LATE BIOLOGICAL EFFECTS OF HEAVY CHARGED PARTICLES: CATARACTS, VASCULAR INJURY AND LIFE SHORTENING IN MICE

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Manned space flights are now a reality and may increase in the future in connection with use of advanced technologies, such as satellite power systems (SPS) to generate electricity. However, many of the risks associated with extended habitation in a space environment remain undetermined. Of particular concern at this time are the hazards to space workers that might result from exposure to high energey heavy ion particles (HZE). Less is known about the biological consequences of HZE than about other types of radiations encountered in space. Conventional types of shielding used for radiation protection do not shield out these particles. No data are available currently to assess lens damage and repair after low doses of HZE particles. Thus, more information is needed about biological effects of HZE in order to assess their potential adverse health hazards. Of considerable importance are the potential effects of HZE particles on the crystalline lens of the eye, because this tissue has proven susceptible to x-and gamma rays and particularly susceptible to the action of other forms of high LET radiation such asfission-spectrum neutrons. Because carcinogenic effects and blood vessel (vascular) damage are also of great importance for radiation risk assessment, several animal experiments are in progress to evaluate dose-response relationships for tumor-induction/promotion and for vascular injury. This presentation concentrates on cataract productions, yet preliminary results on carcinogenic and vascular effects are presented for perspective. A fundamental question addressed by several ongoing studies at Berkeley is the extent to which the biological effects of HZE particles are more or less hazardous than fission neutrons, because fission neutrons and densely ionizing alpha particles are considered the most hazardous radiations to man.

The three radiation sources we use in these studies are 250 kVp x-ray machine, the Lawrence Berkeley Laboratory Bevalac, and the 184 inch cyclotron. All mice evaluated for cataracts by slit-lamp biomicroscopy were given either head only or upper body exposures to charged particles or x-irradiation. Fully stripped heavy charged-particles were obtained from the Lawrence Berkeley Laboratory Bevalac, a national facility. The Bevalac combines two accelerators; the SuperHILAC, a heavy ion linear accelerator and the Bevatron, a protron synchrotron. Particles are first accelerated to appropriately 7-9 MeV in the SuperHILAC and are then injected into the Bevatron thru a transfer line where maximum energies obtained are in the range of 2 GeV. ^{12}C, ^{20}Ne, ^{40}Ar, ^{56}Fe ions were extracted from the Bevalac at a preselected energy.

Eye examinations were performed by first sedating each animal with Diabutal. Dilation was achieved by the use of one drop of 1% Tropicamide. The lenses were then observed with a slit-lamp biomicroscope, and assigned a severity score of 0.0-4.0. The observer did not know the type or dose of radiation that the animals had received. Preirradiation screening of animals for "spontaneous cataracts" was accomplished on many animals and the number rejected was nil.

Cataract evaluations have been done on several strains of hybrid mice involved in five different experiments, only two of which were dedicated cataract experiments.

In Experiment II animals were irradiated with 10-100 rad of spread Bragg peak argon ions (570 MeV) and were evaluated at 7,8,9 and 18 months after irradiation. Nearly 44% (48/108) of the mouse eyes developed some opacification by nine months post exposure. The results suggest that the severity of opacification is dependent upon dose. At nine months, the animals with the most severe opacification are those that had received the highest doses of irradiation. Also, the results suggest that the latency is dependent upon the dose. At nine months post irradiation only one animal in the 10 rad group had begun to develop lens opacification. We therefore evaluated the animals again after a period of 18 months (Table I). At that time, all mice given 10 rad showed lens opacifications. The average opacification score was similar (2.6-2.9) at that time, in mice that received 10, 25, or 50 rad, and we assume that the lack of dose-dependence is due to a plateauing of the response by this time. We will continue to examine these animals to determine if the cataractogenic process proceeds further in these mice.

Table I Average Cataract Scores of the Posterior Lens in LAF_1 Female Mice at 18 Months After Exposure to ^{40}Ar ion (4 cm SOBP)

Dose (rad)	No. Eyes	
0	31	0.5*±0.09
10	21	2.7 ±0.14
25	20	2.9 ±0.18
50	22	2.6 ±0.14
100	13	3.6 ±0.14

*significantly ($P \leq 0.01$) different from all irradiated groups.

Experiment IV compares the effects of plateau irradiation of animals irradiated with argon, neon, carbon and also x-ray. At the onset of the experiment it was postulated that HZE particles might have an RBE of 10 in comparison with x-radiation. Six months after the animals had been irradiated, only minimal lens changes were observed. No dose-response relationship was apparent, and no significant differences emerged among the lenses irradiated with the different particles. This situation changed at 9 months after irradiation. As is apparent from Figure 1, the degree of opacification is strongly dependent upon the ion used. The dose scale for x-irradiated mice must be multiplied by 10. At the highest dose (90 rad), all types of particles produced unmistakable opacification, the extent of which is correlated with the expected LET dependence of the response. That is, the degree of opacification increased progressively with increasing estimated values of LET; namely argon, neon and then carbon. From these data, one cannot accurately determine the RBE for HZE particles in relation to x-radiation. There is no question that the RBE is less than 10. Whereas, the x-ray animals given 900 rad had developed total lens opacification at 9 months, the 90 rad argon-induced cataracts were approximately grade 3, the neon about grade 2 and carbon grade 1. If one considers the data in Figure 1, one observes that 60 rad of argon radiation induces about as much opacification as 300 rads of x-rays; thus, the RBE may be of the order 5. The RBE for carbon would then be about 159/90 or less than 2.0 at 9 months. If average cataract scores plateau with time, estimates of RBE will be time dependent.

