/c σ	BALB/c $\female$	C57BL/6 σ	C57BL/6 $\female$	B6CF$_1$ σ	B6CF$_1$ $\female$	GCM-8 (continued) C57L σ	C57L $\female$
0	84	84	81	84	82	82	165	168	153	143
0.3	60	57	60	60	–	–	120	119	–	–
1.3	83	83	83	84	83	83	168	168	–	–
2.6	47	48	48	48	48	48	96	96	–	–
6.0	48	48	47	46	48	47	96	96	–	–
12.0	46	47	46	46	46	45	48	48	48	48
24.0	46	48	47	48	48	48	48	48	47	46
32.0	24	24	24	23	24	23	24	24	36	24
43.0	22	24	23	24	22	23	24	24	68	60
56.0	24	24	23	24	24	22	23	24	72	36
74.0	–	–	–	–	–	–	–	–	57	60
97.0	–	–	–	–	–	–	–	–	72	36
125.0	–	–	–	–	–	–	–	–	72	35
Total	484	487	482	487	425	421	812	815	625	488
	971		969		846		1627		1113	

TABLE 8 Number of LAF$_1$ Mice Entered in the GCM-9B Test of Age Dependence of Response to Daily Irradiation by [60]Co γ Rays (exposure levels as in GCM-4)

Age[a] (d)	12 R/d ♂	12 R/d ♀	43 R/d ♂	43 R/d ♀	74 R/d ♂	74 R/d ♀	97 R/d ♂	97 R/d ♀	125 R/d ♂	125 R/d ♀	170 R/d ♂	170 R/d ♀
250	–	–	15	15	12	12	12	12	9	9	6	6
400	–	–	18	18	17	17	18	18	15	15	6	6
550	12	18	9	9	9	9	9	9	9	9	6	6
650	12	23	9	15	6	15	6	15	9	15	6	6
725	–	–	8	11	5	7	6	9	7	9	6	6
800	–	–	3	6	3	5	3	5	3	5	–	6
850	–	–	3	9	–	–	–	–	5	6	–	–
925	–	–	–	10	–	–	–	–	–	7	–	–

[a] Age at entry. The 100-d baseline age group taken from GCM-4 (Table 6).

TABLE 9 Number of Mice Entered in the GCM-9B Test of Age Dependence of Response to Daily Irradiation by ^{60}Co γ Rays

Strain	43 R/d		56 R/d		85 R/d		97 R/d		125 R/d		145 R/d		170 R/d		Ages or Age Range (d)
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	
A/He	12	12	–	–	–	–	–	–	12	–	–	–	–	–	250-400
A/Jax	15	18	–	9	–	6	–	–	12	6	18	18	18	18	100, 250-400
BALB/c	6	12	–	–	–	–	9	13	31	18	18	17	–	–	100, 200-400
C3Hf	6	6	–	–	–	–	–	–	9	–	–	–	–	–	300
C57BL/6	12	11	–	–	–	–	–	–	21	6	12	12	12	12	100, 250-400, 550
C57L	12	12	–	–	–	–	–	–	–	–	–	–		–	250-400
BCF$_1$	8	8	–	–	–	–	–	–	8	6	24	24	41	41	60, 100, 250-400

TABLE 10 Number of LAF$_1$ Mice (equal numbers of each sex) in the GAM-2/GFM-1 Test of Response to Single Exposures of ^{60}Co γ Rays at 100 Days of Age (GAM-2), Plus a Split-Dose Series at 450 and 750 R (GFM-1)

Dose[a] (R)	Number of Mice Exposed at Each Interval between the Two Equal Half-Doses:								
	0 d	0.125 d	0.4 d	1 d	3 d	5 d	7 d	14 d	28 d
150	108	–	–	–	–	–	–	–	–
300	108	–	–	–	–	–	–	–	–
450	108	54	54	54	54	54	54	54	54
600	108	–	–	–	–	–	–	–	–
700	54	–	–	–	–	–	–	–	–
750	120	54	54	54	54	54	54	54	54
800	54	–	–	–	–	–	–	–	–
850	54	–	–	–	–	–	–	–	–
900	54	–	–	–	–	–	–	–	–
950	54	–	–	–	–	–	–	–	–
1000	54	–	–	–	–	–	–	–	–
1050	54	–	–	–	–	–	–	–	–
1100	54	–	–	–	–	–	–	–	–

[a] Dose of ^{60}Co γ rays; 3-20 R/min; exposure period of about 55 min.

[b] "0" interval equals a single dose.

TABLE 11 Number of Mice for the XAM-6 Test of Life Shortening Induced at Doses below the XAM-3 Range of Approximately 0.8-1.2 LD$_{50}$ Values[a]

Dose (R, in air)	BALB/c		A/He		C3Hf		C57BL/6		B6CF$_1$	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0	19	19	44	44	51	51	36	35	36	35
100	20	20	44	44	52	52	36	36	36	37
300[b]	19	20	–	–	–	–	–	–	–	–
335[b]	–	–	44	43	–	–	–	–	–	–
355[b]	–	–	–	–	52	52	–	–	–	–
380[b]	–	–	–	–	–	–	36	36	–	–
395[b]	–	–	–	–	–	–	–	–	36	36

[a] 200-kVp x-rays delivered at approximately 22 R/min; age at entry about 100 d.

[b] Exposure level chosen as approximately equal to 60% of the acute LD$_{50}$ value for the given strain or hybrid.

TABLE 12 Number of Mice for the XAM-7 Study of Age Dependence of Response to Single Doses of 200-kVp X-Rays below the Acute Lethal Level

Age at Entry (d)	A/He 0 R ♂	A/He 0 R ♀	A/He 100 R ♂	A/He 100 R ♀	A/He 450 R ♂	A/He 450 R ♀	C3Hf/He 0 R ♂	C3Hf/He 0 R ♀	C3Hf/He 100 R ♂	C3Hf/He 100 R ♀	C3Hf/He 450 R ♂	C3Hf/He 450 R ♀	C57BL/6 0 R ♂	C57BL/6 0 R ♀	C57BL/6 100 R ♂	C57BL/6 100 R ♀
40	7	7	12	14	–	–	41	40	54	54	30	31	–	–	–	–
300	49	54	70	84	30	23	50	43	72	64	31	23	18	3	37	5
500	34	61	53	64	20	56	60	45	89	45	30	32	8	–	18	–

TABLE 13 Inventory of Litter Records

Strain Code[a]	Number of Litters	Strain Code[a]	Number of Litters
01	224	29	45
02	2,013	30	3C
03	2,066	31	15
04	2,172	32	14
05	1,844	33	11
06	2,402	34	100
07	1,250	35	99
08	1,918	37	6
09	203	39	18
10	29	41	20
11	27	43	34
12	125	44	430
13	126	46	203
14	53	47	272
15	327	48	306
16	131	49	328
17	203	50	440
18	90	51	233
19	73	52	334
20	60	53	338
21	175	54	257
22	39	55	212
23	34	56	405
24	46	57	394
25	51	58	459
26	54	61	453
27	62	62	325
28	46		

[a]See Appendix B.

