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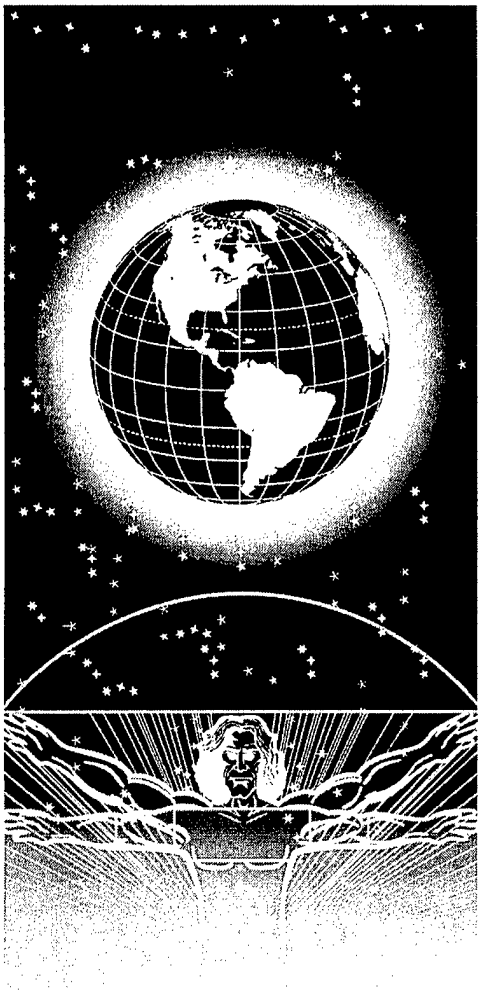

UNITED STATES AIR FORCE RESEARCH LABORATORY

PROTON RADIATION STUDIES

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This report has been reviewed and is approved for publication.

RICHARD L. MILLER, Ph.D.
Chief, Directed Energy Bioeffects Division

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14. ABSTRACT
This project was initiated in 1964 under the joint auspices of the United States Air Force (USAF and the National Aeronautics and Space Administration (NASA). The ongoing trust of the study is to describe and quantify late effects of ionizing radiations in a colony of rhesus monkeys exposed to low and intermediate "whole-body" doses of X-rays, electrons, or, primarily, protons of different energies. This report covers approximately 3.5 years of the study, but relevant earlier data are discussed as well. Since many articles, with detailed descriptions of stochastic and deterministic late effects, have been published in the last 3-4 years, we have included some of them in an appendix for readers interested in particulars of the work. The main body of this report will discuss recent data, highlights and spin-offs of the research, and will incorporate tables and figures only if they have not been published in the references listed; some unpublished data have been included in poster, presentations and abstracts.

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INTRODUCTION

"Proton Irradiation Studies" is a project initiated in 1964 under the joint auspices of the United States Air Force (USAF) and the National Aeronautics and Space Administration (NASA). The ongoing thrust of the study is to describe and quantify late effects of ionizing radiations in a colony of rhesus monkeys exposed to low and intermediate "whole-body" doses of X-rays, electrons, or, primarily, protons of different energies. This report covers approximately 3.5 years of the study, but relevant earlier data are discussed as well.

The main body of this report will discuss recent data, highlights and spinoffs of the research, and will incorporate tables and figures only if they have not been published in the references listed; some unpublished data have been included in posters, presentations and abstracts.

Recent NASA contracts supporting Proton Irradiation Studies have been supplemented by funding for specific projects by other agencies. Data from those enterprises are included in this report because, without the fundamental NASA support, the additional projects could not have been executed, and NASA will be able to use all the data gleaned from the Delayed Effects Colony (DEC) of rhesus monkeys at the Armstrong Laboratory (AL). Other support has come from the USAF Office of Scientific Research (AFOSR), the US Army (USA), the Strategic Environmental Research and Development Program (SERDP), the North Atlantic Treaty Organization (NATO), the Department of Energy (DOE) and other NASA projects including the NASA Specialized Center of Research and Training (NSCORT) in Radiation Health awarded to Colorado State University (CSU) and the Lawrence Berkley Laboratory (LBL). For aspects of animal-to-animal extrapolation, support to CSU by NASA grants NAG 9-10 and NAG 9-583 has been critical to the work, as has been support from the state of Colorado.

Part 1 of the reference section of this report consists of articles and abstracts of which the Principal Investigator (PI) is a co-author. The second part of the list includes publications and abstracts authored by contractors and colleagues other than the PI. The articles dealing with dosimetry are included because they compliment the biological work discussed here; others cover aspects of the research with which the PI was involved indirectly.

LIFE SHORTENING: CARCINOGENESIS

It is well known that ionizing radiations are carcinogenic, and numerous tumors were found in the DEC as post-irradiation time increased. With starting numbers of 57 controls and 301 treated subjects, however, it was difficult to find statistical significance in the incidence of most stochastic effects. Nonetheless, some tumors occurred in statistically significant numbers, notably, glioblastoma multiforme. Furthermore, recent data suggest a correlation between certain intestinal adenocarcinomas and radiation treatment. Single cases of some tumors, while not statistically significant, were suggestive of a relationship between radiation treatment and cancer, and some recent (unpublished) instances are discussed here.

Glioblastoma Multiforme (High grade Astrocytoma or HGA). Glioblastoma Multiforme in monkeys exposed to 55-MeV protons remains the most statistically significant cancer noted to date in the DEC (41). New calculations by D. Leavitt of dosimetry to the heads/brains of rhesus

monkeys showed that there were "hot spots" where doses of 55-MeV protons could be greater than 300% of the surface doses (40, 72, 73). A review of the literature on radiogenic HGA in humans by G. V. Dalrymple et al. revealed that it was most likely the *doses* of radiation in the hot spots rather than a unique property of protons themselves which caused the tumors (10).

Intestinal Adenocarcinomas. In this section, we will discuss only adenocarcinomas of the gastrointestinal tract itself, and not include, e.g., pancreatic tumors, etc. We have divided the animals into three groups for this part of the discussion: 1) Controls, 2) Core doses ≤ 2 Gray and 3) Core doses > 2 Gray. The dose determinations were based on some recalculations of specific proton doses by Dr D. D. Leavitt of the University of Utah. In some instances, surface doses were high, but core doses were, essentially, zero (e.g., following exposure either to 2 MeV electrons or 10 MeV protons). Because those animals were exposed, however, they were included in the "Core doses ≤ 2 Gray" groups.

Figure 1 includes graphs of data obtained from the three groups described above. Indicated on each graph are a) survival data for males, females and both sexes combined (based on the numbers of animals "at risk" at the beginning of each 5-year interval since the subjects first were exposed), b) incidences of all gastrointestinal adenocarcinomas for males, females and both sexes combined, and c) median life spans for both sexes combined.

Table 1 shows estimated median life span data broken down from Figure 1. Inspection of the figure and the table indicates differences among the responses of male and female rhesus monkeys to ionizing radiation exposures. Among the control animals, females fared better than males both at the beginning and the end of the life span, but males generally did slightly better than females just before the median life span was passed. Also, surviving control females were more prone to gastrointestinal (GI) tumors than were males as the end of the life span approached. In the "Core Dose ≤ 2 Gy" group, males did considerably better than females starting at ~15 years post-irradiation, and no GI tumors appeared in either group prior to 21 years post-irradiation. In this group and in the "Core Dose >2 Gy" group, females progressed better than males until ~15 years post-irradiation, but in the higher dose group, female survival continued to be lower than that of males until most of the subjects were deceased. It is interesting to note the increase in late GI tumors among the males in the high dose group. Full statistical analysis of GI tumor data have been initiated by Dr Lief Peterson of NASA (who has published his analysis of GI tumor data from the participants in the Hiroshima-Nagasaki study). Those analyses will be continued and completed during the NASA contract which began in July 1994, and we hope the make direct comparisons with some of the human data already analyzed by Dr Peterson.

