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OPPORTUNITIES FOR ELECTRON MICROSCOPY IN SPACE RADIATION BIOLOGY

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Abstract

Densely ionizing, particulate radiations in outer space are likely to cause to mammalian tissues biological damage that is particularly amenable to examination by the techniques of electron microscopy. This situation arises primarily from the fact that once the density of ionization along the particle track exceeds a certain value, small discrete lesions involving many adjacent cells may be caused in organized tissues. Tissue damage produced by ionization densities below the critical value also afford opportunities for electron microscopic evaluation, as is shown by the damage produced in optic and proximate tissues of the New Zealand white rabbit in terrestrial experiments. Late radiation sequelae in nondividing, or terminally differentiating, tissues, and in stem cell populations, are of special importance in these regards.

It is probable that evaluations of the hazards posed to astronauts by galactic particulate radiations during prolonged missions in outer space will not be complete without adequate electron microscopic evaluation of the damage those radiations cause to organized tissues.

KEY WORDS: Ionizing, radiation, space, hazard, rabbit, cataract, astronaut, forebrain, HZE, skin

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Background and Rationale

Low doses of ionizing radiation represent significant hazards to man from both the terrestrial and extraterrestrial environments. In the latter case, moreover, many of the radiations encountered are unique to space, or else occur to only an insignificant extent in the terrestrial radiation spectrum. This is especially true of the densely ionizing particulate radiations in outer space, radiations believed to have arisen from explosions of supernovae. Such radiations are atoms of high (H) atomic number (Z) that have been stripped of orbital electrons, and hence are ions, and are of high energy (E); so they are called HZE particles. Other ionizing radiations in space are similar in nature, if not energy, to those encountered on earth and consist of electromagnetic radiations, X-(γ-)rays etc., and such particulate radiations as electrons, neutrons, protons, ^{4}He ions (α-particles), etc. I am going to deal primarily with the situation in space radiation biology because it provides interesting opportunities for electron microscopists that can be illustrated by examples selected from HZE particle experiments with the New Zealand white (NZW) rabbit (Oryctolagus cuniculus) performed in this laboratory for the past twelve years.

For the purposes of this discussion, ionizing radiations may be classified into two general groups: sparsely ionizing and densely ionizing. Sparsely ionizing radiations cause relatively few ionizations within tissue, whereas densely ionizing radiations cause numerous ionizations, mostly along the tracks of their passages through tissue. The density of ionization is described in terms of the linear energy transfer (LET) in thousands of electron volts (keV) deposited by a given radiation when it passes through a micrometer of material. Up to a given maximum, which is around 100-200 keV/μm, the effectiveness of ionizing radiations to cause cellular damage, death, etc. increases with LET, except perhaps for certain repair-deficient mutants. Relative biological effectiveness (RBE), therefore, is a useful radiobiological parameter because the biological effect of a dose of radiant energy will depend upon the nature of the radiation depositing the energy, viz., the LET of the radiation. Above

100-200 keV/μm, the effectiveness of ionizing radiations to kill single cells begins to decrease because of overkill. Beyond that point, the additional energy is wasted since energy sufficient to kill the cell already has been deposited. The situation in organized tissues may be quite different, however, because the spread of energy around the particle track, which is caused by secondary radiations (δ-rays) arising from the interactions of the HZE particle with matter, can result in a penumbra of energy deposition that extends into cells adjacent to those through which the particle actually passes. Such a spread in energy deposition can cause a mini(micro)lesion. Diagrammatic representations of minilesions, as visualized by Todd (1983) for two different HZE particles, are shown in Figure 1. According to Todd, minilesions should begin to occur in organized tissues at LETs around 200 keV/μm, and many galactic HZE particles have LETs greater than that in human tissues.