Preliminary results will be presented concerning radiation-induced life span shortening after exposure to 400 MeV spread peak ^{12}C or ^{60}Co gamma radiation. At one year after a single dose of 240 rad, the cumulative mortality is similar to that produced in the same mouse strain given the same dose of fission neutrons. Stopping ^{12}C or ^{20}Ne ions also appear approximately as hazardous as fission neutron for production of damage to mouse coronary blood vessels and heart muscle.

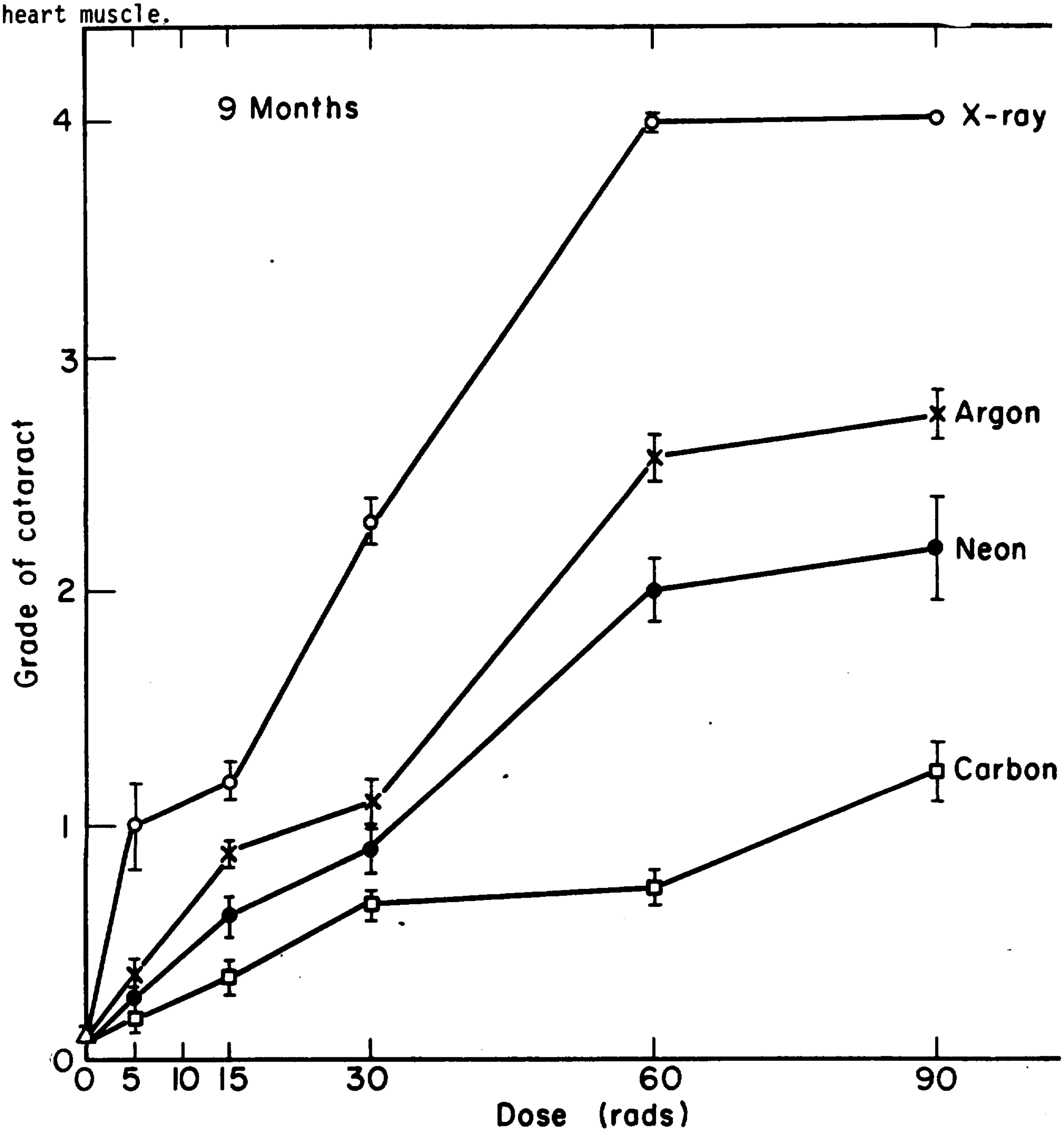

Figure 1. Average cataract severity at 9 months after photon or charged particle irradiation in CB_6F_1 male mice. Average scores and standard errors are based on 32-38 eyes per dose group. Unirradiated controls (38 eyes) had an average score of 0.09±0.03 at 9 months.