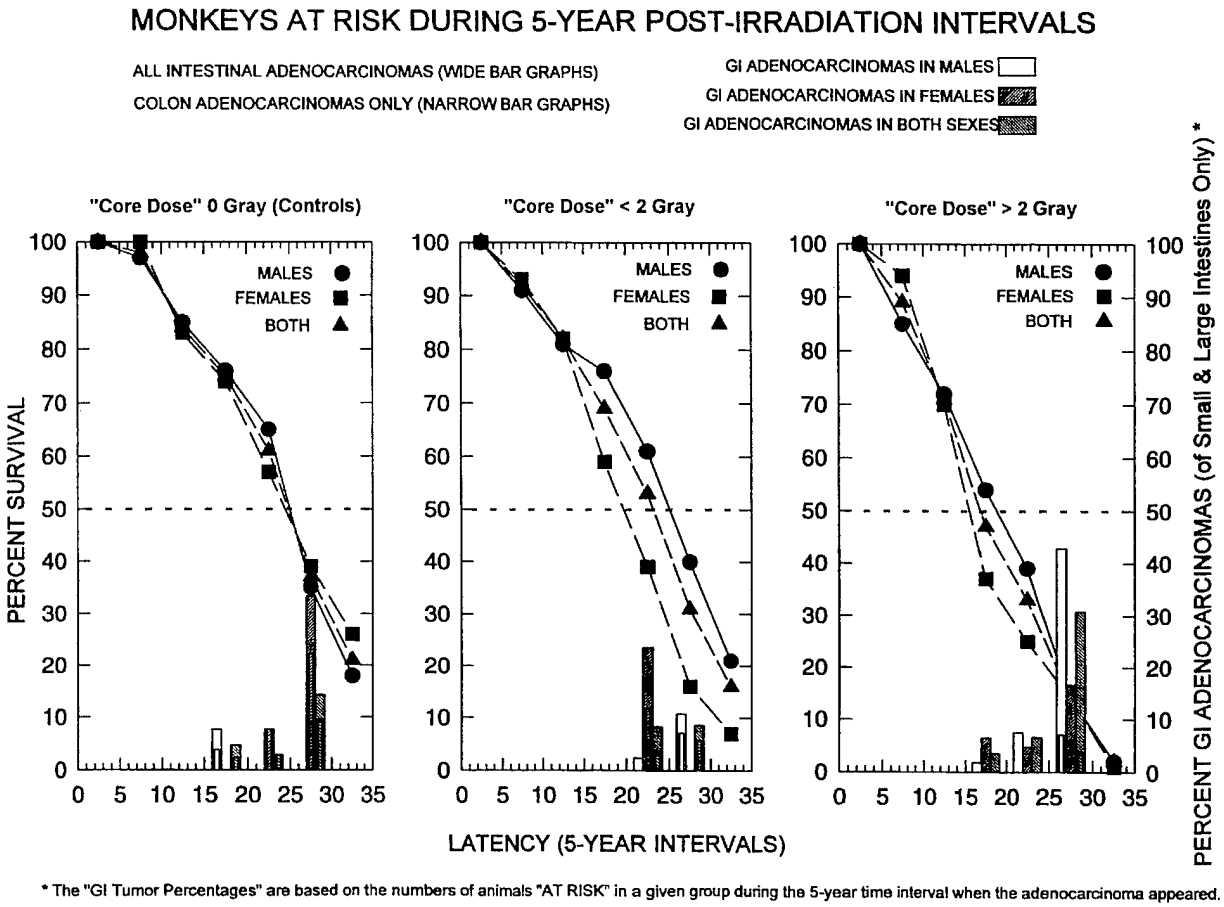


Figure 1. Percent survival as a function of age for monkeys with core dose < 2 Gray (2), core dose > 2 Gray (3) and controls (1). Indicated on each graph are survival data for males, females and both sexes combined; incidence of gastrointestinal adenocarcinomas for males, females, and both sexes combined; and median life spans for both sexes combined.

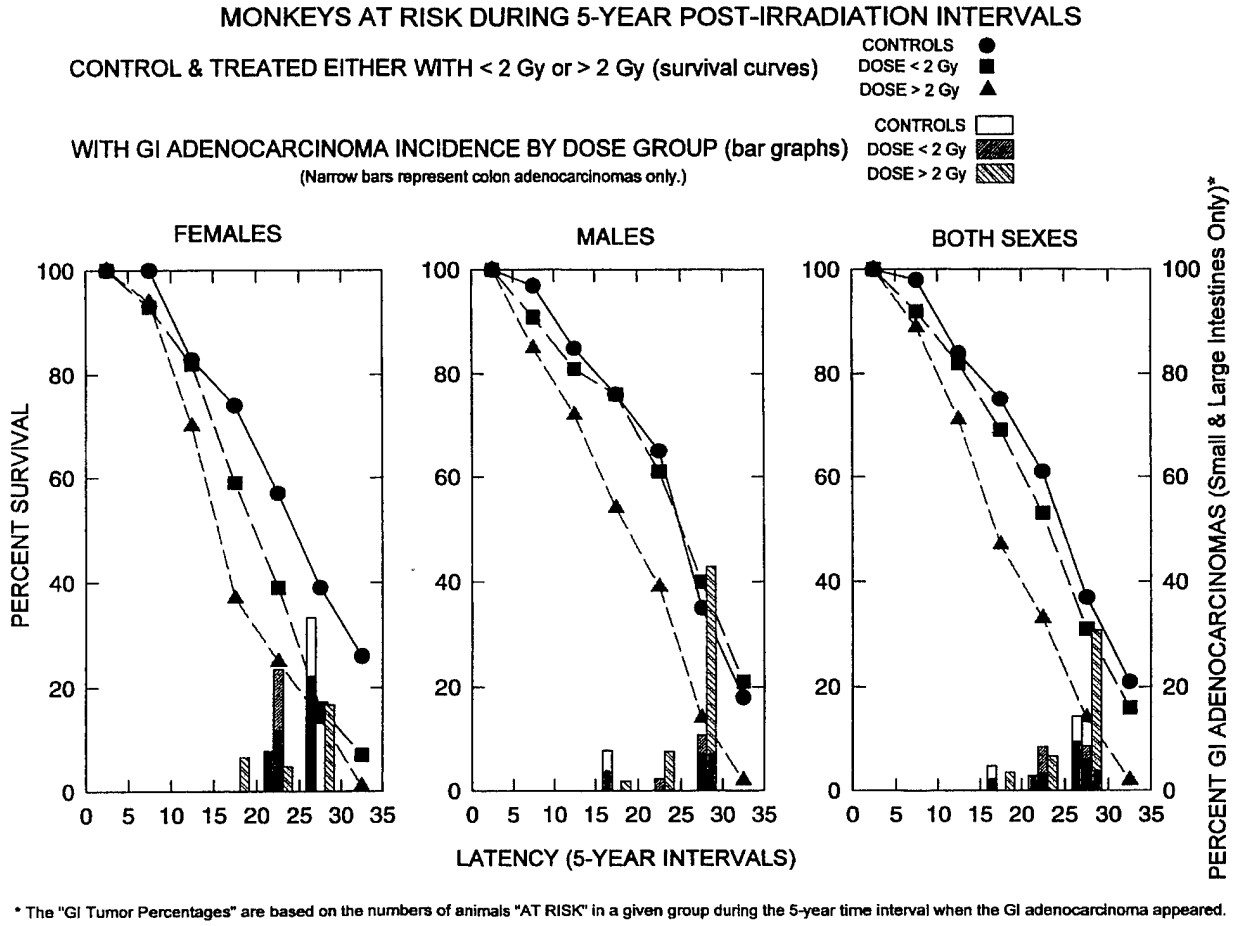
Median Life Spans (in years) for Rhesus Monkeys in the Delayed Effects Colony (DEC)			
	Controls	≤ 2 Gray*	> 2 Gray*
Both Sexes	~24.8	~23	~17
Females only	~24	~20	~15.5
Males only	~25	~25	~19

* *"Core Doses" based on depth dose calculations by Dr D. D. Leavitt, The University of Utah.*

Table 1. Estimated Median Life Spans (MLS) in years for DEC monkeys. The figures are based on data from populations of rhesus monkeys housed and cared for by the staff of the Veterinary Sciences Division, USAF Armstrong Laboratory, Brooks AFB, TX.

A slightly different presentation of the data from Figure 1 appears as Figure 2. In that set of graphs, females, males and pooled sexes are plotted together, but all dose groups appear on the

same graph for each group. GI adenocarcinomas are shown on this set of graphs also, but, in addition, colon tumors are indicated as narrow bars associated with the GI adenocarcinoma bar graphs. Sections of colon tumors and adenomas of the ileocecal junction were tested for the presence of p53. One out of 4 controls with colon cancer, a female, was positive for p53. Among the subjects which received $\geq$ 2 Gray, one animal out of 4, also a female, was positive for p53; this monkey had a tumor of the ileocecal junction, and she had received a total-body dose of 4 Gray (400-MeV protons). Future examinations of tissues will include p53 testing of duodenal and ileal adenocarcinomas. All the colon and ileocecocolic tumors tested were positive for Carcinoembryonic Antigen (CEA).