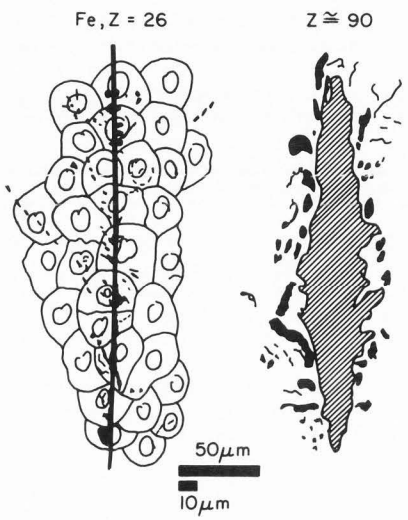


Figure 1. Diagrammatic representation of HZE tracks and a cluster of cells at the same magnification. The track on the left, which was traced from a track-emulsion photograph, represents the path of an iron nucleus showing the track core (straight thick line) and very large delta ray spurs (irregular dashed lines) and blobs (near the track). The diagram on the right represents the track left by an ultra-heavy nucleus in the same emulsion; the shaded area represents the track "core", which is surrounded by very dense delta-ray blobs. Reproduced with permission from Todd (1983).

Apart from LET, significant changes in RBE are caused by the rate of deposition of radiant energy. Not too many years ago, most radiation biologists would have agreed that lowering the dose rate reduced the biological effect. Indeed, fractionated dose regimens are used to good effect to spare normal tissues in the radiation therapy of malignancies. The tissue sparing achieved with sparsely ionizing radiations is often circa 3; i.e., if an acute dose of gamma photons produces a certain biological effect, the same dose given chronically will produce only 1/3 of that effect. For this reason, it was supposed that the low levels of the ambient fluxes of HZE particles in outer space effectively eliminated the hazards to astronauts from those radiations. In more recent years, however, there has been increasing evidence to the contrary. Doses of densely ionizing radiation accumulated at low dose rates are at least as harmful to man as the same doses absorbed acutely (Blakely et al. 1984; Cox et al. 1983; Prichard & Gesell, 1984). In view of the projected increases in human activity in outer space, therefore, the hazards represented by low ambient fluxes of HZE particles are of considerable concern, and the evaluation of those hazards can be assisted by electron microscopic investigation. Furthermore, if minilesions occur, electron microscopy could achieve prominence in studies of the radiobiological phenomena resulting from the exposure of man to HZE particles in space.

From the standpoint of research, the recent findings about the biological effects from low dose rates of HZE particles become somewhat of a blessing in disguise because currently it is very difficult, and extremely expensive, to achieve those low dose rates experimentally. There are two practical options: provide low dose rates terrestrially by operating high energy machines, such as the BEVALAC of the Lawrence Berkeley Laboratory, on continuous or highly repetitive schedules; send the biological materials for lengthy sojourns in outer space. Neither of these options is likely to be viable, especially with live animals, in the near future, but since studies with single acute doses of HZE particles are likely to provide minimum estimates of the biological effects caused when the same doses are delivered chronically, the use of acute doses is warranted in current experiments. In other words, if experiments with acute doses of HZE particles indicate a level of risk that is already of concern in terms of the benefit derived from the professional activity incurring it, then the hazard arising from the real situation with HZE particles in space requires careful evaluation because it is likely to be even more serious. Under all these circumstances, therefore, studies with acute doses of HZE particles provide the logical first approximation to actual extraterrestrial situations, an approximation that probably will be more accurate in the case of radiation exposures arising from major solar flares.

Another approximation requiring careful consideration is the animal model, or series of animal models, that may properly simulate, or be extrapolated to, man. Here the questions are not simply those of biology but include also the cost and time needed to obtain the desired data. If, as has been suggested, the late effects of radiation shorten the life span by advancing natural aging, those late effects will appear in each species at times determined by the longevity of the species. On the other hand, if the radiation response of a tissue is determined

primarily by the nature of that tissue and not by the species in which it resides, the use of short-lived species, such as mice, could result in the deaths of the animals from old age before all the late effects of irradiation have had the opportunity to develop. Because of these considerations, we chose for our studies a relatively long-lived species, the rabbit, which has a median life span in captivity of circa five-seven years. Such a life span was not so short that all the significant late effects would have been missed if tissue were the determining factor, nor was it so long that the experiments could not have been completed in a reasonable time if longevity of the species were the determining factor.