**TABLE 14 Number of Animals
Entered into the Pre-Experi-
mental Stock Cage Record
According to Strain and Sex**

Strain	Males	Females	Total
02	1,405	1,409	2,814
03	1,805	1,737	3,542
04	2,169	2,413	4,582
05	2,086	1,937	4,023
06	2,728	2,302	5,030
07	1,438	1,327	2,765
08	4,693	4,917	9,610
Totals	16,324	16,042	32,366

APPENDIX A:

FILE FORMATS

TABLE A.1 Lorenz Data (File No. 98) Format[a]

Column	Content of Columns
1-3	Project number (031)
4-6	Experiment number (001 or may be blank)
7-9	Replication number (may be blank)
10-11	Strain code: LAF_1 (01); C3Hf (05)
12	Sex: male (1), female (2), castrate female (4)
13-17	Animal number
18-21	Cage number
22-27	Dose (roentgens in air from Ra^{226} point source) Note that there are two decimal places
28-32 33-37 38-42	Birth Calendar dates Entry month (00), day (00), year (0) Death e.g., Dec. 7, 1946 = 12076
43	Mode of death (exit code): dead (1), sacrificed or moribund (2), missing (3), accidental death (4), discard (5)
44-47	Age at death (d)
48-51	Age at entry and start of irradiation (d)
52-55	Survival time, from start of irradiation (d)
56-60 61-65	Parents (not otherwise specified in available notes)
66-73	Survival time squared: $(Col. 52\text{-}55)^2 = Col. 66\text{-}73$

[a] Survival data from the studies performed at the National Cancer Institute by Egon Lorenz in the period 1943 to 1953.

TABLE A.2 XAM-3 Data (File No. 96) Format[a]

Column	Content of Columns
1-3	Project number (006)
4-6	Experiment number (002)
7-9	Replication number (blank for controls)
10-11	Strain code
12	Sex
13-17	Animal number
18-21	Cage number
22-27	Dose (R)
28-31	Mating number
32-33	Parity
34-35	Number born (for given mating and parity)
36-37	Number weaned (for given mating and parity)
38-40	Age of dam (d)
41-44	Age at entry and age at exposure (d)
45	Mode of death (exit code)
46-49	Survival time (d) from exposure
50	Autopsy code
51-54	Age at exit (d)
55-62	Pathology codes (4 pairs of 2-digit codes)
63-65	Body weight at entry (g)
66-67	Month born
68	Blank
69	Coat color

[a] Acute and chronic response of young adult inbred, hybrid, and mutant stocks of mice to single doses of 200-kVp x-rays.

TABLE A.3 GCM-4 Data (File No. 87) Format[a]

Column	Content of Columns
1-3	Project number (010)
4-6	Experiment number (001)
7-9	Replication number
10-11	Strain Code LAF_1 (01)
12	Sex
13-17	Animal number
18-21	Cage number
22-27	Dose (R/d)

28-31	Cage position (location in the radiation field)
	    28-29 = Rack number
	        30 = Shelf number
	        31 = Position on shelf
	
	Note: Rack 20 = control group A, 3 per cage, in corridor of γ room
	        Rack 21 = control group B, 3 per cage, in mouse room
	        Rack 22 = control group C, 9 per cage, in mouse room

32-34 35-37 38-40	Body weights (g) preceding entry and on day of entry into γ-ray room, taken at 2-week intervals
41-44	Age at entry and start of irradiation (d); all 0100 in this experiment
45	Mode of death (exit code)
46-49	Survival time, from start of irradiation (d)
50	Autopsy code
51-54	Blank
55-64	Pathology codes (five pairs of two-digit codes; no pathologic findings at doses ≥64 R/d)

[a] Acute and chronic response of young adult LAF_1 mice to daily duration-of-life ^{60}Co γ irradiation.

TABLE A.4 GCM-8 Data (File No. 59) Format[a]

Column	Content of Columns
1-3	Project number (001) and (010) for strain 07 from GCM-12
4-6	Experiment number (011) and (014) for strain 07 from GCM-12
7-9	Replication number
10-11	Strain code
12	Sex
13-17	Animal number
18-21	Cage number
22	Subcage number 1, 2, 3, and 4 (if no subcage, = 0)
23-28	Dose (R/d)
29-33	Cage Position (location in the radiation field) 29-30 = Rack number 31 = Shelf number 32-33 = Position on shelf
34-36 37-39 40-42	Body weights (g) preceding entry and on day of entry into γ-ray room, taken at 2-wk intervals
43-46	Age at entry and start of irradiation (d)
47	Mode of death (exit code)
48-51	Survival time, from start of irradiation (d)
52	Autopsy code
53-56	Age at exit (d)
57-64	Pathology codes (four pairs of two-digit codes)
66-68	Mating number
69-70	Parity of litter within mating number for mouse involved

TABLE A.4 (Cont.)

Column	Contents of Colums
71	Coat color (blank if an inbred or non-segregating generation)
72-75	Paired cage (most entries involved a pair, 1 male and 1 female cage, three per cage)
76-79	Blank
80	Code 1 = Pool F1's (strains 08 and 09) Code 2 = Pool F2's (strains 12 and 13)

[a] Acute and chronic response of young adult inbred and hybrid mice to daily duration-of-life ^{60}Co γ irradiation.

TABLE A.5 GCM-12 Data (File Nos. 66 and 27) Format[a]

Column	Content of Columns
1-3	Project number (010)
4-6	Experiment number (014)
7-9	Replication number
10-11	Strain code
12	Sex
13-17	Animal number
18-22	18-21 = cage number 22 = subcage number 1, 2, 3, and 4 (if no subcage, = 0)
23-28	Dose (R/d); one decimal place (col. 28)
29-34	Cage position (location in the radiation field) 29-30 = Rack number 31-32 = Shelf number 33-34 = Position on shelf (If a room number, all zeroes)
35-38	Mating number
39-40	Parity of litter within mating number
41-44	Age at entry and start of irradiation (d)
45	Mode of death (exit code)
46-49	Survival time, from start of irradiation (d)
50	Autopsy code
51-54	Age at exit (d)
55-70	Pathology codes (eight pairs of two-digit codes)
71-73	Body weight at entry (g); to one decimal place

[a] Acute and chronic response of young adult inbred and hybrid mice to daily duration-of-life ^{60}Co γ irradiation.

TABLE A.6 GCM-9A Data (File No. 75) Format[a]

Column	Content of Columns
1-3	Project number (010)
4-6	Experiment number (002)
7-9	Replication number
10-11	Strain code (01)
12	Sex
13-17	Animal number
18-21	Cage number •
22-27	Dose (R/d); all zeroes for these pre-irradiation data
28-31	Cage position; all zeroes for these pre-irradiation data
32-34 35-37 38-40	Body weights (g) preceding entry $\Big\{$ −4 weeks −2 weeks 0 weeks, day of entry
41-44	Age at entry (d); all 0100 in this experiment
45	Mode of death (exit code)
46-49	Survival time or time from entry (d)
50	Autopsy code
51-52	Future replication in an irradiation series (may be blank or zeroes)
53-54	Future experiment (incomplete information)

[a] Dependence of response to daily duration-of-life ^{60}Co γ irradiation upon age at first exposure; pre-irradiation data for LAF_1 mice.

TABLE A.7 GCM-9B Data (File No. 75) Format[a]

Column	Content of Columns
1-3	Project number (010)
4-6	Experiment number (002)
7-9	Replication number
10-11	Strain code
12	Sex
13-17	Animal number
18-21	Cage number
22-27	Dose (R/d)
28-31	Cage position (location in the radiation field) 28-29 = Rack number 30 = Shelf number 31 = Position on shelf
32-34	Body weight (g) at entry into γ-ray room
35-38	Previous cage number
39-40	Blank
41-44	Age at entry and start of irradiation (d)
45	Mode of death (exit code)
46-49	Survival time, from start of irradiation (d)
50	Autopsy code
51-54	Age at exit (d)

[a] Dependence of response to daily duration-of-life ^{60}Co γ irradiation upon age at first exposure for inbred and hybrid mice.