* The "GI Tumor Percentages" are based on the numbers of animals "AT RISK" in a given group during the 5-year time interval when the GI adenocarcinoma appeared.

Figure 2. Percent survival as a function of age during 5-year post-irradiation intervals indicated on each graph is control and dose >2 Gray and controls, for females, males and both sexes combined, respectively.

Figures 3 and 4 are illustrations of depth doses to the abdominal and pelvic regions of rhesus monkeys. Calculations were performed by Dr D. D. Leavit and his colleagues at the University of Utah using software created for human proton radiation therapy protocols. In Figure 3 (an abdominal section) it can be seen that doses to parts of the GI tract could be as high as >140% of the surface dose of 55-MeV protons. Nonetheless, certain parts of the GI tract received doses less that 100% and even less than 60% of the surface dose. In Figure 4 (a pelvic section), there is

a "hot spot" where the dose delivered is $\geq$ 180% of the surface dose. The section shown does not indicate that the hot spot affects a part of the GI tract, but the organ is so extensive in this region that chances are such a hot spot might well have affected a part of the gut. Of the 9 GI adenocarcinomas that appeared in the group of monkeys which received core doses >2 Gy, one was in an animal that received a surface dose of 0.25 Gy of 55-MeV protons. Of the 15 GI adenocarcinomas in the group which received core doses > 2 Gy, three were animals exposed to surface doses of 2 Gy of 55-MeV protons. All of the 55-MeV GI tumors were in males.

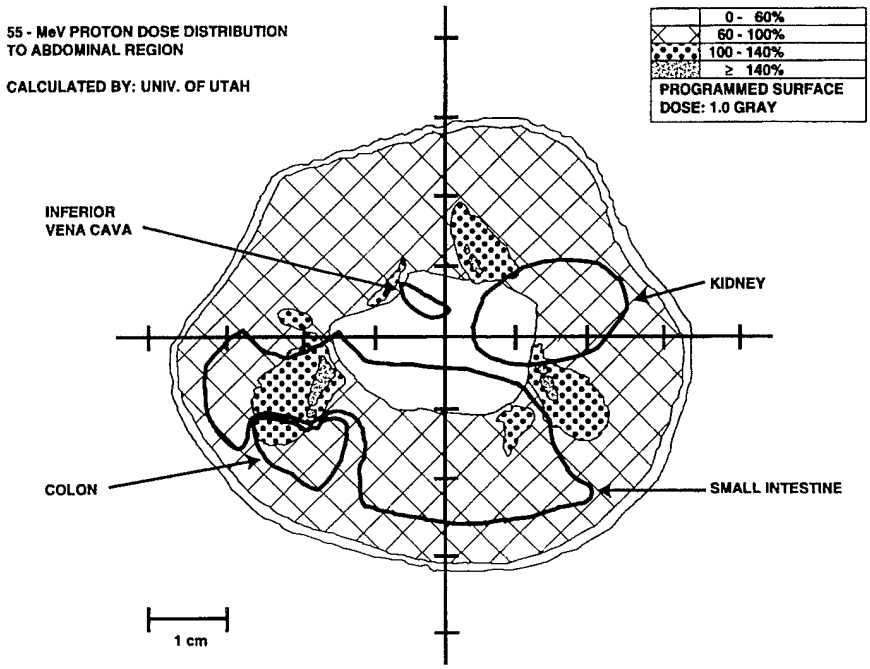


Figure 3. 55-MeV proton depth dose distribution to the abdominal region of a rhesus monkey. The programmed surface dose was 1 Gray (see also 39, 40, 55).

It is interesting to note that while colon adenocarcinomas are relatively common in aging humans, tumors of the small intestines are not. Among the monkeys in the DEC, duodenal and ileal, but not jejunal, tumors appeared (data are shown in Figures 1 and 2).

Amelanotic Melanoma. One animal which received 9.0 Gy of 2-MeV electrons in 1969 presented with a possible amelanotic melanoma 22.6 years later. The tumor was extremely invasive and became quite large before it was detected. It appears to have originated on the skin surface of the monkey in the abdominal region. It was Dr. M. Hanes' impression that no tumors of this type have ever been reported in the literature for rhesus monkeys. We presume the tumor was caused by the extremely high surface dose of electrons received by this subject. The occurrence of the tumor has some implication for possible hazards of Bremsstrahlung during space missions.

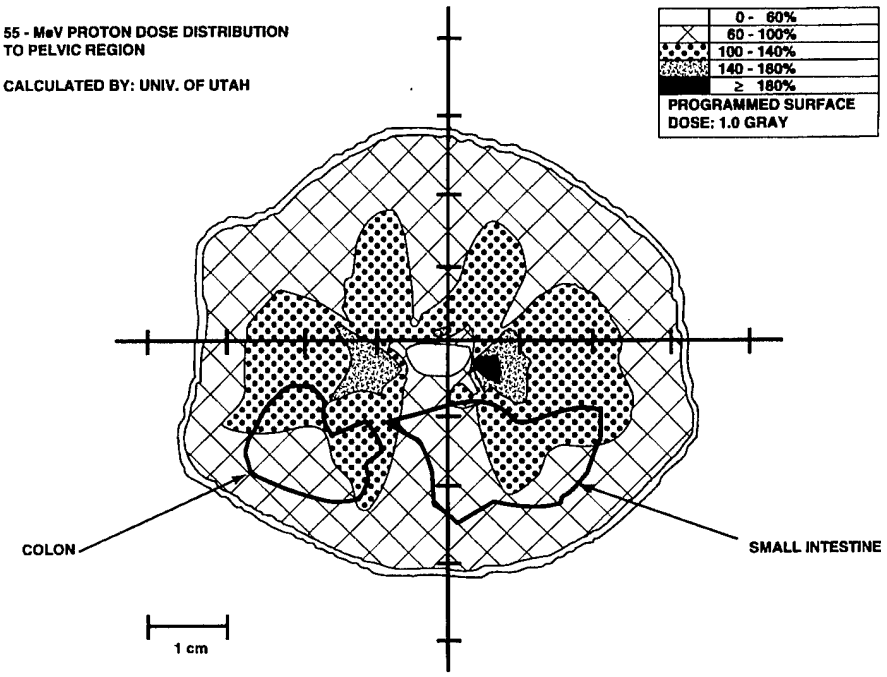


Figure 4. 55-MeV proton depth dose distribution to the pelvic region of a rhesus monkey. The programmed surface dose was 1 Gray (see also 39, 40, 55).

Adenocarcinomas of the Breast. There were fewer females than males in the original study (40% of the controls and 42.5% of the irradiated animals were females.) As far as female *cancers* are concerned, we have limited data, not only because we started with smaller numbers of females, but also because many female monkeys developed endometriosis (see below), which in the early days of the experiment proved fatal to some.

In general, adenocarcinomas of the rhesus breast do not metastasize widely, although there are some exceptions to that rule (J. W. Fanton, personal communication). Three control females from the DEC developed breast cancers. One of those controls had a tumor which metastasized widely, but tumors from the other two controls did not metastasize. In fact, one of the females is still alive at this writing at the age of 28, despite two recurrences of her tumor since it first appeared when she was 19 years old. When tested, none of the control tumors was positive for estrogen receptors or p53, but some of the tumors from irradiated subjects were positive for those entities. Figure 5 shows the incidence of mammary tumors in female rhesus monkeys exposed to the "surface" doses indicated, and percentages of animals which tested positive for p53 are indicated as well.

One male developed a mammary adenocarcinoma. He was an irradiated monkey which had recieved 3.6 Gy of 138-MeV (fully penetrating) protons 27.8 years before the tumor was diagnosed. No DEC male controls have presented with mammary adenocarcinomas.

