Space Travel: A Suggested Method for Predicting Human Response to Ionizing Radiation

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THE NEED for more information with which to predict the response of man to ionizing radiation is becoming more apparent each day. Military planners, and their civilian counterparts faced with the problem of civilian defense, are constantly beset by lack of information regarding "time of productive activity" following injury caused by ionizing radiation in doses near the median lethal range, as well as probabilities of morbidity after exposures of differing magnitude. Nor is this a problem confined to the possible consequences of misunderstanding between earth peoples. The space age has brought into sharp focus the need for better definition of biological effects of ionizing radiation. The future of the space sciences depends, to a degree, on how well man's response to radiation stresses can be outlined prior to their possible application.

Hazard of Ionizing Radiation in Space: There are insufficient data to allow authorities to reach accord on the importance of the radiation problem to space travelers, yet most agree that ionizing radiation exists in the cosmos.[2, 13, 19, 21, 23, 25] Van Allen[25] suggests that in the sphere of radiation bearing his name intensities may reach 100 roentgens per hour over the earth's equatorial axis. This is but one aspect of the problem. Solar flares from our sun produce "radiation storms" unpredictable as to time and intensity.[21, 23] Newell and Naugle[19] have estimated doses of 3×10^4 roentgens per hour in solar proton beams. It is not unreasonable to anticipate similar activity on other suns, which when summated, result in "radiation storms," traversing the cosmos. Just as pilots of intra-atmospheric craft fear thunderstorms and take every

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This certifies that the experiments described in this paper were conducted according to the "Rules Regarding Animal Care" as established by the American Medical Association.

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precaution to insure avoidance, space crews will be faced with "radiation storms," much more difficult to detect, and practically impossible at present to evade.

Shielding of the space craft and judicious selection of exit, cruise, and entry orbits will do much to reduce the hazards of radiation. But because of the uncertainty of intensity of astroradiation and its time of appearance, exposures greater than anticipated may occur. Just as aircraft are not constructed to withstand all types of severe stresses, such as sudden deceleration, space vehicles will not be built to completely protect inhabitants from all quantities and qualities of ionizing radiation. Of prime importance at this juncture is information on recovery rates in man following exposures to varying amounts of ionizing radiation delivered at different rates. Such data may provide a basis for recall of the mission, when such is possible, or in some cases, provide justification for completing the task, even though considerable radiation exposure has occurred.

Effect of Dose Rate on Radiation Injury: Aside from total absorbed dose, the rate at which radiation is applied to an organism is probably the single most important factor influencing subsequent injury. The lethality of a given dose of ionizing radiation may be notably altered by decreasing its rate of application from a high rate (greater than 10 r/min.) to a lower one (less than 5 r/min.). Michaelson[14] has shown that dogs could tolerate doses of 720 r (250 KVP) when given at the rate of 2 r/minute. When the rate was increased to 10 r (or 50), a total of 300 (1000 KVP) caused 50 per cent mortality. In mice, mortality was reported[3] unchanged if a lethal dose of x-ray was delivered at rates of 10 or 100 r per minute. Langham,[11] discussing the same species, noted the LD 50/30 to decrease from 2000 to 700 r, when the rate was increased from 1.4 to 30 r/minute. Co^{60} served as the source of energy. But there are species differences in this regard. Logie,[12] using rats and Co^{60} as radiation source, studied mortality over a 2000-fold span of dose rates and found doses between 1900-2100 r necessary to kill 50 per cent of the subjects when the rate of delivery was less than 1 r/minute. At 3.4 r/minute, 1277 r was LD 50/30, and at 55 and 474 r/minute, it was 1044 and 908 r, respectively. A marked decrease in lethality of a given dose was noted between rates of less than 1 and 3.4 r/minute. Recovery processes operating during the period of exposure may be accelerated at very low dose rates, but at higher ones, they may be ablated or greatly slowed down. This point could be investigated by dividing a group of animals in half and to one give a fixed daily dose on a continuous basis, and to the other, the same daily dose, but during a brief period of exposure (i.e., 10 r/minute or more), both schedules continued until death of the animals.

Approached from the position of a daily dose, given as a brief exposure, the amount per day is also quite critical, at least in the dog. Table I summarizes data obtained in this laboratory. A daily difference of only 19 r caused a marked difference in mortality.