TABLE A.8 GAM/GFM Data (File No. 73 [GAM-2] and File No. 82 [GFM-1] combined) Format[a]

Column	Content of Columns
1-3	Project number (010)
4-6	Experiment number (005 and 004)
7-9	Replication number
10-11	Strain code (01)
12	Sex
13-17	Animal number
18-21	Cage number
22-23	Interval between split dose: 450 and 750 were split in half and delivered with one of 9 intervals between halves. Interval code: 0 (00), 0.125 d (02), 0.4 d (03), 1 d (04), 3 d (05), 5 d (06), 7 d (07), 14 d (08), 28 d (09).
24-27	Dose, ^{60}Co γ-rays (R)
28-31	Cage position (all zeroes in these experiments)
32-34 35-37 38-40	Body weights (g) preceding entry { −4 weeks −2 weeks 0 weeks, day of entry
41-44	Age at entry (d); all entries are 0100
45	Exit code
46-49	Survival time from irradiation (d)
50	Autopsy code
51-54	Age at exit (d)
55-64	Pathology codes (five pairs of two-digit codes)
65	Start time: 1 = day 0, 2 = day 14, 3 = day 28

[a] Acute and chronic response of young adult LAF_1 mice to single and split doses of ^{60}Co γ irradiation.

TABLE A.9 XAM-6 Data (File No. 67) Format[a]

Column	Content of Columns
1-3	Project number (006)
4-6	Experiment number (004)
7-9	Replication number
10-11	Strain code
12	Sex
13-17	Animal number
18-22	Cage and subcage number
23-28	Dose (R); one decimal place
29-34	Cage position (all zeroes in this experiment)
35-38	Mating number
39-40	Parity
41-44	Age at entry and exposure (d)
45	Exit code
46-49	Survival time from exposure (d)
50	Autopsy code
51-54	Age at exit (d)
55-62	Pathology codes (four pairs of two-digit codes)
63-71	Blank
72-74	Body weight at entry (g); one decimal place

[a] Chronic effects of sublethal single doses of 200-kVp
x-rays on young adult inbred and hybrid mice.

TABLE A.10 XAM-7 Data (File No. 69) Format[a]

Column	Content of Columns
1-3	Project number (006)
4-6	Experiment number (005)
7-9	Replication number
10-11	Strain code
12	Sex
13-17	Animal number
18-22	Cage and subcage number
23-28	Dose, (R); one decimal place
29-34	Cage position (all zeroes in this experiment)
35-38	Mating number
39-40	Parity
41-44	Age at entry and exposure (d)
45	Exit code
46-49	Survival time from exposure (d)
50	Autopsy code
51-54	Age at exit (d)
55-62	Pathology codes (four pairs of two-digit codes)
63-71	Blank
72-74	Body weight at entry (g)

[a] Influence of age on the chronic effects of sublethal single doses of 200-kVp x-rays on inbred and hybrid mice.

TABLE A.11 Pre-Experimental Stock Cage Record (File No. 94) Format[a]

Column	Content of Columns
1-3	Project number (000)
4-9	Blank
10-11	Strain code
12	Sex
13-17	Animal number
18-21	Cage number
22	Blank
23-28	Birth date: 23-24, month; 25-26, day; 27-28, year
29-34	Exit date: 29-30, month; 31-32, day; 33-34, year
35-38	Mating number
39-40	Parity
41-44	Blank
45	Exit code
46-49	Blank
50	Autopsy code
51-54	Survival time (d); (Col. 29-34 minus Col. 23-28)
55-62	Pathology codes (four pairs of two-digit codes)
63-65	Future projects
66-68	Future experiments
69-71	Future replication

[a] Survival record from weaning to experimental use or discard for six inbred and one hybrid mouse stocks during the period 1958–1969.

TABLE A.12 Mating Record (File No. 88) Format

Column	Content of Columns
1-3	Project number (011)
4-5	Strain
6	Blank
7-9	Generation
10-12	Dam strain
13-17	Dam animal number
18-20	Sire strain
21-25	Sire animal number
26-29	Mating number
30-35	Dam birth date: 30-31, month; 32-33, day; 34-35, year
36-41	Date mated: 36-37, month; 38-39, day; 40-41, year
42-47	Date discarded: 42-43, month; 44-45, day; 46-47, year
48	Reason for discard:

48 — Reason for discard:

1 Dam dead	5 Sire discard (sacrifice)
2 Sire dead	6 To a new mating
3 Retired (discarded)	7 Sire to age dependency
4 Dam discard (sacrifice)	

TABLE A.13 Litter Record (File No. 95) Format[a]

Column	Content of Columns
1-3	Project number (011)
4-5	Strain
6-9	Page number (page number in the strain pedigree book)
10-12	Generation number ⎤
13-17	Animal number ⎦ Dam
18-20	Generation number ⎤
21-25	Animal number ⎦ Sire
26-29	Mating number
30-31	Parity
32-36	Birth date: 32-33, month; 34-35, day; 36, year
37-41	Date weaned: 37-38, month; 39-40, day; 41, year
42-49	Number born: 42-43, number born; 44-45, male; 46-47, female; 48-49, unknown
50-55	Number weaned: 50-51, male; 52-53, female; 54-55, total weaned
56-73	Number dead (by following age intervals): 0-5 d: 56-57 (M), 58-59 (F), 60-61 (unknown) 6-15 d: 62-63 (M), 64-65 (F), 66-67 (unknown) 16 d-weaning: 68-69 (M), 70-71 (F), 72-73 (unknown)
74-76	Age (d) of dam (at birth of given parity)

[a] Record of all matings with at least one litter born for all strains, hybrids, and mutant stocks during the period 1953–1969.

TABLE A.14 Combined Mating and Litter Records 1953-1969 (File Nos. 88 and 95) Format

Column	Content of Columns
1-3	Project number (011)
4-5	Strain of litter (see code list in Appendix B)
6-9	Page number in the strain pedigree book
10-12	Generation number (from Mating Record)
13-15 16-20	Strain code (from Mating Record) ⎱ Dam Animal number ⎰
21-23 24-28	Strain code (from Mating Record) ⎱ Sire Animal number ⎰
29-32	Mating number
33-34	Parity
35-40	Birth date: 35-36, month; 37-38, day; 39-40, year
41-46	Date weaned: 41-42, month; 43-44, day; 45-46, year
47-54	Number born: 47-48 (number born), 49-50 (male) 51-52 (female), 53-54 (unknown)
55-60	Number weaned: 55-56, male; 57-58, female; 59-60, total weaned
61-78	Number dead (by following age intervals): 0-5 d: 61-62 (M), 63-64 (F), 65-66 (unknown) 6-15 d: 67-68 (M), 69-70 (F), 71-72 (unknown) 16 d-weaned: 73-74 (M), 75-76 (F), 77-78 (unknown)
79-81	Age (d) of dam (at birth of given parity)
82-87	Dam birth date (from Mating Record: month, day, year)
88-93	Date mated (from Mating Record: month, day, year)
94-99	Date discarded (from Mating Record: month, day, year)
100	Reason for discard: 1 Dam dead 5 Sire discard (sacrifice) 2 Sire dead 6 To a new mating 3 Retired (discarded) 7 Sire to age dependency 4 Dam discard (sacrifice)

APPENDIX B:

STRAIN CODES, STRAIN DESIGNATIONS, AND BRIEF NOTES ON CHARACTERISTICS

STRAINS

Code	Designation	Brief Characteristics and Other Comments
01	LAF_1	Purchased from Jackson Labs, 1954-1957 $(C57L \times A/J)F_1$
02	A/He	From W.E. Heston, NCI, May 1953, at $F_{90,92}$
03	A/J	From Jackson Labs, April 1953, at $F_{85,86,87}$
04	BALB/cJ	From Jackson Labs, April 1953, at $F_{53,55,56}$
05	C3Hf/He	From W.E. Heston, NCI, March 1953, at F_{20} from time of foster nursing to eliminate mammary tumor virus
06	C57BL/6J	From Jackson Labs, April 1953, at $F_{37,39}$
07	C57L	From W.E. Heston, NCI, June 1954, at $F_{58,59}$
08	$B6CF_1$	C57BL/6 ♀ × BALB/c ♂ F_1 ⎫ Combined into single Code 08
09	$CB6F_1$	BALB/c ♀ × C57BL/6 ♂ F_1 ⎭
10	BCA	$B6CF_1 \times A/J$ ⎫ Limited tests/production discnt'd/no data in files
11	CBA	$CB6F_1 \times A/J$ ⎭
12	$CB6F_2$	$CB6F_1 \times CB6F_1$ ⎫ Combined into single Code 12
13	$B6CF_2$	$B6CF_1 \times B6CF_1$ ⎭
14	CB/BC F_3	From matings of F_2 mice, Codes 12 and 13
15	BC_I	Progeny of first backcross of the $B6CF_1$ mated to BALB/c (the P_1), using reciprocal matings (F_1 ♀ × P_1 ♂ and P_1 ♀ × F_1 ♂)
16	BC_{II}, albino	Progeny of second backcross to BALB/c ($BC_I \times$ BALB/c), using the albino BC_I parent and reciprocal matings
17	BC_{II}, brown agouti	Progeny of second backcross to BALB/c, using brown agouti BC_I parent and reciprocal matings
18	BC_2	Progeny of first backcross of the $B6CF_1$ mated to C57BL/6 (the P_2); reciprocal matings
19	BC_{III}, albino	Third backcross to BALB/c ($BC_{II} \times$ BALB/c), using the albino BC_{II} parent and reciprocal matings
20	BC_{III}, brown agouti	Third backcross to BALB/c, using the brown agouti BC_{II} parent and reciprocal matings
21	C57BL/6-G	Progeny from irradiated C57BL/6 parents — limited tests and little data in file
22	BC_{IV}, albino	Fourth backcross to BALB/c ($BC_{III} \times$ BALB/c), using the albino BC_{III} parent and reciprocal matings
23	BC_{IV}, brown agouti	Fourth backcross to BALB/c, using the brown agouti BC_{III} parent and reciprocal matings
24	BC_v, albino	Fifth backcross to BALB/c ($BC_{IV} \times$ BALB/c), using the albino BC_{IV} parent and reciprocal matings
25	BC_V, brown agouti	Fifth backcross to BALB/c, using the brown agouti BC_{IV} parent and reciprocal matings
26	BC_{VI}, albino	Sixth backcross ($BC_V \times$ BALB/c), albino BC_V parent, reciprocal matings
27	BC_{VI}, brown agouti	Sixth backcross, brown agouti BC_V parent, reciprocal matings

Code	Designation	Brief Characteristics ana Other Comments
28	BALB/c-N7F$_1$	First inbred generation following seven outcross/backcross generations; both parents BC$_{VI}$ brown agouti
29	BALB/c-N7F$_1$	Brown agouti × albino; BC$_{VI}$ brown agouti × BC$_{VI}$ albino, reciprocal matings
30	BALB/c-N7F$_1$	Both parents albino, BC$_{VI}$ albino
31	BALB/c-N7F$_2$	Second inbred generation; brown agouti parents
32	BALB/c-N7F$_2$	Brown agouti × albino, reciprocal matings
33	BALB/c-N7F$_2$	Albino parents
34	BC$_1$ × B6CF$_1$ (albino)	Progeny of the mating of the B6CF$_1$ with first backcross progeny (code 15), using albino BC$_1$ and reciprocal matings
35	BC$_1$ × B6CF$_1$ (brown agouti)	As for strain code 34, using the brown agouti BC$_I$ and reciprocal matings
37	BC$_{VII}$, brown agouti	Progeny of the seventh backcross to the BALB/c inbred parent (BALB/c-N7F$_2$-brown agouti (31) × BALB/c), reciprocal matings
39	BC$_{VIII}$, brown agouti	Eighth backcross (BC$_{VII}$ - brown agouti × BALB/c), reciprocal matings
41	BC$_{IX}$, brown agouti	Ninth backcross (BC$_{VIII}$ - brown agouti × BALB/c), reciprocal matings
43	BC$_X$, brown agouti	Tenth backcross (BC$_{IX}$ - brown agouti × BALB/c), reciprocal matings
44	BALB/c-N11, brown agouti (BALB/c-C(N11)	BALB/c strain maintained by full-sib matings following eleven outcross/backcross generations; parents selected for brown agouti color (non-albino)
46	C57BL/6-A^y	Dominant mutant "yellow" (A^y) from Jackson Lab in 1963, maintained on inbred C57BL/6 strain
47-58, 61		Inbred strains and genetic marker stocks obtained from Prof. J.W. Gowen, Dept. of Genetics, Iowa State University, in September 1963. No generation number was available for the inbred strains, so the stocks were started as if from "0" generations of inbreeding with the first full-sib matings set up at ANL, September 23, 1963. All of the strains were of long standing, however, some dating back to the 1920s. Some brief remarks are given for each strain in the continuation of this Appendix.

Code	Designation	Brief Characteristics and Other Comments
47	C	These four strains were differentiated by Webster (1937) at the
48	K	Rockefeller Institute for Medical Research according to their
49	Q	resistance (R) or susceptibility (S) to bacterial (B) infection
50	N	(*Salmonella enteritidis*) and viral (V) infection (St. Louis encephalitis). The 4-letter designations of BRVS, (strain C); BRVR, (strain K); BSVR, (strain Q); BSVS, (strain N) were used originally at Rockefeller, but the single-letter designations were initiated at Iowa State where the strains were established by Gowen when he moved there from Rockefeller Institute in 1938. Their survival following exposure to a standard dose of *S. typhimurium* at Iowa State was: K, 51%; C, 30%; N, 17%; Q, 2% (Gowen 1963). References to strains BRVR and BSVS are in the Jay (1963) and Staats (1968) listings of inbred strains of mice, and all four strains are listed in Festing (1975) as being available in the United States from the National Cancer Institute.
51	S	Characterized by their resistance or susceptibility to
52	Z	*S. typhimurium.* Survival following a standard dose was S,
53	E	84% Z, 34%; E, 24%; and Bab, <1% (Gowen 1963). Strain S
54	Bab (BALB/Gw)	was differentiated by Schott (1932) at Iowa State. Strain Z came from the Rockefeller Institute yellow fever laboratory, and E from a dealer in Pennsylvania (Jay 1963). The Bagg albino strain was given to Gowen in 1932 by MacDowell, who had inbred the strain for 27 generations. The line originally dates to 1906 and is widely held by many institutions (Jay 1963). The albino gene covers brown agouti traits (*AAbbcc*).
55	BaB (BALB/Gw-B)	Derived from Bab as a result of a mutation at the brown locus. The color genes are *AABBcc*.
56	Ruby belt	Non-inbred genetic marker stock ($a^t a^t$ *bb* $c^{ch} c^{ch}$ *btbt ruru*)[a]
57	7pl	Non-inbred genetic marker stock ($a^e a^e$ *bb lnln pp btbt wa-2 wa-2*)[a]
58	P	Non-inbred genetic marker stock (*aa bb pp dse/dse*)[a]
61[b]	MWA	Non-inbred genetic marker stock ($a^e a^e$ W^a+)[a]
62	CF #1	ANL-raised Carworth Farms #1 (CF #1) inbred strain

[a] Gene symbols: A^y: yellow; *A*: wild type agouti; a^t: black & tan; *a*: non-agouti; a^e: extreme non-agouti; *B*: wild type; *b*: brown; c^{ch}: chinchilla; *c*: albino; *bt*: belted; *ln*: leaden; *p*: pink-eyed dilute; *ru*: ruby-eye; *wa-2*: waved hair; W^a: Ames dominant white spotting; *dse*: dilute color, short-ear (closely linked genes).