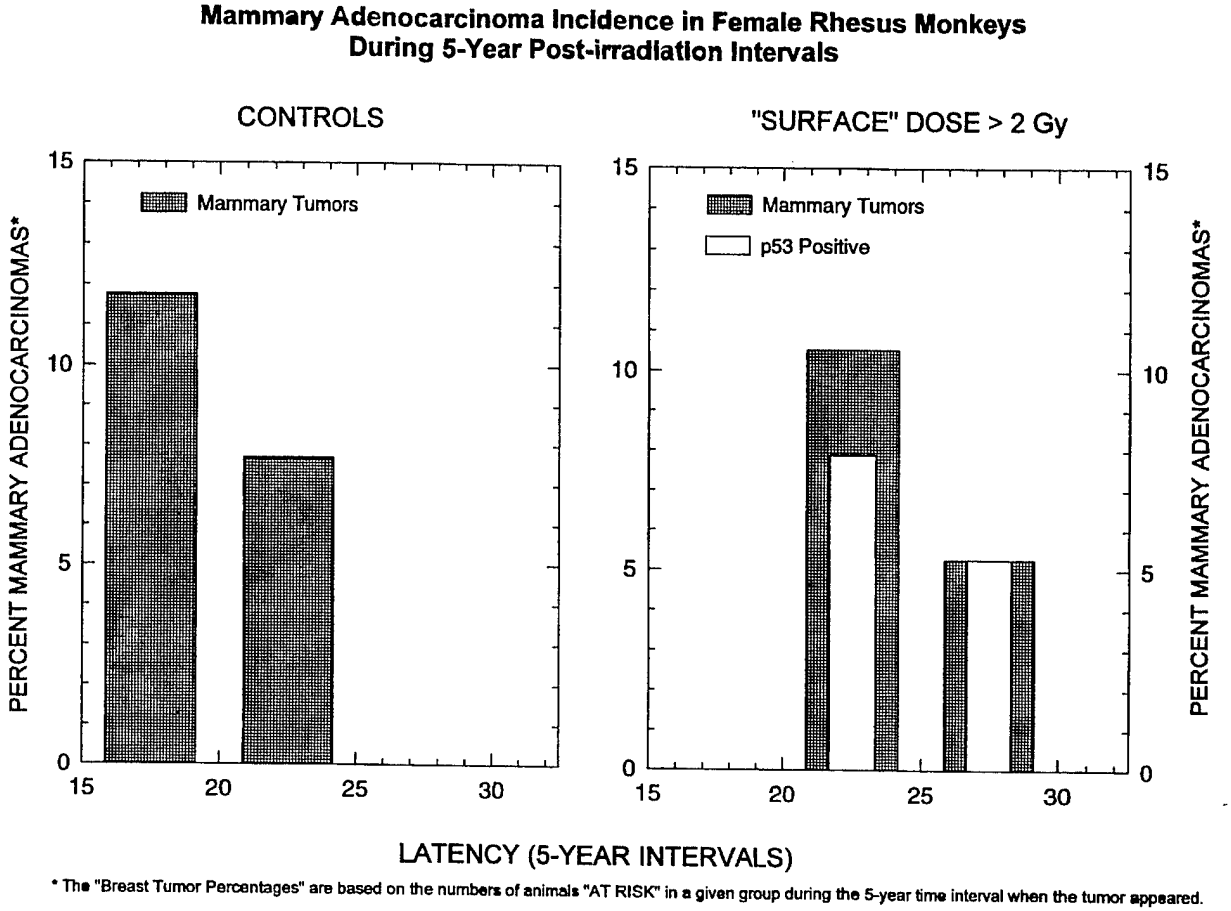


Figure 5. Percent mammary adenocarcinoma in female rhesus monkeys during 5-year post-irradiation intervals; also shown is percentage of animals testing positive for p53.

LIFE SHORTENING: ENDOMETRIOSIS

Incidence of Endometriosis in Control and Irradiated Female Subjects. Endometriosis is abnormal growth of endometrial cells outside the uterus. It is a disease which affects 10-15% of human females of reproductive age. In addition to occasionally extreme periodic pain in affected individuals, the illness can cause serious reproductive problems as well as adhesions and numerous other complications. Endometriosis occurs naturally only in animals (including humans and nonhuman primates) which have menstrual cycles; it does not arise in animals which have estrous cycles (e.g., mice and rats). Among females in the Delayed Effects Colony (DEC), the disease appeared in 26% of controls and 53% of all irradiated individuals (42). This was an unexpected finding, and, it turned out that that disease proved fatal to a number of female monkeys early in the experiment (as far as we know, the disease is not fatal in humans). Dr J. W. Fanton, our veterinary surgeon, added pelvic examinations to the routine physical examinations of female subjects several years ago, and thus was able to save several of the

afflicted individuals by surgically inducing menopause before the disease became fatal to them. Details of the endometriosis study may be found in reference 42 by J. W. Fanton and J. G. Golden.

Although it is not completely clear why some women and macaques develop endometriosis, it appears to involve reduced immune system functions (W. P. Dmowski, personal communication). Before the 1920's endometriosis was considered to be a "benign cancer". Only after the 1920's was it defined as a separate disease. It is now known that displacement of endometrial cells (e.g., in the peritoneum) occurs naturally in 100% of women and monkeys. If 100% of normal female primates exhibit this phenomenon, why then do only 10-15% of humans and 10-26% of rhesus monkeys present with endometriosis? It appears that deficits in both cell-mediated and humoral immunity are responsible for the unchecked growth of endometrial cells outside the uterus. Specifically, there are functionally different (peritoneal) macrophages present in endometriosis patients. Furthermore, it has been found by cancer immunologists that macrophages from patients suffering from lung and stomach cancer are functionally abnormal in the same way that macrophages from endometriosis patients are. It is Dr. Dmowski's contention that changes leading to endometriosis are caused primarily by 1) genetic predisposition and 2) environmental effects on the immune system. An increase in the incidence of endometriosis since the 1920's may be the result of improved diagnostic methods, but environmental influences must not be discounted, especially since it is known that polychlorinated biphenyls and dioxin as well as ionizing radiation suppress the immune system.

Spinoff of Endometriosis Findings. Following the publication by Fanton and Golden in 1991 (42), Dr Dmowski brought the paper to the attention of participants in an endometriosis workshop at NIH. Several scientists recalled that endometriosis has appeared in macaques exposed to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin or polychlorinated biphenyl compounds, but that the results had not been published. It transpired that 17 female macaques exposed to dioxin survived in a colony at the University of Wisconsin, and funds were found to support these monkeys. All were examined for endometriosis and significant increases in the disease were found in individuals exposed to 5 or 25 parts per trillion (ppt) of dioxin for 4 years. The first of a series of articles on the dioxin monkeys was published in 1993 by Rier and her colleagues (50). When controls were compared with subjects which received 5 ppt dioxin, the increase in incidence was significant at the $p<0.05$ level by chi square analysis; for the animals which received 25 ppt dioxin, the increase was significant at the $p<0.001$ level.

Publications of references 42 and 50 have inspired new interest in endometriosis, not only in humans but also in monkey populations. Significant improvements in quality of life for human and nonhuman female primates should occur as a result of this work.

CATARACTOGENESIS & OTHER OPTICAL ENDPOINTS

Delayed Effects Colony. In 1985, the USAF awarded a contract to Colorado State University to monitor radiogenic cataracts in the DEC. That contract was extended and finally terminated in 1995. The system for scoring of lenticular opacifications by Dr A. C. Lee was the same as that used for quantitating cataracts in New Zealand white rabbits exposed to heavy ions or ^{60}Co γ rays, dogs exposed to ^{60}Co γ rays and rats exposed to protons. Several human ophthalmologists

(MD's) including Dr Will Meecham (supported in part by the NSCORT program, NASA order #W-180002), looked at both rabbits and DEC monkeys as part of an effort to calibrate among several different cataract-scoring systems. A series of publications stemmed from his work (1, 2, 3, 5, 7, 9, 13,). Some promising spinoffs of this part of the project are discussed below.