These results also suggest that the interval between exposures may be important in determining the injury from a given total dose of x-ray. Hagen and Simmons[9] found a similar type of response after irradiating their

TABLE I. INFLUENCE OF DAILY DOSE AND FREQUENCY OF EXPOSURE ON MORTALITY IN BEAGLES

Total Dose "r"	Dose per Exposure "r"	Frequency of exposure	No. of Dogs	Percent Mortality	Day of Death Mean	Day of Death Median
225	56	q 24 hrs x 4	7	0	—	—
300	75	q 12 hrs x 4	5	40	22	—
300	75	q 24 hrs x 4	7	86	18	16
300	75	q 48 hrs x 4	5	0	—	—
300	300	single	6	33 1/3	14	—

rats daily (single brief exposure) until death. At a daily rate of 87 to 182 r, the mean survival times were between 15.8 and 10.9 days. But when the daily insult was reduced to 50 r, mean survival time increased to 48.2 days.

If one recognizes Blair's[5] assumption that "irreparable and unrepaired injury add in all proportions and become lethal when their sum becomes equal to the injury, resulting from the acute lethal dose at the time in question," then injury, as measured by total dose, is equal to reparable plus irreparable damage. In the mouse, the only species that has been tested in the required manner, this relationship appears to be linear, but definitely dependent on daily dose rate.

Blair[5] has analyzed Mole's[17] data on mice and his findings are summarized in Figure 1, which illustrates

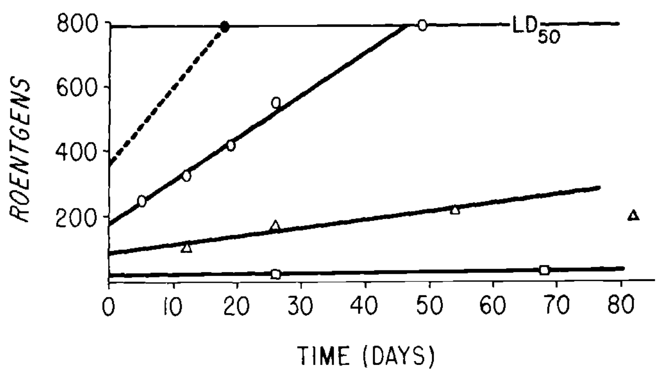

Fig. 1. Accumulation of radiation injury in mice (Blair).

the manner of change of LD 50/30 values following various daily (5 x per week) exposure rates. Groups of animals were given daily doses of x-rays at rates of 10, 25, and 50 r. At varying times, "aliquots" from each group were given brief doses in order to determine the LD 50/30. As the number of daily doses increased, the LD 50/30 decreased and the points represent the difference between the normal LD 50/30, i.e., 792 r, and the values found at varying periods after small, daily doses. The slope of the line connecting appropriate points gives the rate of accumulation or irreparable injury, in roentgens, and the values at the intercept represent reparable injury if daily exposures had been stopped short of lethality. The nearly horizontal line shows the accumulation of injury when exposures of 10 r per day were given, which is less than 10 per cent (1 r) of the daily dose. The next lines, in sequence from below upward, are for daily doses of 25 and 50 r, and describe irreparable injury accumulation at rates of 10 per cent (2.2 r) and 26 per cent (13 r) of the daily dose. The broken line is drawn from the point where 100 r per day produces an LD 50/30, to a point on the intercept twice that for the 50 r per day line. The slope represents 24 r/day; the accumulation or irreparable injury is thus 24 per cent (24 r) of the daily dose, a figure not greatly unlike that for 50 r/day.

Figure 1 also illustrates an additional factor which could be of major significance provided man's response is similar. Animals given repeated daily exposures of ionizing radiation to an accumulation nearly lethal, and at a high daily rate, will have a greater percentage of resulting injury in the reparable compartment than those exposed to near lethal dose, but at a low daily rate. The value at the intercept for a daily dose of 25 r per day is less than at 50 r/day, which in turn is less than 100 r/day, indicating a greater amount of reparable injury as the daily dose rate increases. Mole[18] observed numerous deaths in the nine month period following near lethal exposures at 25 r/day, a smaller number at 50 r, and few deaths after 100 r/day. In mice, it appears that within limits, the more rapid the daily accumulation of near lethal dose of irradiation, the more complete the recovery, as measured by survival time.