[b] In the mating record, mice coded 61 derived from mice coded 59 and 60, reciprocally mated. 59 = $a^e a^e$++ and 60 = $a^e a^e$ W^a+. These were not specific strains but were segregants of 61, since 61 was heterozygous at the W^a locus. This use of strain codes 59 and 60 was a record-keeping convenience, thus they are not listed in Appendix B.

APPENDIX C:

DATA CODES AND RADIATION PROTOCOLS

TABLE C.1 Pre-JANUS Data Codes

Sex Codes

    1 Male
    2 Female

Mode of Exit Codes

    1 Natural death
    2 Sacrifice
    3 Missing
    4 Accidental
    5 Discard
    6 Sacrifice moribund
    7 Breeder
    8 (no pre-JANUS code)
    9 Removal to another experiment

Autopsy Codes

    0 No autopsy code recorded
    1 Autopsy (tissues saved)
    2 Autopsy (gross only)
    3 No autopsy

Coat Color Codes

    1 Albino cc
    2 Black $B\_$
    3 Brown bb
    4 Black agouti $A\_B\_$
    5 Brown agouti A_bb
    6 Extreme non-agouti $a^e a^e$
    7 Ames dominant white spotting $W^a\_$

TABLE C.2 Equivalence of Pre-JANUS and JANUS Codes

Autopsy Codes

Pre-JANUS		*JANUS*
0 No autopsy code	=	No JANUS code
1 Autopsy, tissue saved	=	A (autopsied) + MACRO and MICRO record
2 Autopsy, gross only	=	A (autopsied) + MACRO record only
3 No autopsy	=	N (not autopsied), C (cannibalized), and D (decomposed)

Exit Codes

Pre-JANUS		*JANUS*
1 Natural death	=	1 Radiation death
2 Sacrifice (programmed)	=	4 Programmed sacrifice
3 Missing	=	3 Missing
4 Accidental	=	3 Accidental death
5 Discard	=	5 Discard
6 Sacrifice moribund	=	2 Sacrifice moribund
7 Breeder	=	8 Breeders
8 (no pre-JANUS code)		
9 Removal to another experiment	=	6 Removal to another experiment

Experiment Numbers

Pre-JANUS	*JANUS*
GFM-1	51
GAM-2	52
XAM-3	53
GCM-4	54
XAM-6	56
XAM-7	57
GCM-8	58
GCM-9B	59
GCM-12	62

TABLE C.3 Pathology Codes (Used with Autopsy Code 1 or 2, but not 3)

Pathology	Pre-JANUS Code	JANUS Code	Combined Pathology File and Group Code	Group Code Definition
Inflammatory Diseases				
Enteritis	11	ENT	E <O_NT>	Other non-tumor
Hepatitis	12	HEP	E <MHEP>	Hepatitis
Nephritis	13	Note a	E <MCRD>	Renal disease
Pneumonia	14	PNU	E <MPNU>	Pneumonia
Pseudotuberculosis	15	NEC	E <O_NT>	Other non-tumor
Miscellaneous	16	ACI	E <O_NT>	Other non-tumor
Non-Inflammatory Diseases				
Chronic hepatitis	21	CIR	E <MHEP>	Hepatitis
Chronic nephritis	22	CRD	E <MCRD>	Renal disease
Amyloidosis	23	AMY	E <MAMY>	Amyloidosis
Anemia	24	ANE	E <O_NT>	Other non-tumor
Miscellaneous	25	MIS	E <O_NT>	Other non-tumor
Dermatitis	26	DER	E <O_NT>	Other non-tumor
Tumors				
Leukemia, thymic	31	TTY_	E <LR_T>	Lymphoreticular tumors
Leukemia, non-thymic	32	NTY_	E <LR_T>	Lymphoreticular tumors
Ovarian	33	TOVE	E <TOVE>	Ovarian tumors
Pulmonary	34	TADN	E <TADN>	Respiratory tumors
Liver	35	TLIV	E <TLIV>	Liver tumors
Intestinal tract	36	TMID	E <TGI_>	Gastrointestinal tract tumors
Skin, connective tissue, muscle, bone	37	TMIC	E <TCON>	Connective tissue tumors
Mammary	38	TMGL	E <TMAM>	Mammary gland tumors
Miscellaneous	39	TMIS	E <TEPO>	Other epithelial tissue tumors

TABLE C.3 (Cont.)

Pathology	Pre-JANUS Code	JANUS Code	Combined Pathology File and Group Code	Group Code Definition
Additional Codes by Fry for GCM-12				
Adrenal tumor	50	TADR	E <TADR>	Adrenal tumors
Adrenal metaplasia	51	ADR	E <O_NT>	Other non-tumor
Adrenal tissue saved	52	—	—	
Ovarian cyst	53	Note a	E <MOCY>	Ovarian cyst
Hemangioma	54	TVAS	E <TVAS>	Vascular tumors
Atrial thrombus	55	THR	E <MCVD>	Cardiovascular disease
Secondary in lung	56	Note a	H <TRW_>	Metastases in lung
Bone tumor	57	TBON	H <TBON>	Bone tumors
Connective tissue tumor	58	TCON	E <TCON>	Connective tissue, excl. LR_T and TVAS
Eliminate	30	CDU	E <MCDU>	Cause of death unknown
Unknown	All 0's	CDU	E <MCDU>	Cause of death unknown
Added by Grahn and Wright	66	—	—	Lost record, autopsy code 1

[a] No JANUS MACRO code equivalent.