Our other main biological objective was to irradiate only small volumes of tissue, see Figure 2, so that none of the experimental animals would die from damage to radiosensitive

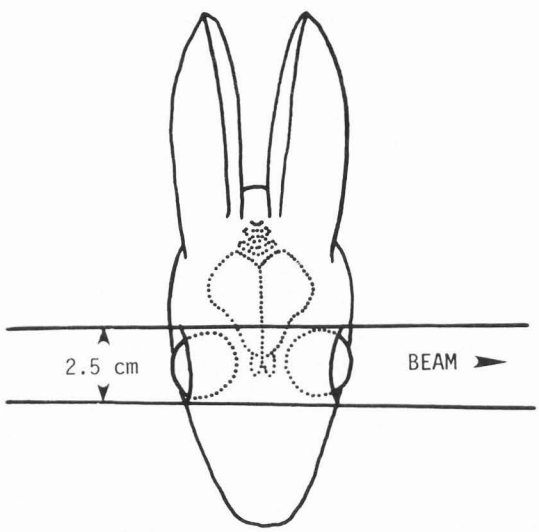


Figure 2. Diagrammatic representation of the alignment of a rabbit in the heavy-ion beam; exposed portions of eyes, skin and brain are indicated. Reproduced with permission from Lett et al. (1980).

organs before late effects in other tissues could be determined. The site of local irradiation was chosen not only because it constituted a representative cross-section of many types of mammalian tissues but also because radiation sequelae in optic and nervous tissues can be incapacitating (Lett et al. 1980). The use of local irradiation, of course, anticipated therapies that may use heavy ions for the treatment of malignancies in man, and since the rabbit experiments had to be extended to the lowest doses practicable, the best place to start was with regimens comparable to those used in therapy. In the foreseeable future, documented experience with therapy patients will be the best source of information on the effects of densely ionizing radiation in humans (Lett et al. 1980).

Radiation Responses of Optic and Proximate Tissues of the NZW Rabbit

General Considerations

When optic and proximate tissues of the young (6-8 wk old) NZW rabbit were exposed to γ-photons radiation sequelae developed in the two general ways illustrated in Figure 3. Nondividing, or very slowly proliferating, tissues responded as shown in Figure 3a: an early response to a approximately constant, intermediate level of damage was followed subsequently by late progressive degeneration. In proliferating tissues (Figure 3b), the early response was followed by recovery to the intermediate level of damage which was the prelude to the late degenerative phase.

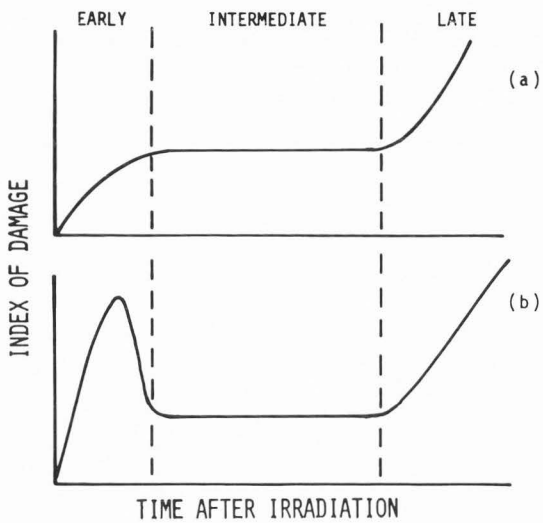


Figure 3. Heuristic representations of the development of tissue damage after irradiation. The temporal alignment between the two parts of the figure is simply for diagrammatic convenience. (a) Behavior representative of nondividing and terminally differentiating tissue. (b) Behavior representative of proliferating tissue. There may be tissues that will exhibit mixed responses. Reproduced with permission from Lett et al. (1980).