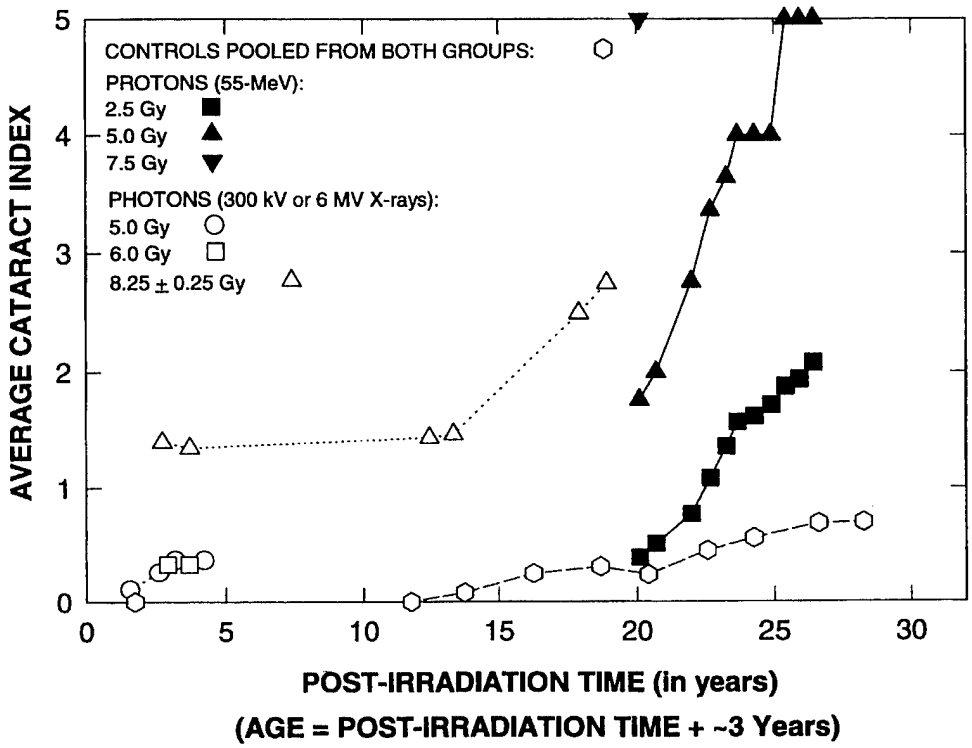
Optical Coherence Tomography (OCT) Examinations of Cataractous Lenses. OCT is a non-invasive imaging technique that produces a two-dimensional cross-sectional image of intraocular tissue similar to an ultrasound B scan, except that it is obtained using light rather than acoustic waves. In OCT the images are formed by measuring optical reflections from the tissue being examined. In June 1994, doctoral candidate Stephen Boppart was invited by Dr W. P. Roach to bring a prototype OCT scanner from MIT to AL for some retina studies. Dr C. D. DiCarlo suggested that the equipment could be used to measure lenticular opacities as well, and since the DEC included several individuals with unquestionable radiogenic and senile cataracts, we agreed to refocus the equipment and measure cataracts in selected DEC subjects. Dr D. A. Gagliano, a human ophthalmologist (MD) agreed to look at the monkeys using several different scoring systems, including those used by Will Meecham (see above). We found remarkably good correlation among the scoring systems of Lee, Meecham and Gagliano, and the OCT images of the monkey lenses were detailed and informative. One article on this subject has been published [1] (16) and two abstracts have been approved for presentations at meetings (33 and 35). It is apparent, however, that the DEC served as a means by which the prototype OCT equipment could be tested on nonhuman primates with cataracts, and the OCT prototype has provided us with new, corroborative, data on a very important nonstochastic late effect of protons.

Rijswijk Monkeys. Two sets of cataract examinations were performed on rhesus monkeys irradiated with photons and rescued with bone marrow transplant (BMT) or other means at The Radiobiological Institute, TNO, Rijswijk in The Netherlands; some data from the first set of evaluations may be found in reference (5). The funding for these measurements came from NATO, Colorado State University and the University of Leiden. Additional measurements were made of the retinas of the Rijswijk monkeys by Dr Monique Niemer-Tucker and her colleagues concurrently with Dr Lee's lenticular examinations. There was no apparent increase in fundus lesions in the majority of the animals tested by fundoscopy and fluorescence angiography, even at long post-irradiation times (>15 years) after relatively high doses (e.g., $\geq$ 6 Gray) of X rays. An article on this part of the study has been published (15). An updated version of the comparative cataract graph for DEC and TNO monkeys is presented as Figure 6. It should be noted that, even in the oldest subjects from both groups of animals, control levels of cataracts are comparable. Also, because Dr Lee has been able to examine lenses from BMT-rescued animals quantativley, one can see from Figure 6 that we have been able to fill in some of the "holes" in our database which are there because we started looking at the majority of the DEC monkeys 20 years post-irradiation. Finally, even though the DEC monkeys were exposed to protons and the TNO macaques were irradiated with photons, the fact that the relative biological effectiveness (rbe) for the protons used in this study is not more than 1.5 and, in fact, is probably closer to 1,

[1] An additional article published in 1999 is titled: "Comparison of Optical Coherence Tomography Imaging of Cataracts with Histopathology." The authors are Cheryl D. DiCarlo, W. P. Roach, Donald A. Gagliano, Stephen A. Boppart, Daniel X. Hammer, Ann B. Cox and James G. Fujimoto. The reference is Journal of Biomedical Optics, 4(4), 450-458 (October 1999).

the cataract data are closely comparable at this time. It gives us an excellent opportunity to continue the animal-to-animal extrapolation segment of our study as preparation for future animal-to-human extrapolations.

RADIOGENIC CATARACTS IN AGING RHESUS MACAQUES



PROTON-IRRADIATED PRIMATES FROM ARMSTRONG LABORATORY (San Antonio, USA)

PHOTON-IRRADIATED SUBJECTS FROM TNO (Rijswijk, The Netherlands)

Figure 6. Radiogenic cataract development in aging rhesus monkeys exposed either to high-energy X-rays or to high-energy protons.

Human Data: Radiotherapy Patients. Although there are abundant data on photon effects in humans, exposures of human eyes to protons and helium ions have been relatively infrequent. During the last 20 years or so, however, radiotherapy (using protons or helium ions) for ocular melanomas in humans has become a preferred treatment for some cases; not only can many tumors be eradicated by well-focused proton or helium-ion beams, but the eye can be retained by the cured patient with minimal loss of vision. Nonetheless, part of the lens may be irradiated unavoidably in patients, and late lenticular damage may become evident. Blakely et al. have begun to look for cataracts in the lenses of patients who have undergone helium-ion radiation therapy for uveal melanoma. The subjects chosen had either 1- 10% or < 1% of their lenses exposed during radiotherapueutic treatments. Asymmetrical cataracts were found in 48% of all

the treated patients, and details of the preliminary study may be found in reference 9. This preliminary study marks an early effort in the development of our animal-to-human extrapolation system for late ionizing radiation effects as they relate to human risk estimates.

Human Data: Hiroshima Study Participants. In November 1993, a visit to the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan, gave us an opportunity to examine medical charts from selected bomb victims preparatory to applying our cataract scoring system to human participants in the RERF long-term studies. Based on the chart data, Dr J. T. Lett assigned cataract scores and estimated doses to individual study participants based on those numbers. In the approximately 4/30 cases for which Dr Lett's estimated dose did not match the estimated dose in the basic chart, re-examination of other data on those individuals (including recently obtained chromosome aberration data and pre-bomb lens status, for example) showed that indeed the cataracts seen, even in these 4 patients, were good indicators of optical radiation doses. We hope to follow up on this study in the near future with rigorous examinations of more Adult Health Study participants' records.

CHROMOSOME ABERRATIONS

Basic Techniques for Measuring Chromosome Aberrations in Rhesus Monkey Lymphocytes. In the early 1990's, techniques for rapid measurement of aberrations in human chromosomes were developed. Molecular probes were developed for each human chromosome so that specific genetic material could be "painted" using fluorescence in situ hybridization ("FISH") techniques. It was found by Lucas et al. (6) that probes designed for humans could be used to "paint" chromosomes from macaques. Standard mitogens such as phytohemagglutinin (PHA) could be used successfully with human or *Macaca fascicularis* (crab-eating macaque) lymphocytes, but relatively few mitoses were obtained from *M. mulatta* (rhesus) lymphocytes using the same technique, and the efficiency of using FISH to measure aberrations in rhesus monkeys was limited. Hill et al. (12) developed a technique using staphylococcal enterotoxin A (SEA) to stimulate mitosis in rhesus lymphocytes, and that method enabled her lab to determine aberration frequency as efficiently for rhesus as for human chromosomes. Currently there are articles in preparation, one of which was published in 1996,[2] which will present data from 5 DEC subjects exposed to 3 different doses (0.56, 1.13 or 2.25 Gy) of 2.3 GeV (fully penetrating) protons in 1965. Data from lymphocytes show a distinct dose response and data from skin fibroblasts (from the same subjects) currently are being analyzed. The monkey lymphocyte data correlate very nicely with data from humans exposed to radiations from the Hiroshima bomb, and the reader should see the article by J. N. Lucas et al. titled "Rapid Translocation Frequency Analysis in Humans Decades after Exposure to Ionizing Radiation" in the International Journal of Radiation Biology, vol 62, pp.53-64 (1992) for further details of that study. One value of the monkey data is that the doses to the blood-forming organs are known accurately rather than estimated as they are for the Hiroshima study participants. A spin-off from this work (both in humans and nonhuman primates) is that chromosome painting probes are being used to detect persistent as well as early chromosome aberrations in workers exposed chronically to relatively high doses of

[2] Lucas, J. N., Hill, F. S., Burk, C. E., Cox, A. B. and Straume, T. Stability of the translocation frequency following whole-body irradiation measured in rhesus monkeys. Int. J. Radiat. Biol. 70 (3) (309-317) (1996).

such chemicals as benzene. The new studies have implications both for NASA and the USAF as far as measurements of genetic damage from substances such as jet and rocket fuels (and their derivatives) are concerned.