TABLE C.4 Pre-JANUS Pathology Codes (Used with Autopsy Code 1 or 2, but not 3) with SNOMED Codes Assigned

Pathology	Pre-JANUS Code	JANUS Code	Pre-JANUS TOPOG	Pre-JANUS MORPH
Inflammatory Diseases				
Enteritis	11	ENT	50500	M40000
Hepatitis	12	HEP	56000	M41000
Nephritis	13	Note a	71000	M40000
Pneumonia	14	PNU	28000	M40000
Pseudotuberculosis	15	NEC	00003	M54000
Miscellaneous	16 ·	ACI	00003	M41400
Non-Inflammatory Diseases				
Chronic hepatitis	21	CIR	56000	M49500
Chronic nephritis	22	CRD	71000	M43000
Amyloidosis	23	AMY	00003	M55100
Anemia	24	ANE	00010	M40100
Miscellaneous	25	MIS	00003	M00010
Dermatitis	26	DER	01000	M40000
Tumors				
Leukemia, thymic	31	TTY_[b]	00020	MYY953
Leukemia, non-thymic	32	NTY_[b]	00020	MYY933
Ovarian	33	TOVE	87000	M80001
Pulmonary	34	TADN	28000	M80001
Liver	35	TLIV	56000	M80001
Intestinal tract	36	TMID	50000	M80001
Skin, connective tissue, muscle, bone	37	TMIC	1X005	M80001
Mammary	38	TMGL	04000	M80001
Miscellaneous	39	TMIS	00003	M80001
Additional Codes by Fry for GCM-12				
Adrenal tumor	50	TADR	93000	M80001
Adrenal metaplasia	51	ADR	93000	M00010
Adrenal tissue saved	52	—	—	—
Ovarian cyst	53	Note a	87000	M33400
Hemangioma	54	TVAS	40000	M80001
Atrial thrombus	55	THR	30000	M35100
Secondary in lung	56	Note a	28000	M80006
Bone tumor	57	TBON	1X500	M80001
Connective tissue tumor	58	TCON	1X200	M80001
Eliminate	30	CDU	00010	FY3500

TABLE C.4 (Cont.)

Pathology	Pre-JANUS Code	JANUS Code	Pre-JANUS TOPOG	Pre-JANUS MORPH
Unknown	All 0'S	CDU	00010	FY3500
Added by Grahn and Wright	66	—	—	—

[a] No JANUS MACRO code equivalent, so the SNOMED was coded for the pre-JANUS definition.

[b] Used TTYG and NTYG SNOMED codes.

TABLE C.5 Pre-JANUS Radiation Protocol

Expt. No.	Treatment Code	Radiation Quality[a]	Rads (total)	Time (min)	Frac- tions	Fraction/ unit time[b]	Comments[c]
51	0A	G	134.50	60	1		150 R[d]
51	0B	G	268.99	60	1		300 R[d]
51	0C	G	403.49	60	1		450 R[d]
51	2C	G	403.49	60	2	1/3h	450 R[d]
51	3C	G	403.49	60	2	1/10h	450 R[d]
51	4C	G	403.49	60	2	1/d	450 R[d]
51	5C	G	403.49	60	2	1/3d	450 R[d]
51	6C	G	403.49	60	2	1/5d	450 R[d]
51	7C	G	403.49	60	2	1/w	450 R[d]
51	8C	G	403.49	60	2	1/2w	450 R[d]
51	9C	G	403.49	60	2	1/4w	450 R[d]
51	0D	G	537.98	60	1		600 R[d]
51	0F	G	672.48	60	1		750 R[d]
51	2F	G	672.48	60	2	1/3h	750 R[d]
51	3F	G	672.48	60	2	1/10h	750 R[d]
51	4F	G	672.48	60	2	1/d	750 R[d]
51	5F	G	672.48	60	2	1/3d	750 R[d]
51	6F	G	672.48	60	2	1/5d	750 R[d]
51	7F	G	672.48	60	2	1/w	750 R[d]
51	8F	G	672.48	60	2	1/2w	750 R[d]
51	9F	G	672.48	60	2	1/4w	750 R[d]
51	0N	G	134.50	60	1		150 R[e]
51	0P	G	268.99	60	1		300 R[e]
51	0Q	G	403.49	60	1		450 R[e]
51	2Q	G	403.49	60	2	1/3h	450 R[e]
51	3Q	G	403.49	60	2	1/10h	450 R[e]
51	4Q	G	403.49	60	2	1/d	450 R[e]
51	5Q	G	403.49	60	2	1/3d	450 R[e]
51	6Q	G	403.49	60	2	1/5d	450 R[e]
51	7Q	G	403.49	60	2	1/w	450 R[e]
51	8Q	G	403.49	60	2	1/2w	450 R[e]
51	9Q	G	403.49	60	2	1/4w	450 R[e]
51	0R	G	537.98	60	1		600 R[e]
51	0S	G	672.48	60	1		750 R[e]
51	2S	G	672.48	60	2	1/3h	750 R[e]
51	3S	G	672.48	60	2	1/10h	750 R[e]
51	4S	G	672.48	60	2	1/d	750 R[e]
51	5S	G	672.48	60	2	1/3d	750 R[e]
51	6S	G	672.48	60	2	1/5d	750 R[e]
51	7S	G	672.48	60	2	1/w	750 R[e]
51	8S	G	672.48	60	2	1/2w	750 R[e]
51	9S	G	672.48	60	2	1/4w	750 R[e]
51	0T	G	134.50	60	1		150 R[f]
51	0U	G	268.99	60	1		300 R[f]
51	0V	G	403.49	60	1		450 R[f]
51	2V	G	403.49	60	2	1/3h	450 R[f]

TABLE C.5 (Cont.)

Expt. No.	Treatment Code	Radiation Quality[a]	Rads (total)	Time (min)	Frac- tions	Fraction/ unit time[b]	Comments[c]
51	3V	G	403.49	60	2	1/10h	450 R[f]
51	4V	G	403.49	60	2	1/d	450 R[f]
51	5V	G	403.49	60	2	1/3d	450 R[f]
51	6V	G	403.49	60	2	1/5d	450 R[f]
51	7V	G	4C3.49	60	2	1/w	450 R[f]
51	8V	G	403.49	60	2	1/2w	450 R[f]
51	9V	G	403.49	60	2	1/4w	450 R[f]
51	0W	G	537.98	60	1		600 R[f]
51	0X	G	672.48	60	1		750 R[f]
51	2X	G	672.48	60	2	1/3h	750 R[f]
51	3X	G	672.48	60	2	1/10h	750 R[f]
51	4X	G	672.48	60	2	1/d	750 R[f]
51	5X	G	672.48	60	2	1/3d	750 R[f]
51	6X	G	672.48	60	2	1/5d	750 R[f]
51	7X	G	672.48	60	2	1/w	750 R[f]
51	8X	G	672.48	60	2	1/2w	750 R[f]
51	9X	G	672.48	60	2	1/4w	750 R[f]
52	0A	G	134.50	60	1		150 R
52	0B	G	268.99	60	1		300 R.
52	0C	G	403.49	60	1		450 R
52	0D	G	537.98	60	1		600 R
52	0E	G	62..35	60	1		700 R
52	0F	G	672.48	60	1		750 R
52	0G	G	717.31	60	1		800 R
52	0H	G	762.14	60	1		850 R
52	0I	G	806.98	60	1		900 R
52	0J	G	851.81	60	1		950 R
52	0K	G	896.64	60	1		1000 R
52	0L	G	941.47	60	1		1050 R
52	0M	G	986.30	60	1		1100 R
53	D0	C	0		1		0 R
53	DA	X	348.55	18.18	1		400 R
53	DB	X	365.98	19.09	1		20 R
53	DC	X	379.05	19.77	1		435 R
53	DD	X	392.12	20.45	1		450 R
53	DE	X	409.55	21.36	1		470 R
53	DF	X	413.91	21.59	1		475 R
53	DG	X	418.26	21.82	1		480 R
53	DH	X	426.98	22.27	1		490 R
53	DI	X	431.33	22.5	1		495 R
53	DJ	X	435.69	22.73	1		500 R
53	DK	X	444.40	23.18	1		510 R
53	DL	X	453.12	23.64	1		520 R
53	DM	X	457.47	23.86	1		525 R
53	DN	X	461.83	24.09	1		530 R
53	DO	X	470.55	24.55	1		540 R

TABLE C.5 (Cont.)