As the LET of the incident radiation (^{20}Ne, ^{40}Ar ions) was increased, there was a corresponding decrease in the dose required to produce a given level of intermediate damage, i.e., the RBE increased. The RBEs for ^{20}Ne and ^{40}Ar ions (LETs: ~35 and ~90 keV/μm respectively) were ~2 and ~3.5, respectively (Figure 4). At the higher LETs there were increases also in the rate at which the intermediate level of damage was reached, and the onsets of late degeneration occurred earlier. Hence, in other than the intermediate region, the RBE varied with post-irradiation time, e.g. Keng et al. (1982), a situation that can cause confusion when the effects of low doses of ionizing radiation are assessed (Keng et al. 1982). For present

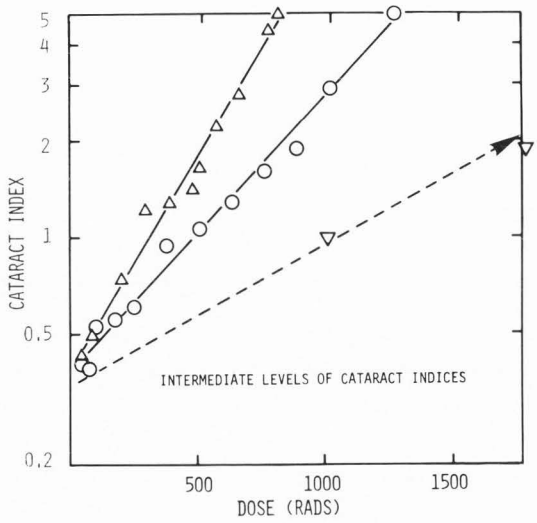
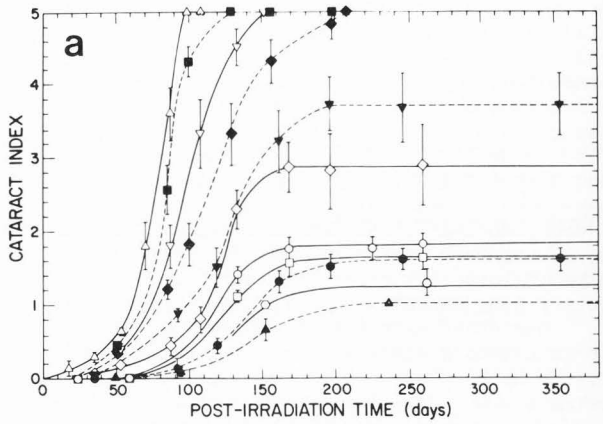


Figure 4. Levels of radiation-induced cataracts in the rabbit lens reached at the intermediate level of development illustrated in Figure 3(a). Radiation: 530 MeV/u ^{40}Ar ions (LET: 90 ± 5 keV/μm), Δ; 365 MeV/u ^{20}Ne ions (LET: 35 ± 3 keV/μm), 0; ^{60}Co γ-rays (0.3 keV/μm), ∇. Reproduced with permission from Lett et al. (1980). The lenticular characteristics used in grading the severities of radiation-induced cataracts recorded in this and other figures are:

Grade	Characteristics
0	Suture lines visible only under direct illumination Lens clear Fundic details easily observed
1	Prominent posterior or anterior suture lines A few mild posterior cortical streaks or vacuoles may be observed Fundic details clear
2	Prominent posterior or anterior sutures Anterior and/or posterior cortical streaks and vacuoles Fundus still observable
3	Numerous anterior and posterior cortical streaks and/or vacuoles which may obscure suture opacities Nucleus relatively clear Fundus partially obscured
4	Many anterior and posterior cortical opacities Fundic details not observable Fundic reflex still present
5	Opaque lens No fundic reflex