SUMMARY AND CONCLUSIONS

CANCERS. The majority of radiogenic cancer data highlighted in this report are not unique to the radiations studied (protons and electrons in addition to X-rays). Rather, they appear to have resulted from the geometry of energy deposition unique to energetic particulate radiations. In addition, the anatomy of the irradiated nonhuman primates discussed in this report is similar enough to that of humans to make animal-to-human extrapolation much more straightforward from DEC data than it might be from laboratory rodents, the sizes and shapes of which are quite dissimilar to those of humans.

ENDOMETRIOSIS. The incidence of endometriosis was higher in all irradiated DEC cohorts than it was in control females. The higher disease levels were found in individual females exposed to all types of radiation *including electrons* (surface doses only). The immunolgical implications of this particular phenomenon remain to be explored. The fact that the treated DEC females exhibited increased frequencies of endometriosis due to radiation exposure has important implications for human and animal health, and new interest in environmental causes of endometriosis has been kindled by our study.

CATARACTS. In numerous publications on radiogenic cataracts monitored in the DEC and other model species, we have discussed the implications of all our animal data. Our conclusions on the subject at this time include the following: 1) Long-lived model species (monkeys, rabbits, dogs) which do not exhibit high endogenous levels of cataract serve as better representations for intermediate and late radiation cataracts than do rodents; 2) Treated with thoughtful care (e.g., considering post-irradiation time, cataract level at a given time and comparisons with age-matched controls), data on lenticular opacifications in monkeys, dogs, rabbits and humans can serve to an extent as biological dosimeters; 3) The time courses of radiation cataract development in long-lived species are such that risks for intermediate or late cataracts from ionizing radiations may be less alarming than once was thought for astronauts and high-flying air crews.

IONIZING RADIATION EFFECTS ON NEURONS. Although not pursued directly under NASA contracts #T13215 and W18571, there has been a constant concern, based on work by Lett et al. with rabbit models (NASA Grants NAG 9-10 and NAG 583), that neuronal loss and DNA damage (in the photoreceptor cells of the retina, considered by some to be a "mini-brain" model) may prove to be a problem among the DEC subjects. With future experiments in mind, we have been freezing retinas from euthanized monkeys in liquid nitrogen, and now have more than 30 specimens (plus 39 control retinas from macaques of different ages)[3] for future cell

[3] Note added in 2002: Additional tissues were frozen in liquid nitrogen from 1995-1998. It is this writer's understanding that those priceless tissues continue to be maintained at Brooks AFB.

counts and measurements. It is our plan, should funding become available, to have Professor Lett's group measure damage in the monkey retinas and determine whether or not it correlates with their data from aging rabbit retinas exposed to ^{60}Co γ-rays, or various heavy ions (^{20}Ne, ^{40}Ar or ^{56}Fe). This is an example of a project impossible to perform with human tissues due to the rapid loss of DNA integrity after death, but feasible with nonhuman primate materials frozen within 5 minutes of euthanasia.

CHROMOSOMES. Our chromosome studies are an excellent example not only of accurate biological dosimetry in vivo but also of techniques which can "spin off" into studies of chemical damage to genetic materials. The DEC subjects have provided cells for this work which received *KNOWN* doses of radiation and thus can be used as "standards" to calibrate other systems both in humans and animal models.

ANIMAL-TO-HUMAN EXTRAPOLATION. Much of the extrapolation of DEC data will come in the future. It is important to reiterate here, that the nonhuman primate model, unlike rodent models, has provided (and should continue to provide) us with information not obtainable from rodents. Geometry of energy deposition, endometriosis, cataractous lenses available for OCT measurements, chromosomes for aberration analyses, and, we hope, frozen retinas for future neurocytochemcial measurements all will enhance our abilities to predict radiation risks for astronauts and high-flying air crew which will be accurate without causing undue concern for managers and personnel.

The DEC study is one of the most valuable animal research projects to date in radiobiology, and NASA and the USAF are to be commended for their continued support.

REFERENCES

1. Lett, J. T., Lee, A. C., and Cox, A. B. Late cataractogensis in rhesus monkeys irradiated with protons and radiogenic cataract in other species. Radiat. Res.126:147-156. (1991)

2. Shinn, J. L., Wilson, J. W., Cox, A. B., and Lett, J. T. A study of lens opacification for a Mars mission. Proc. 21st International Conference on Environmental Systems, SAE Technical Paper Series #911354. (1991)

3. Cox, A. B., Lee, A. C., Williams, G. R., and Lett, J. T. Late cataractogenesis in primates and lagomorphs after exposure to particulate radiation. Adv. Space Res. 12, (2): 379-384. (1992)

4. Cox, A. B., and Lett, J. T. Combined effects: radiation, microgravity, trauma and other factors. Introductory remarks. Adv. Space Res. 12, (2): 149. (1992)

5. Cox, A. B., Salmon, Y. L., Lee. A. C., Lett, J. T., Williams, G. R., Broerse, J. J., Wagemaker, G. and Leavitt, D. Progress in the extrapolation of radiation catractogenesis data across longer-lived mammalian species. Proceedings of NATO Advanced Study Institute on *Biological Effects and Physics of Solar and Galactic Cosmic Radiation*, part A. (C. E. Swenberg, G. Horneck and E. G. Stassinopoulos. Editors), 99:177-184, Plenum Press, New York. (1993)

6. Lucas, J. N., Cox, A. B. and McLean, J. Human chromosome "painting" probes used to measure chromosome translocations in non-human primates: extrapolations from monkey to man. Radiat. Protection Dosim. 46:253-256. (1993)

7. Cox, A. B., Salmon, Y. L., Hanes, M., Fanton, J. W., Lett, J. T., Lee, A. C. and Williams, G. R. Radiological risk estimates for space flight based on long-term studies in proton-irradiated primates. Proc. 23rd International Conference on Environmental Systems, SAE Technical Paper Series #932213. (1993)

8. Stone, W. H., Saphire, D. G., Hackleman, S. M., Braun, A. M., Pennington, P., Scheffler, J., Wigle, J. C., and Cox, A. B. Effects of radiation and age on immunoglobulin levels in rhesus monkeys *(Macaca mulatta),* Radiat. Res., 138: 401-408. (1994)

9. Blakely, E. A., Daftari, I. K., Meecham, W. J., Alonso, L. C., Collier, J. M., Kroll, S. M., Gillette, E. L., Lee, A. C., Lett, J. T., Cox, A. B., Castro, J. R., and Char, D. H. Helium-ion induced human cataractogenesis. Adv. Space Res. 14, (10): 501-505. (1994)

10. Dalrymple, G. V., Leichner, P. K., Harrison, K. A., Cox, A. B., Hardy, K. A., Salmon, Y, L. and Mitchell, J. C. Induction of high grade astrocytoma (HGA) by protons: molecular mechanisms and RBE considerations. Adv. Space Res. 14, (10): 267-270. (1994)

11. Wood, D., Cox, A. B., Hardy, K., Salmon, Y. and Trotter, R. Head and neck tumors after energetic proton irradiation in rats. Adv. Space Res. 14, (10): 681-684. (1994)

12. Hill, F. S., Cox, A. B., Salmon, Y. L., Cantu, A. O. and Lucas, J. N. Comparison of mitogenic response of irradiated and unirradiated rhesus monkey lymphocytes to phytohemagglutinin and staphylococcal enterotoxin A. International Journal of Radiation Biology 66: 381-384. (1994)

13. Lett, J. T., Lee, A. C. and Cox, A. B., Risks of radiation cataracts from interplanetary space missions. *Acta Astronautica* 32: 739-748. (1994)