Expt. No.	Treatment Code	Radiation Quality[a]	Rads (total)	Time (min)	Frac-tions	Fraction/ unit time[b]	Comments[c]
53	DP	X	479.26	25.0	1		550 R
53	DQ	X	483.62	25.23	1		555 R
53	DR	X	492.33	25.68	1		565 R
53	DS	X	496.69	25.91	1		570 R
53	DT	X	501.04	26.14	1		575 R
53	DU	X	505.40	26.36	1		580 R
53	DV	X	509.76	26.59	1		585 R
53	DW	X	514.11	26.82	1		590 R
53	DX	X	522.83	27.27	1		600 R
53	DY	X	532.41	27.77	1		611 R
53	DZ	X	535.90	27.95	1		615 R
53	EA	X	544.61	28.41	1		625 R
53	EB	X	548.97	28.64	1		630 R
53	EC	X	553.33	28.86	1		635 R
53	ED	X	562.04	29.32	1		645 R
53	EE	X	566.40	29.55	1		650 R
53	EF	X	575.11	30.0	1		660 R
53	EG	X	583.82	30.45	1		670 R
53	EH	X	588.18	30.68	1		675 R
53	EI	X	601.25	31.36	1		690 R
53	EJ	X	609.97	31.82	1		700 R
53	EK	X	614.32	32.05	1		705 R
53	EL	X	618.68	32.27	1		710 R
53	EM	X	627.39	32.72	1		720 R
53	EN	X	631.75	32.95	1		725 R
53	EO	X	640.46	33.41	1		735 R
53	EP	X	653.54	34.09	1		750 R
53	EQ	X	670.96	35.0	1		770 R
53	ER	X	675.32	35.23	1		775 R
53	ES	X	697.10	36.36	1		800 R
53	ET	X	740.67	38.64	1		850 R
53	EU	X	784.24	40.91	1		900 R
54	A0	C	0	600	999	1/d	0 R/d
54	AA	G	4.48	600	999	1/d	5 R/d
54	AB	G	10.76	600	999	1/d	12 R/d
54	AC	G	21.52	600	999	1/d	24 R/d
54	AD	G	28.69	600	999	1/d	32 R/d
54	AE	G	38.56	600	999	1/d	43 R/d
54	AF	G	43.94	600	999	1/d	49 R/d
54	AG	G	50.21	600	999	1/d	56 R/d
54	AH	G	57.38	600	999	1/d	64 R/d
54	AI	G	66.35	600	999	1/d	74 R/d
54	AJ	G	76.21	600	999	1/d	85 R/d
54	AK	G	86.97	600	999	1/d	97 R/d
54	AL	G	112.08	600	999	1/d	125 R/d
54	AM	G	130.01	600	999	1/d	145 R/d
54	AN	G	152.42	600	999	1/d	170 R/d
54	AO	G	197.26	600	999	1/d	220 R/d
54	AP	G	242.09	600	999	1/d	270 R/d
54	AQ	G	295.89	600	999	1/d	330 R/d

.TABLE C.5 (Cont.)

Expt. No.	Treatment Code	.tadiation Quality[a]	Rads (total)	Time (min)	Frac- tions	Fraction/ unit time[b]	Comments[c]
54	AR	G	367.62	600	999	1/d	410 R/d
54	AS	G	448.32	600	999	1/d	500 R/d
54	AT	G	546.95	600	999	1/d	610 R/d
54	AU	G	672.48	600	999	1/d	750 R/d
54	AV	G	986.30	600	999	1/d	1100 R/d
54	AW	G	1479.46	600	999	1/d	1650 R/d
54	AX	G	2241.60	600	999	1/d	2500 R/d
58	B0	C	0	600	999	1/d	0 R/d
58	BA	G	4.48	600	999	1/d	5 R/d
58	BB	G	10.76	600	999	1/d	12 R/d
58	BC	G	21.52	600	999	1/d	24 R/d
58	BD	G	28.69	600	999	1/d	32 R/d
58	BE	G	35.56	600	999	1/d	43 R/d
58	BF	G	50.21	600	999	1/d	56 R/d
58	BG	G	57.38	600	999	1/d	64 R/d
58	BH	G	66.35	600	999	1/d	74 R/d
58	BI	G	76.21	600	999	1/d	85 R/d
58	BJ	G	86.97	600	999	1/d	97 R/d
58	BK	G	112.08	600	999	1/d	125 R/d
58	BL	G	152.43	600	999	1/d	170 R/d
58	BM	G	197.26	600	999	1/d	220 R/d
62	C0	C	0	600	999	1/d	0 R/d
62	CA	G	0.27	600	999	1/d	0.3 R/d
62	CB	G	1.17	600	999	1/d	1.3 R/d
62	CC	G	2.33	600	999	1/d	2.6 R/d
62	CD	G	5.38	600	999	1/d	6 R/d
62	CE	G	10.76	600	999	1/d	12 R/d
62	CF	G	21.52	600	999	1/d	24 R/d
62	CG	G	28.69	600	999	1/d	32 R/d
62	CH	G	38.56	600	999	1/d	43 R/d
62	CI	G	50.21	600	999	1/d	56 R/d
62	CJ	G	66.35	600	999	1/d	74 R/d
62	CK	G	86.97	600	999	1/d	97 R/d
62	CL	G	112.08	600	999	1/d	125 R/d

[a] G = γ ray; C = control; X = x-ray.

[b] h = hour; d = day; w = week.

[c] Roentgen values are original measurements.

[d] 1 = day 0 (see Table A.8).

[e] 2 = day 14 (see Table A.8).

[f] 3 = day 28 (see Table A.8).

TABLE C.6 JANUS Radiation Protocol

Expt. No.	Treat- ment Code	Radia- tion Quality[a]	Rads (total)	Time (min)	Frac- tions	Fraction/ Unit Time[b]	No. of Repeats	Comments
2	AC	C	0	15	72	3/w		
2	DC	C	0	45	24	1/w		
2	EC	C	0	360	24	1/w		
2	HC	C	0	180	6	1/m		
2	S0	C	0	20	1			
2	AI	G	855	15	72	3/w		
2	BI	G	855	45	24	1/w		
2	DI	G	1110	45	24	1/w		
2	EI	G	855	360	24	1/w		
2	HI	G	855	180	6	1/m		
2	S1	G	90	20	1			
2	S2	G	268	20	1			
2	S3	G	788	20	1			
2	Y2	G	268	20	1			Age 194 d
2	Y3	G	788	20	1			Age 194 d
2	Z2	G	268	20	1			Age 287 d
2	Z3	G	788	20	1			Age 287 d
2	AI	N	240	15	72	3/w		
2	BI	N	240	45	24	1/w		
2	DI	N	80	45	24	1/w		
2	EI	N	240	360	24	1/w		
2	HI	N	240	180	6	1/m		
2	S1	N	20	20	1			
2	S2	N	80	20	1			
2	S3	N	240	20	1			
2	Y2	N	80	20	1			Age 194 d
2	Y3	N	240	20	1			Age 194 d
2	Z2	N	80	20	1			Age 287 d
2	Z3	N	240	20	1			Age 287 d
3	S0	C	0	20	1			
3	S4	G	90	20	1			
3	S5	G	143	20	1			Females discarded
3	S6	G	206	20	1			Females discarded
3	S7	G	417	20	1			
3	S8	G	569	20	1			Some females discarded
3	S4	N	20	20	1			
3	S5	N	40	20	1			Females discarded
3	S6	N	60	20	1			Females discarded
3	S7	N	120	20	1			Females discarded
3	S8	N	160	20	1			
3	SL	N	240	480	1			Males; no MICROS
3	SH	N	240	20	1			Males; no MICROS
4	K0	C	0	45	24	1/w		
4	K1	G	206	45	24	1/w		Females reassigned
4	K2	G	417	45	24	1/w		
4	K3	G	959	45	24	1/w		Females reassigned
4	K4	G	1919	45	24	1/w		Most females reassigned
4	K5	G	3820	45	24	1/w		Male. & a few females; no MICROS
4	K6	G	5111	45	24	1/w		No MICROS
4	K1	N	20	45	24	1/w		
4	K2	N	40	45	24	1/w		Females reassigned
4	K3	N	60	45	24	1/w		Females reassigned
4	K4	N	120	45	24	1/w		Females reassigned
4	K5	N	168	45	24	1/w		
4	K6	N	320	45	24	1/w		Females reassigned

TABLE C.6 (Cont.)