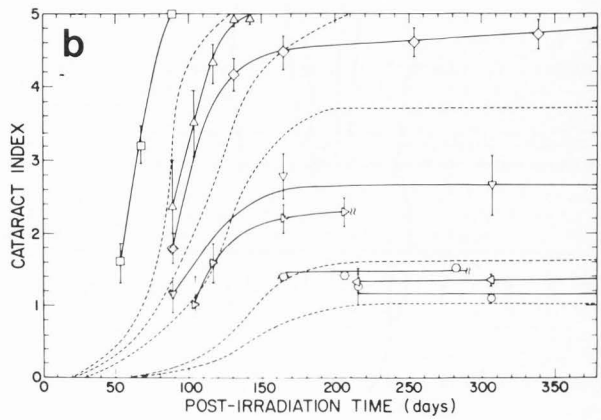


Figure 5. Early and intermediate changes in cataract severity in the rabbit with time. (a) Eyes were exposed to ^{60}Co γ-photons, (---), or ^{20}Ne ions, (———). Doses of ^{60}Co γ-photons: 32.1 Gy, ■ ; 26.7 Gy, ◆; 21.4 Gy, ▼, 17.8 Gy, ●; 10.0 Gy, ▲. Doses of Ne ions: 15 Gy, Δ; 12.5 Gy, ∇; 10.0 Gy, ◇; 8.75 Gy, 0; 7.5 Gy, □ ; 6.25 Gy, ⬡ . (b) Eyes were exposed to ^{40}Ar ions, (———). Doses: 11.4 Gy, □ ; 8.2 Gy, Δ; 7.3 Gy, ◇; 6.4 Gy, ∇; 5.5 Gy, ▷ ; 4.6 Gy, ⬡ ; 3.6 Gy, ◁ ; 2.8 Gy, 0. Dashed lines represent results of exposure to ^{60}Co γ-photons, as given in (a). Error bars represent standard errors of the means, which are not recorded if they lie within the size of the symbol, and beam energies and LET's are those given in Figure 4. Reproduced with permission from Keng et al. (1982).

purposes, the radiation responses of three rabbit tissues will be considered: the lens, the retina and the skin, and in the latter case, consideration also will be given to the extension of the experiments to a primate, viz. the monkey.

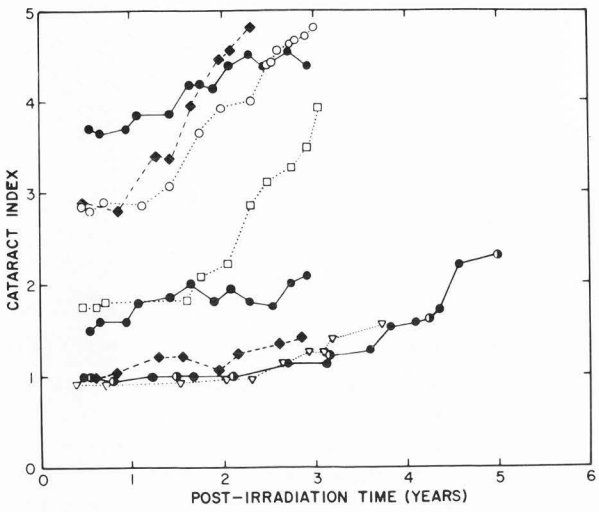


Figure 6. Intermediate and late changes in cataract severity in the rabbit with time. Eyes exposed to ^{60}Co Υ-photons, ●. Doses: 21.4 Gy, upper line; 17.8 Gy, middle line; 10.0 Gy, lower line; ● —— ● , two separate experiments conducted over a period of ten years. Eyes exposed to ^{20}Ne ions. Doses: 10.0 Gy, ○; 8.75 Gy, □ ; 5.0 Gy, ▽. Eyes exposed to ^{40}Ar ions, ◆. Doses: 6.4 Gy, upper line; 2.8 Gy, lower line. Representative doses of each radiation type, the energies and LET's for which are given in Figure 4, were selected for similarity in the 'plateau' response. The cataract score for control animals (n=87) was 0 until they reached the age of 5 years, and rose to 0.2 by the time they reached the age of 7 years. The median lifespan of these rabbits in captivity is 5-7 years. Reproduced with permission from Keng et al. (1982).

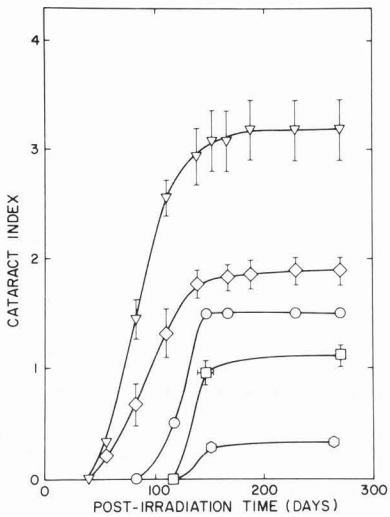


Figure 7. Early and intermediate cataractogenesis in the young NZW rabbit following exposure to 460 MeV/u ^{56}Fe ions (LET of primaries: 223 ± 31 keV/ μm). Doses in Gray: ▽, 5.0; ◇, 4.0; ○, 3.0; □ , 2.0; ⬡ , 0.5. The error bars represent the standards errors of the mean, which are not recorded if they lie within the size of the symbol. Reproduced with permission from Lett et al. (1985).