Duration of Irreparable Injury: Evidence on the duration or irreparable injury is meager, but in the dog, this portion remains quite constant over a period of eight months,[15] and in the rat for at least 60 days.[10] If one considers radiation exposure sequences which very possibly could be experienced on prolonged space missions or during forseeable circumstances on earth, the necessity for more definitive information on this question becomes obvious.

Little attention has been given to correlating the late or delayed effects of radiation injury with the magnitude of irreparable injury as measured by above cited method. While the data appear to describe irreparable injury, there is no evidence that what is being measured causes late effects other than decreased life span noted in mice.

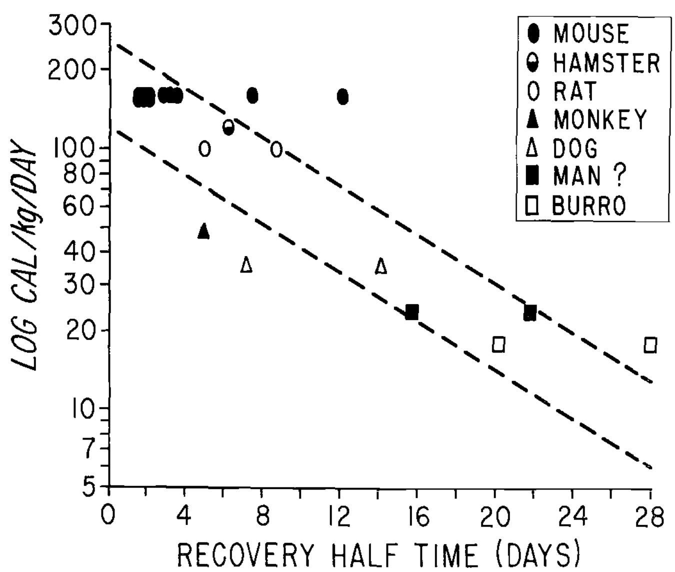

Fig. 2. Metabolic rate and recovery from radiation injury.

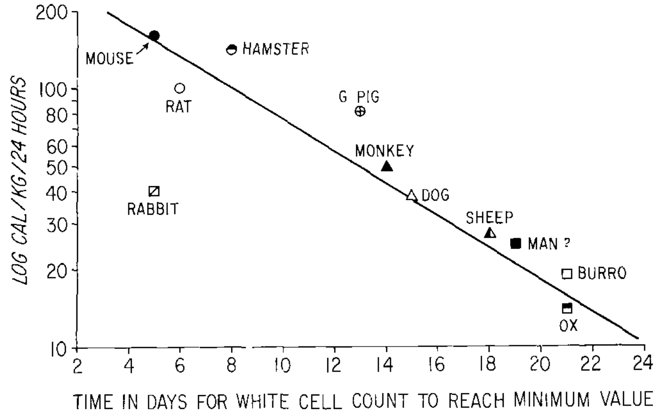

Fig. 3. Leukocyte depression after X-irradiation (LD 50/30 dose range).

Species Differences and Metabolic Rate: The LD 50/-30 dose of ionizing radiation varies considerably from species to species.[7] Likewise, recovery rates from radiation injury, as measured by paired dose techniques, differ widely with the species under study (Figure 2), but not in any consistent manner with the LD 50/30 dose. In the search for some common parameter with which to relate the apparent random variations in recovery rates, Michaelson and Odland[16] have suggested the species metabolic rate.

The role of metabolism in radiation illness was clearly stated 35 years ago and supported by experimental data.[1] Five years later, Vintemberger[26] wrote "The duration of survival of an irradiated cell is inversely proportional to its activity after irradiation." Animals irradiated at reduced metabolic rates (i.e., hibernation and/or cooling) show marked resistance to radiation injury until warmed to normal temperature[20, 6, 8] at which time the injury is manifested in the usual manner. (Astronauts, who by accident receive a near lethal dose of radiation, may possibly be "stored" by hypothermia until the vehicle returns to earth where complete medical treatment facilities would be available.)