Expt. No.	Treatment Code	Radiation Quality[a]	Rads (total)	Time (min)	Fractions	Fraction/ Unit Time[b]	No. of Repeats	Comments
4	L0	C	0	1320	5	5/w	23	Males
4	LC	C	0	1320	5	5/w	59	Males
4	L1	G	206	1320	5	5/w	23	Males
4	L2	G	417	1320	5	5/w	23	Males
4	L3	G	959	1320	5	5/w	23	Males
4	L4	G	1918	1320	5	5/w	23	Males
4	L5	G	529	1320	5	5/w	59	Males
4	L6	G	1070	1320	5	5/w	59	Males
4	L7	G	2460	1320	5	5/w	59	Males
4	W0	C	0	45	24	1/w		Females; no MICROS
4	W1	G	807	45	24	1/w		Females; no MICROS
4	W2	G	2690	45	24	1/w		Females; no MICROS
4	W1	N	80	45	24	1/w		Females; no MICROS
4	W2	N	240	45	24	1/w		Females; no MICROS
7	00	C	0	20	0			
7	Q1	G	417	45	60	1/w		MICROS of males only
7	Q2	G	1918	45	60	1/w		MICROS of males only
7	Q1	N	40	45	60	1/w		MICROS of males only
7	Q2	N	160	45	60	1/w		MICROS of males only
7	R1	G	206	20	1			Age at start 515 d
7	R2	G	569	20	1			Age at start 515 d
7	R1	N	40	20	1			Age at start 515 d
7	R2	N	160	20	1			Age at start 515 d
8	U0	C	0	45	999	1/w		MICROS of males and females
8	U1	G	6.95	45	999	1/w		MICROS of males only
8	U2	G	17.38	45	999	1/w		MICROS of males only
8	U3	G	31.9	45	999	1/w		Males & a few females; no MICROS
8	U1	N	0.667	45	999	1/w		MICROS of males and females
8	U2	N	1.67	45	999	1/w		Males & a few females; no MICROS
8	U3	N	2.67	45	999	1/w		Males & a few females; no MICROS
9	XC	C	0	20	1			Females
9	X0	C	0	45	1			No MICROS
9	XX	C	0	45	24	1/w		Females; no MICROS
9	X1	G	22.5	20	1			Females
9	X2	G	45	20	1			Females
9	X3	G	90	20	1			Females
9	XX	N	10	45	24	1/w		Females; no MICROS
9	X2	N	5	5	1			Females; no MICROS
9	X3	N	10	10	1			No MICROS
9	X4	N	1	20	1			Females
9	X5	N	2.5	20	1			Females
9	X6	N	5	20	1			Females
9	X7	N	10	20	1			Females
9	X8	N	20	20	1			Females
9	X9	N	40	20	1			Females
10	V0	C	0	45	24	1/w		*P. leucopus* males; no MICROS
10	W0	C	0	20	1			*P. leucopus* males; no MICROS
10	V1	G	90	20	1			*P. leucopus* males; no MICROS

TABLE C.6 (Cont.`

Expt. No. `	Treat- ment Code	Radia- tion Quality[a]	Rads (total)	Time (min)	Frac- tions	Fraction/ Unit Time[b]	No. of Repeats	Comments
10	V2	G	143	20	1			*P. leucopus* males; no MICROS
10	V3	G	206	20	1			*P. leucopus* males; no MICROS
10	V4	G	417	20	1			*P. leucopus* males; no MICROS
10	VV	N	40	45	24	1/w		*P. leucopus* males; no MICROS
10	V1	N	20	20	1			*P. leucopus* males; no MICROS
10	V2	N	40	20	1			*P. leucopus* males; no MICROS
10	V3	N	80	20	1			*P. leucopus* males; no MICROS
10	V4	N	160	20	1			*P. leucopus* males; no MICROS
10	VW	N	160	45	24	1/w		*P. leucopus* males; no MICROS
12	J0	C	0		0			Males; no MICROS
12	J1	N	240	20	1	1/w		Males; no MICROS
12	J2	N	240	20	2	1/w		Males; no MICROS
12	J4	N	240	20	4	1/w		Males; no MICROS
12	J6	N	240	20	6	1/w		Males; no MICROS
13	0A	C	0	20	60	1/w		
13	0B	C	0	20	60	1/w		
13	0C	C	0	20	60	1/w		
13	0X	C	0	20	60	1/w		
13	1A	G	100	20	60	1/w		
13	1B	G	100	20	60	1/w		
13	1C	G	100	20	60	1/w		
13	1X	G	100	20	60	1/w		
13	2A	G	200	20	60	1/w		
13	2X	G	200	20	60	1/w		
13	3A	G	300	20	60	1/w		
13	3X	G	300	20	60	1/w		
13	4A	G	450	20	60	1/w		
13	4X	G	450	20	60	1/w		
13	5A	G	600	20	60	1/w		
13	5X	G	600	20	60	1/w		
13	1A	N	2	20	60	1/w		
13	1B	N	2	20	60	1/w		
13	1C	N	2	20	60	1/w		
13	1X	N	2	20	60	1/w		
13	2A	N	7.5	20	60	1/w		
13	2X	N	7.5	20	60	1/w		
13	3A	N	13.5	20	60	1/w		
13	3X	N	13.5	20	60	1/w		
13	4A	N	21	20	60	1/w		
13	4X	N	21	20	60	1/w		
13	5A	N	30	20	60	1/w		
13	5X	N	30	20	60	1/w		
13	6A	N	40	20	60	1/w		
13	6X	N	40	20	60	1/w		
14	0P	C	0	20	1			WR2721
14	0S	C	0	20	1			Saline
14	C0	G	206	20	1			No injection
14	CP	G	206	20	1			WR2721

TABLE C.6 (Cont.)

Expt. No.	Treat- ment Code	Radia- tion Quality[a]	Rads (total)	Time (min)	Frac- tions	Fraction/ Unit Time[b]	No. of Repeats	Comments
14	DP	G	417	20	1			WR2721
14	A0	N	10	20	1			No injection
14	AP	N	10	20	1			WR2721
14	AR	N	10	20	1			WR151327
14	BP	N	40	20	1			WR2721
14	BR	N	40	20	1			WR151327

[a] C = control; G = γ ray; N = neutron.

[b] w = week; m = month.

DISTRIBUTION FOR ANL-94/26

Internal

ANL Technical Publications Services   D.E. Nadziejka (8)
N. Clodi (2)   B.A. Carnes (100)

External

U.S. Department of Energy Office of Scientific and Technical Information (12)
Manager, U.S. Department of Energy Chicago Field Office
ANL-E Libraries (2)
ANL-W Library