Radiation Cataractogenesis

Lenticular opacification and cataract formation are serious sequelae of radiation exposure and require careful quantification. The responses of the NZW rabbit to doses of electromagnetic and particulate radiations that range downwards from the radiotherapeutic towards the environmental are shown in Figures 4, 5 and 6. Analyses of those data indicate that the lens of the NZW rabbit responds comparably to those of the dog, monkey and man (Keng et al. 1982), and hence provide one step in the validation of the use of the rabbit as a model for simulating radiation effects in man. Rodents, on the other hand, seem less useful in this regard (Keng et al. 1982; Lett et al. 1985).

The HZE particle, ^{56}Fe, is perhaps the most dangerous component of the galactic heavy ion spectrum when considered in terms of its ambient flux and probable RBE (Silberberg et al. 1984). Early results from a long-term, ^{56}Fe experiment with the young NZW rabbit are shown in Figure 7, where it can be seen that the general features of cataractogenesis found so far are analogous to those from previous studies with ^{20}Ne and ^{40}Ne ions (Figures 3 & 4). At the doses employed to date, the RBE for the intermediate level of lenticular opacification (stationary cataract) is around 4-6 (Lett et al. 1985). The more important response, of course, will be the late degenerative phase.

Although the responses of young animals must be studied in order to provide the base line for post-irradiation effects, the effect of animal age at the time of irradiation is of much practical importance because the majority of radiotherapy patients have ages in the latter half of the human life span and, in the foreseeable future, most astronauts and space workers will be mature adults. In a preliminary investigation of this matter, groups of NZW rabbits at different ages throughout their median lifespan were exposed to a single dose of ^{20}Ne ions. The dose was chosen to be of sufficient magnitude that the experiment would be completed in 3-4 years. Experiments with aging animals are expensive, time consuming and often very difficult, and in the current fiscal climate they require elaborate justification; but as can be seen in Figure 8, the results justified the effort (Lett et al. 1985). The late degenerative phase of radiation cataractogenesis was much more severe when animals were irradiated during the middle third, or so, of the lifespan.

From all the cataract experiments performed to date with the NZW rabbit, the lesson is very clear: effort must be directed now at late degenerative cataractogenesis in animal models

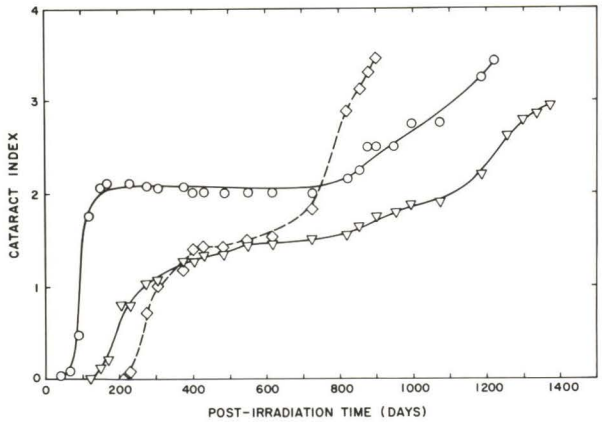


Figure 8. Progression of radiation cataracts in New Zealand white rabbits irradiated locally through the eyes with 9.0 Gy of 400 MeV/u ^{20}Ne ions (LET: 32 ± 3 keV/μm) at different ages throughout the median lifespan of the species. Age: 9 ± 0.3 wk, o; 1.0 ± 0.5 yr, ∇; 4.5 ± 1.3 yr, ◇. This pilot experiment was terminated in 1985 but analysis of the data is incomplete as yet. Reproduced with permission from Lett et al. (1985).