14. Facius, R. and Cox, A. B. Preface for "Radiation Effects and Dosimetry" and Radiation Protection Guidelines, "Proceedings of the 9th IAA Symposium on Man in Space, *Acta Astronautica* 32: xi-xiii, (1994)

15. Niemer-Tucker, M.M.B., Sterk, C. C., Lee, A.C., Lett, J. T., Cox, A. B., Emmanouilidis-van der Spek, K., Davelaar, J. and Broerse, J. J. Late ophthalmological complications after total body irradiation in nonhuman primates. Int. J. Radiat. Biol.75: 463-472, (1999)

16. DiCarlo, C. D., Boppart, S. A., Gagliano, D. A., Amnotte: R; Smith. A. B., Hammer, D. X., Cox, A. B., Hee, M. R., Fujimoto, J. Swanson, E. and Roach, W. P. A new noninvasive imaging technique for cataract evaluation in the rhesus monkey. IN *Lasers in Surgery: Advanced Characterization, Therapeutics, and Systems V, Proc. SPIE*, 2395: 636-643 (1995)

17. Cox. A.B., Lett, J. T., and Lee, A.C. Late cataractogenesis in primates exposed to protons. Abstracts - Radiation Research Society - 38th Annual Meeting, New Orleans, LA, (1990)

18. Cox, A.B., Lett, J.T., and Lee, A.C. Late cataractogenesis in primates exposed to protons. Abstracts - COSPAR - 28th Plenary Meeting, The Hague, The Netherlands, (1990)

19. Lett, J. T. and Cox. A. B. Risks of radiation cataracts from interplanetary space missions. Abstracts. 9th IAA Symposium on Man in Space. Köln. Germany, June 1991.

20. Lucas, J. N., Poggenssee. M., Cox. A. B., McLean. J. R. N. and Brooks A. L. Chromosome translocation studies in irradiated primates using fluorescence in situ hybridization. Abstracts – Radiation Research Society – 40th Annual Meeting. Salt Lake City Utah. (1992)

21. Cox, A. B., Lee, A. C., Williams G. R., and Lett, J. T. Late Radiogenic cataracts from high-energy particles in selected animal species: a comparative study. Abstracts: World Space Congress Committee on Space Research (COSPAR). Washington DC. 28 Aug – 5 Sep 1992.

22. G. V. Dalrymple, P.K. Leichner, A. B., Cox &. K. A, Hardy. Induction of high-grade astrocytoma (HGA) by protons: molecular mechanism and RBE considerations, Abstracts, World Space Congress Committee on Space Research (COSPAR). Washington, DC. 28 Aug.5 Sept 1992.

23. D. H. Wood, A.B. Cox & R.W. Trotter. Head and neck tumors after energetic proton irradiation in rats, Abstracts. World Space Congress Committee on Space Research (COSPAR), Washington, D.C. 28 Aug- 5 Sept 1992.

24. Broerse, J. J., Niemer-Tucker, M. M. B., Wagemaker, G., Van Bekkum, D. W., Zurcher, C., Lee, A. C., Williams, G.R. and Cox. A. B. Late effects on high-dose total body irradiation in rhesus monkeys and the extrapolated risk to man. Abstract - European Society of Radiation Biology, Ehrfurt, Germany, October 1992.

25. Cox, A. B., Salmon, Y. L., Hanes, M., Fanton, J. W., Lett, J. T., Lee, A. C. and Williams, G. R. Radiobiological risk estimates for space flight based on long-term studies in proton-irradiated primates. Abstract- 23rd International Conference on Environmental Systems, Colorado Springs, CO, 11-15 July 1993.

26. Cox, A. B. Radiation Risk Estimates for Aerospace Operations. Abstract for Workshop on "Strategies for Conduct of Functionally Oriented Life Sciences Research in Support of Human Space Flight" (J. Bagian, organizer), Aerospace Medical Association Annual Meeting, San Antonio, TX, 8-12 May 1994.

27. Cox, A. B., Hanes, M.A., Trotter, R.W., DiCarlo, C.D., Fanton, J.W., Lett, J. T., Lee, A.C. and Lucas, J. N. A nonhuman primate model for Particulate Radiation Risk Estimates. Abstract for International Symposium, "Heavy Ion Research: Space Radiation Protection and Therapy," Sophia-Antipolis, France, 21-24 March 1994.

28. Cox, A., Hill, F., Burk, C., Cantu, A., Salmon, Y., Straume, T., and Lucas, J. Stability and Variability or Reciprocal Translocation Frequencies Measured 29 Years after Exposure to Ionizing Radiations. Abstract for 42nd Annual Scientific Meeting, Radiation Research Society, Nashville, TN, 29 April-4 May 1994.

29. Cox, A. B., Salmon, Y. L., Hardy, K. A., Hanes, M. A., Trotter, R. W., DiCarlo, C. D., Fanton, J. W., Lett, J. T., Lee, A. C., Williams, G, R., and Lucas, J. N. Nonhuman primates exposed to high-energy protons: a model for late space radiation effects extrapolated to man. Abstracts for Fifth Annual Space Radiation Health Investigators' Workshop, Houston, TX, 27-28 April 1994, p. 59.

30. Cox, A. B. Nonhuman Primates Exposed to High Energy Protons: A Model for Late Space Radiation Effects Extrapolated to Man, Abstract for 30th Scientific Assembly, Committee on Space Research (COSPAR), Hamburg. Germany, 11-21 July 1994.

31. Cox, A.B., Hanes, M.A., Trotter, R.W., DiCarlo, C.D., Fanton. J.W., Lett, J.T., Lee, A.C. and Williams, G.R. Late Effects of Protons in Nonhuman Primates: Deterministic and Probabilistic Data Relevant to Space Radiation Risk Estimates, Abstract for 30th Scientific Assembly, Committee on Space Research (COSPAR), Hamburg. Germany, 11-21 July 1994.

32. Hanes, M.A., Cox, A. B., Trotter. R. W., Fanton, J. W., and DiCarlo, C. D. Colon Cancer in Aged Rhesus Monkeys. Abstract for 4th Annual Symposium, on Cancer Research, San Antonio, TX, 22 July 1994.

33. DiCarlo, C. D., Boppart, S. A., Hee, M. R., Fujimoto, J. G., Gagliano, D. A., Swanson, D. A., Cox, A. B., Amnotte, R. E., Smith, A, B. and Roach. W. P. A New Noninvasive Imaging Technique for Cataract Evaluation in the Rhesus Monkey. Abstract for Biomedical Optics '95, section on Lasers in Veterinary Medicine, 6 Feb 1995.

34. Cox, A. B., Fanton, J. W., Hardy, K. A. and Leavitt, D. D., Space Radiobiological Studies with Mammalian Model Systems: Applications to Terrestrial Medicine. Abstract for NASA/AIAA hosted conference "Applications of Space Life Sciences, Today's Imperative: Bringing Space Benefits Down to Earth," 3-6 April 1995.

35. Gagliano, D. A., DiCarlo, C. D., Boppart, S. A., Cox. A. B., Hammer, D. X., Fujimoto, J. G, Roach, W. P. and Struck, B. E. Optical Coherence Tomography (OCT) Evaluation of Lenticular Opacification in Nonhuman Primates. Abstract for ARVO (Association for Research in Vision and Ophthalmology) meetings, May 1995.