From the work of Davidson,[7] it is possible to show a relationship between metabolic rate and two often used indices of radiation injury. Figure 2 demonstrates how recovery rates (based on paired dose techniques) relate to heat production of the species.[4] The datum for man is inserted on the basis of his metabolic rate, and is not at great odds with estimates in the literature.[7] Figure 3 reveals a similar relationship between metabolic rate and the time for leukocyte count to reach maximum depression after a near LD 50/30 dose of radiation. Based on metabolic rate, man's leukocytes would show maximum depression around day 18-20 post exposure. It must be emphasized that Figures 2 and 3 are based on data from many sources, obtained under widely different investigative environments, and subsequent to a variety of radiation doses, dose rates, energies, and methods of exposure. Under rigidly standardized experimental conditions, the variability shown on these figures could be greatly reduced.

Influence of Quantity and Quality of Ionizing Radiation: Irreparable injury from particle (neutrons, protons) radiation may be considerably greater than from wave radiation, and less from high energy wave radiation than from low.[5]

The Basic Problem and a Suggestion for its Solution: The forseeable circumstances under which man may be exposed to significant amounts of ionizing radiation require consideration of two questions.

1. What dose of ionizing radiation can be accumulated without significant decrement in performance capability of the individual(s) for the duration of the mission, and

2. What is the penalty, in terms of delayed or late effects, that will be imposed for this dose?

Evidence cited indicates that biological injury from radiation varies depending on dose rate per minute for large doses given continuously, and daily rate for brief, repetitive, smaller ones. In order to predict tolerance to radiation injury (or remaining tolerance once exposures have occurred), it will be necessary to know the dose (in rem), its rate of application, rate of recovery of reparable damage, and rate of accumulation of irreparable injury. To anticipate the quantity and quality of late effects, we must know, in addition, whether or not irreparable injury is, in fact, permanent, and the relation between it and the magnitude of delayed injuries.

Figure 4 is a brief sketch of the experimental approach the authors believe will provide a method for predicting human response to ionizing radiation. Five species are considered the minimum necessary to span the spectrum of metabolic rates represented by the

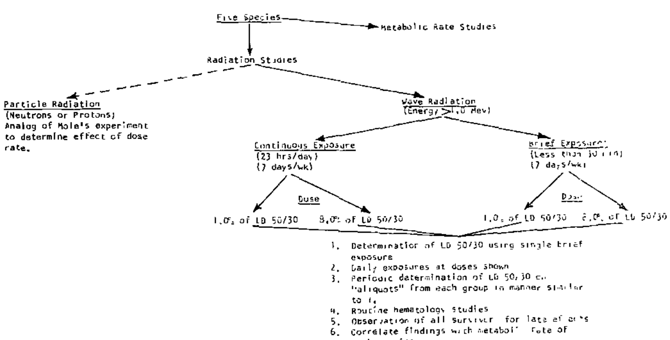

Fig. 4. A suggested experimental approach to the problem of injury and recovery in mammals following radiation exposures.

mouse or shrew at one end and the ox or burro at the other. An analog of Mole's experiment[17] is suggested to determine the effect of the dose rate when particle radiation is considered, as there is a suggestion[24] that irreparable injury from particle radiation is greater than that from wave, but it may not be as dose dependent. One energy has been selected for the wave radiation experiments, and for technical reasons, that from a radioactive isotope, is considered the most desirable. Both brief and continuous exposures are necessary to detect the influence of dose rate. A fixed percentage of the LD 50/30 is required if the members of each species are to be injured to a comparable degree.

No consideration has been given to the differences in linear energy transfer that probably exist between radiations proposed for use in this study and those which will be a consequence of exposures to astroradiation. This has not been an oversight. In the event the proposed study is realized, it will be relatively simple to repeat segments of it using the higher energies characteristic of astroradiation, but as yet, not reproducible on earth. From comparison of results, factors of relative biological effectiveness could be estimated for the various parameters studied.

Metabolic rate studies are necessary to confirm observations of earlier workers,[4] and should be accomplished on randomly selected individuals from the experimental population, prior to exposures, and at various periods throughout the study, from the control group.

SUMMARY

The hazards of ionizing radiation to manned space travel are reviewed. Some of the important factors in determining biological injury to ionizing radiation are discussed, and the relationship between metabolic and recovery rate is described.

It is suggested that an experiment be supported by interested agencies wherein several species of mammals are studied under identical conditions in order to define rates of accumulation and repair of injury caused by ionizing radiation as these relate to species metabolic rate. Results from the proposed study would provide information allowing more detailed planning for space exploration and civilian and military defense.

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