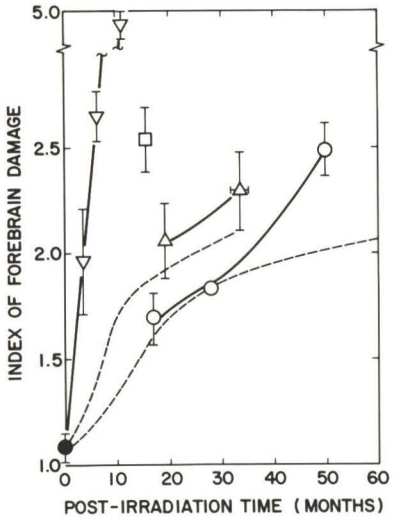


Figure 9. Progression of forebrain damage after irradiation with ^{20}Ne ions (energy and LET given in Figure 4). Doses in Gray: 0, 5.6 ± 0.6; Δ, 9.4 ± 0.6; □ , 12.5 ± 0.6; ∇, 15.5 ± 1.2; the dashed lines represent the responses to 10 Gy and 20 Gy doses of ^{60}Co γ-radiation. The indices of forebrain damage were scored:

Index of forebrain damage	Descriptions of forebrain damage (irradiated-unirradiated forebrain differences)
0	No difference
1	Detectable difference in intensity of color (all stains)
2	Overt difference in intensity of color (all stains)
3	Additional localised color differences suggestive of necrosis; initial appearance of small infarcts
4	Small infarcts present in all slides; tentative identification of beam boundary; demyelination in some cases
5	Extensive infarcts; beam boundary well-defined; extensive demyelination in some cases

Reproduced with permission from Cox et al. (1982), where all other information about the histochemical procedures is given.

which simulate accurately a primate with a long lifespan, viz., man. Electron microscopy should assume an important role in those studies, especially if minilesions are involved. Early damage involving minilesions in the cornea already has been detected by electron microscopy following terrestrial and extraterrestrial exposures of animals to HZE particles, e.g. (Philpott et al. 1978; Philpott et al. 1980; Nelson & Tobias, 1983).

Damage to the Forebrain

Electron microscopy comes into its own, perhaps, for the exploration of pathologies in nervous tissue. Many such studies have been recorded in the extant literature, of course, and it would be inappropriate to identify specific examples here. The point to be made from the rabbit experiments, however, is that once again evaluation of late radiation sequelae is vital. As can be seen from Figure 9, histochemically detectable damage to the forebrain progresses in the fashion shown in Figure 3a, and the RBEs for the "intermediate" levels of damage are similar to those for cataractogenesis (Cox et al. 1982). Although the histochemical evaluations are being complemented by computer analyses of changes in structural anatomy (Cox & Kraft, 1984), the need for refinement to the levels detectable by electron microscopy is compelling.

Damage to the Skin

Evaluations of skin damage are important for radiation therapy and space travel. In the former case, for example, the severity of the early skin reactions often is used to define the practical magnitude of a given radiotherapeutic regimen. In the latter case, a significant hazard for astronauts is exposure during extravehicular activity (EVA) to the radiations accompanying a major solar flare. Although such radiations consist mainly of protons and electrons that have limited penetration in tissue, the protection afforded by the space suit during EVA is limited, and the dose absorbed by

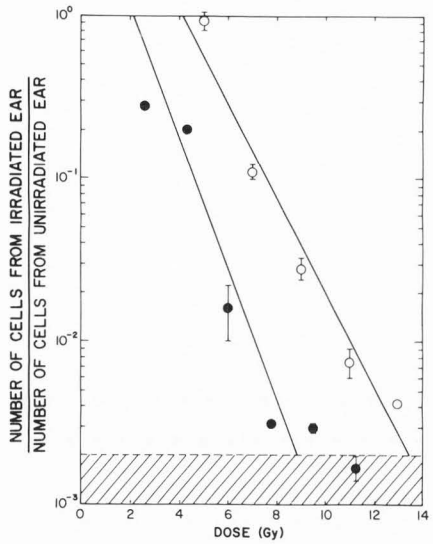


Figure 10. Apparent survival of rabbit skin stem cells 2-4 years after exposure to ^{20}Ne ions, O, or ^{40}Ar ions, ●. The energies of the incident beams are given in Figure 4. Surviving fractions were calculated from the growth characteristics of skin fibroblast cultures in vitro. The lines through the data points were fitted by eye. The cross-hatched area represents the region of survival where the extrapolations of the growth curves indicated that only one stem (precursor) cell had survived. Reproduced with permission from Bergtold et al. (1983).