36. Lett, J. T., Damage to DNA and chromatin structure from ionizing radiations, and the radiation sensitivities or mammalian cells. Progr. Nucl. Acid Res. Molec. Biol. 39: 305-352 (1990)

37. Lett, J. T., Atwell, W. and Golightly, M. J. In Solar Terrestrial Predictions: Proceedings of a Workshop at Leura, Australia. 1989 (R.J. Thompson et al., Eds.) Vol. 1:140-153. NOAA/ERL, Boulder, CO (1990)

38. Dalrymple, G. V., Lindsay, I. R., Mitchell, J. C. and Hardy, K. A. A review of the USAF/NASA proton bioeffects project: national and acute effects. Radiat. Res. 126(2): 117-119. (May 1991)

39. Hardy, K. A., Dosimetry methods used in studies of the effects of proton on primates: a review. Radiat. Res. 126(2): 120-126. (May 1991)

40. Leavitt, D. D. Analysis of primate head irradiations with 55-MeV Protons. Radiat. Res. 126(2): 127-131. (May 1991)

41. Wood, D. H. Long-term mortality and cancer risk in irradiated rhesus monkeys. Rad. Res. 126(2): 132-140. (May 1991)

42. Fanton, J. W. and Golden, J. G. Radiation-induced endometriosis in Macaca mulatta. Radiat. Res. 126(2): 141-146. (May 1991)

43. Lett. J. T. Damage to cellular DNA from particulate radiations, the efficacy of its processing and the radiosensitivity of mammalian cells: emphasis on DNA double strand breaks and chromatin breaks. Radiat. Environm. Biophys. 31: 257-277. (1992)

44. Konradi, A., Atwell. W., Badhwar, G. D., Cash, B. L. and Hardy. K. A. Low earth orbit radiation dose distribution in a phantom head. Nucl. Tracks Radiat. Meas.: Int. J. Radiat. Applic. and Instrumentation. Part D., 20(1): 49-54. (1992)

45. Lett. J. T. and Peters, E. L. Deoxyribonucleoprotein structure and radiation injury: cellular Radiosensitivity is determined by LET-dependent DNA damage in hydrated deoxyribonucleoproteins and the extent of its repair. Adv. Space Res. 12(2-3): 51-58. (1992)

46. Golightly, M. J., Hardy, A., Atwell, W., and Hardy, K. A. Description analysis and impact of major solar activity during recent U. S. Shuttle missions. Adv. Space Res. 12(2-3): 335-338. (1992)

47. Lett, J. T. Further consideration of classical and modern approaches to cellular radiosensitivity: A reply to Dr Rossi. Letter to the Editor. Radiat. Environ. Biophys. 32: 277-284. (1993)

48. Lett, J, T, and Williams, G, R. Effects of linear energy transfer on the formation and fate of radiation damage to the photoreceptor cell complement of the rabbit retina: implication for the projected manned mission to Mars. Proceedings of NATO ASI, Biological Effects and Physics of Solar and Galactic Cosmic Radiation: Part A (Life Sciences vol, 243 A), (C. E. Swenberg, G. Homeck and E. G. Stassinopoulos, Eds.), pp. 185-201, Plenum Press, New York (1993)

49. Lett, J. T. and Hagen, U. World Space Congress, Meeting F2.3-M: Mechanisms Underlying Cellular Radiosensitivity and RBE. Report. COSPAR Information Bulletin #127, 16-17, Pergamon Press, Oxford. (1993)

50. Rier, S. E., Martin, D. C., Bowman, R, E., Dmowski, W. P., and Becker, J. L. Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fund. Appl. Toxicol. 21: 433-441. (1993)

51. Lett, J. T. The renaissance in basic cellular radiobiology and its significance for radiation therapy. Adv. Radiat. Biol. 18: 181-223. (1994)

52. Williams, G. R. and Lett, J. T. Effects of ^{40}Ar and ^{56}Fe ions on retinal photoreceptor cells of the rabbit: implications for manned missions to Mars. Adv. Space Res. 14(10): 217-220. (1994)

53. Lett, J. T. Mechanisms underlying cellular radiosensitivity and RBE: concluding remarks. Adv. Space Res. 14(10): 295-296. (1994)

54. Golightly, M. J., Hardy A. C. and Hardy, K. Results of time-resolved radiation exposure measurements made during U.S. Shuttle missions with a tissue equivalent proportional counter. Adv. Space Res. 14(10): 923-926. (1994)

55. Hardy, K, A. and Leavitt, D. D. Experimental simulation of proton space radiation environments: a dosimetric perspective. Adv. Space Res. 14(10): 959-967. (1994)

56. Gupta, R. C. and Albanese, R, A. Survival analyses of irradiated animals incorporating competing risks and covariates. Environmetrics 5: 365-379. (1994)

57. Lett, J. T. The end of an hiatus in cell survival theory and its significance for radiation therapy (Lecture Abstract). J. Cancer Res, Clin. Oncol. 116 (Suppl., Part II): 844 (1990)

58. Lett. J. T., Atwell, W. and Golightly, M. .J. Radiation hazards to humans in deep space: a summary with special reference to large solar particle events. Presented at the National Oceanic and Atmospheric Administration (NOAA) Space Environment Services Center Users' Conference, Boulder, CO, 15-17 May 1990.

59. Golightly, M. J., Atwell, W., Hardy, A. C., Hardy, K., Quam, W. and Riehl, K., Time resolved dose and dose equivalent measurements during high inclination shuttle missions made with the U. S. Air Force radiation monitoring equipment (RME) III. Presented at the 61st Annual. Meeting of the Aerospace Medical Association New Orleans, LA, 13-17 May 1990.

60. Hardy, K, A., Atwell, W., Golightly, M. J., Hardy, A. C., Quam, W., Real-time and time-resolved dose measurements on Space Shuttle missions with the radiation monitoring equipment (RME) III. Presented at the 35th Annual Meeting of the Health Physics Society, Anaheim, CA, 24-28 June 1990 (Paper No. TAM-B9).

61. Fanton, J. W. and Golden, J. G, Radiation-induced endometriosis in Macaca mulatta. Presented at the Workshop on Basic Pathophysiology of Endometriosis, Washington, DC, September 1991.

62. Hardy, K. A., Golightly, W. and Quam, W. Radiation monitoring equipment dosimeter experiment. Presented at the NASA/DoD Space Technology Interchange Conference, Monterey. CA. 4-9 October 1992.

63. Lett, J. T. Radiation cataracts: Extrapolation across species. Third Annual Investigators Meeting on Space Radiation Research, Houston, TX, 14-15 April 1992.

64. Blakely, E. A., Daftari, I. K., Gillette, E. L., Lee. A, C., Lett. J. T., Castro, J. R. and Char, D. H. Helium-ion induced human cataractgenesis. In: Abstracts, 29th Plenary Meeting of the Committee on Space Research, Washington, DC, 28 August-5 September 1992, p. 557.

65. Hardy, K. A. and Leavitt, D. D. Experimental simulation of proton space radiation environments: a dosimetric perspective. In: Abstract. 29th Plenary Meeting of the Committee on Space Research, Washington, DC, 28 August-5 September 1992, p. 545.

66. Konradi, A., Badhwar, G.D., Hardy, A. C., Cash, B. L, Golightly, M. J., Atwell. W., and Hardy, K. A; Space shuttle radiation measurements and the radiation models. In: Abstracts, 29th Plenary Meeting of the Committee on Space Research, Washington DC, 28 August – 5 September 1992, p. 544.

67. Lett, J. T., Lee, A. C. and Williams, G. R. Effect of age at exposure on the responses of optical tissues to ^{56}Fe ions. Abstracts for the International Symposium, "Heavy Ion Research: Space Radiation Protection and Therapy," Sophia-Antipolis, France, 21-24 March 1994.

68. Lett. J. T., Lee, A. C. and Williams, G. R. Effect of age at exposure on the response of optical tissues to ^{56}Fe ions. Abstracts for Fifth Annual Space Radiation Health Investigators' Workshop, Houston, TX, 27-28 April 1994, p. 60.

69. Lett, J. T. Relevance of model systems for evaluating DNA damage in mammalian chromatin in situ. Abstracts, 30th COSPAR Scientific Assembly. Hamburg, Germany, 11-21 July 1994, p 295.

70. Williams, G. R. and Lett, J. T. Effects of ^{56}Fe ions on retinal cells of the rabbit. Abstracts, 30th COSPAR Scientific Assembly, Hamburg. Germany, 11-21 July 1994, p. 296.

71. Stone, W. H. and Miller, M. L. Late Immunobiological Effects of Space Radiation. Brooks AFB. TX: USAF School of Aerospace Medicine, USAF-SAM-Technical Report 90-39 (1990)

72. Leavitt, D. D. Proton depth dose distribution: 3-D Calculation of Dose Distributions from Solar Flare Irradiation. USAF School of Aerospace Medicine Report TP-90-17 (1990)

73. Leavitt, D. D. Proton Arc Doses to the primate head. USAF School of Aerospace Medicine Report TP-90-24. (1990)

74. Butler, T. M. Program review: The lifetime effects of space radiation in rhesus monkeys. USAF School of Aerospace Medicine Technical Report USAFSAM-TR-90-3 (1990)

75. Stone, W. H. and Miller, M. L. Effects of space radiation on humoral and cellular immunity in rhesus monkeys. Brooks AFB TX: Armstrong Laboratory Technical Report 1992-0101 (1992)

76. Gupta, R. C. Survival analyses of radiated animals incorporating competing risks and covariates. Final Report for Summer Research Program, Armstrong Laboratory, 1992.

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