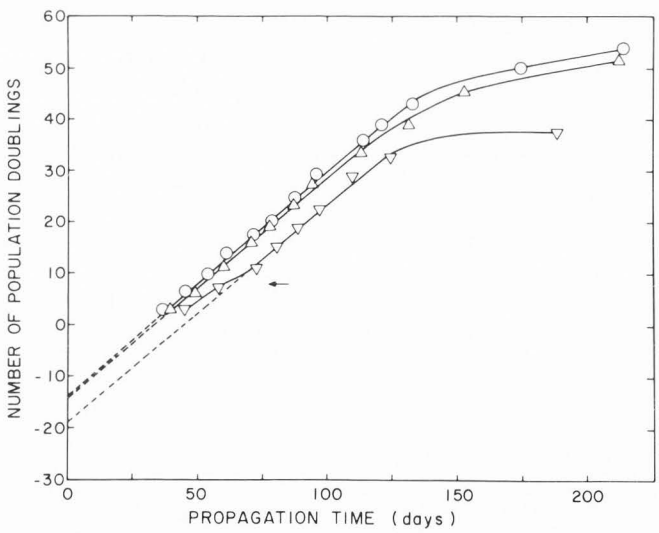


Figure 11. Examples of growth to terminal senescence of skin fibroblasts taken in 1983-1984 from rhesus monkeys irradiated in 1964 with whole-body skin doses of 32 MeV protons (range in tissue ~1 cm). Dose: none, O; 2.8 Gy, Δ; 5.6 Gy, ∇. Reproduced with permission from Lett et al. (1984).

the skin, dermis, etc. can be large, and in extreme cases, fatal.

For the skin studies with the NZW rabbit, one ear was irradiated with heavy ions and the other served as control (Cox et al. 1981). Biopsies of defined size were taken from both ears at specific times after irradiation, and then the skin fibroblasts were propagated to terminal senescence in primary culture (Bergtold et al. 1983). The results from the experiments were translated into survival curves which indicate progressive damage to the stem (precursor) cells in the skin (Figure 10) from increasing doses of radiation (Bergtold et al. 1983). Indeed, when the dose is large enough few stem cells remain undamaged (Figure 10) with the result that the wound caused by the biopsy never heals properly and, moreover, shows signs of progressive necrosis (Bergtold et al. 1983).

On the basis of these results, the examination of skin damage was extended to animals in a colony of rhesus monkeys irradiated in 1964 with proton fluxes comparable to those anticipated from major solar flares. By the use of procedures similar to those employed with the rabbit, damage to the stem cells of the skin of the monkey, see Figure 11, has been detected some twenty years after irradiation (Lett et al. 1984). Complementary examination of the damaged skin by electron microscopic techniques probably will provide further valuable insights into the processes underlying the expression of late damage (by the stem cells) in the skin.

Concluding Remarks

From the examples of late tissue damage selected for illustration here, it is clear that electron microscopic examination of the damaged tissues can provide information that is difficult to obtain by other means. Furthermore, these examples are not exceptional because a survey of the literature shows that there is increasing evidence and opinion that late radiation sequelae are both degenerative and progressive in nature, so the impact of electron microscopic studies can be widespread. Perhaps the most valuable contribution, however, will come from the examination of the formation and fate of minilesions produced by ions from the heavy end of the galactic HZE particle spectrum, an area where progress already has been made with terrestrial and in-flight experiments, e.g. (Philpott et al. 1978; Philpott et al. 1980; Nelson & Tobias, 1983).

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Discussion with Reviewers

D. E. Philpott: What are typical doses of high and low LET radiation expected for a 1 week shuttle mission, for example? What is expected in deep space?
Author : These are difficult questions to answer without exhaustive discussion. Such discussion is provided by Benton and Henke, (1983), Silberberg et al. (1984) and Todd (1983).

D. E. Philpott: Is anything known about the probability of malignant transformation in cells exposed to secondary radiation in the periphery of an HZE particle track?
Author : Not directly, but probabilities could be inferred from experiments with sparsely ionizing radiations.