Symposium on Aerospace Radiobiology

VII. Review of Biological Effects of Galactic Cosmic Radiation

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THE REGION OF SPACE occupied by our solar system experiences a steady light rain of high energy atomic nuclei from outer space. Superimposed on this relatively constant galactic primary cosmic radiation background are occasional intense storms of relatively low energy protons violently emitted from the sun. These solar outbursts rightfully are receiving serious concern from space-minded radiobiologists. Planetary bodies with appreciable associated magnetic fields are girdled by radiation rings known for the earth as the Van Allen radiation belts. They extend into space several planetary diameters. This paper discusses just galactic cosmic radiation mentioning for comparison some aspects of solar cosmic rays, since the two overlap in composition and energy. The nature of these various kinds of radiation and their relative significance to manned space flight has been reviewed.[8,19,22]

TRACK PRODUCING RADIATION

The biologic effects of space radiations can be interpreted in terms of two physical models: A multiple agent and single agent model. Transposed from their submicroscopic atomic scale to a macroscopic scale, the physical difference between their effect is comparable to the difference between the effect of being hit by a charge of birdshot vs a rifle bullet. The multiple agent (birdshot) model characterizes the radiation effects produced by gamma rays, electrons, mesons, neutrons, and other familiar light weight atomic radiations. Each particle produces occasional ionization events along its path. These ionization events are rarely close enough together in space to interact with one another.

By contrast, the single agent (rifle bullet) model describes the track producing ionization pattern of heavy primary cosmic rays. Successive ionizing events produced along the path of a heavy particle are physically close enough in tissue to interact with one another on an atomic scale. Effectively the ionizing events produced in adjacent molecules and atoms occur simultaneously. Successive events occur before adjacent molecules have time to move from each other due to thermal velocity. The interaction products of these contiguous simultaneous ionizations observed along the path of heavy atomic particles are termed "track effects." Whenever a primary particle inelastically collides with a target atom the track effect radiation pattern becomes a spray of secondary atomic particles (multiple agents).

The track effects observable as the result of traversal by a heavy primary cosmic ray particle can be divided into four stages.[10] First, a physical stage lasting approximately 10^{-13} (less than a millionth of a millionth) second, a physiochemical stage lasting approximately 10^{-11}

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second, a purely chemical phase lasting approximately 10^{-6} second, and finally a biological phase which may extend over many generations.

During the extremely brief (approximately 10^{-13} second) physical stage, energy of the original particle is transferred to atoms and molecules of the material through which it is passing in two ways. It may be transferred as ionization or by excitation which temporarily places an atom in a higher energy state. Both mechanisms affect the sensitized emulsion of nuclear track plates.

The longer (approximately 10^{-11} second) physio-chemical stage follows. The original products now undergo transforming reactions. The excited molecules either spontaneously dissociate to become ions or dispose of their energy as heat, retaining their original identity. The ions collide with each other and with normal molecules forming new molecules or molecular fragments. The net result of this stage is a group of newly formed atoms and molecules which may or may not be different from those originally present. Chemically unstable atomic species and molecular fragments (free radicals) are included.

At this point, the third (duration approximately one micro-second) chemical stage follows. The newly formed molecules and free radicals react chemically with each other, with the molecules previously present, and with the milieu in which the reactions occur. The highly reactive free radicals frequently disrupt nearby stable molecular groups creating biologically harmful products.

The fourth and final biological stage includes all reactions of the biological system to the foreign chemical substances. The biological reaction will be determined first by the changes these substances produce on the structure and function of the cells in which the products have been formed. Later effects will be determined by the resulting changes in the structure and functions of the tissue formed by affected cells, and finally by the consequent functional alternations of this tissue as it relates to the total economy of the organism and its descendants.

With this physical picture in mind one would expect the biological effects from track producing radiation to depend strongly upon the location and type of cells through which the track passes in the body.

It is difficult to appreciate the extremely short intervals involved during the physical, physiochemical, and the chemical stages. The comparison between a one-second exposure to proton radiation producing 10,000 ion pairs and a heavy primary particle producing 10,000 ion pairs in less than 10^{-12} second is more comprehensible when translated to a macroscopic time scale. If 10^{-12} second is transposed to one second, one second becomes 30,300 years, several times longer than recorded history. It also becomes apparent that dose units which are defined in terms of total ion production or total energy absorption throughout large volumes of tissue are most valuable when applied to radiation of the multiple agent (bird shot) type. These include units such as rep (roentgen equivalent physical) and rad, as well as their derivative concepts such as RBE (relative biological effectiveness). Dose values obtained from exposure to multiple agent radiations for periods of the order of a second may not be applicable to track effects initiated in 10^{-12} second. Attempts to define the biological effect of track producing radiation in terms of these units frequently fail to consider the importance of defining the specific type of cells concerned.

Dose terminology that expresses the number and kinds of tracks facilitates correlation of the heavy ion exposure with the nature and type of biological damage observed. Since the radiation pattern changes along the path of a heavy primary particle as it loses energy simple identification of the particle producing the radiation is not sufficient. Both the charge of the particle and its energy influence the biological effect it may produce. Only experiments can resolve the importance of these factors.

Primary galactic cosmic rays consist of ions ranging from hydrogen nuclei (protons) to iron nuclei. Fichtel[5] has recently reported details of the charge and energy spectrum. Solar outbursts contain protons and electrons, but only the protons produce track effects. The solar protons generally have a lower energy[18] than the cosmic ray primaries. Solar outbursts vary greatly in the maximum energy and the energy distribution of particles ejected. By contrast, the cosmic radiation spectrum is relatively constant. However, some variations are firmly established. Simpson[24] describes a marked increase in the flux of low energy galactic cosmic ray protons during the solar cycle minimum as compared to the flux observed during solar cycle maximum. The peak of this difference occurs in particles with a total energy between 100 Mev/n (Million electron volts per nucleon) and 1 Bev/n (Billion electron volts per nucleon). Careful measurement of the increase in flux of protons and the heavy component of the primary cosmic radiation above 1 Bev energy during solar maximum[5,18] shows an increase of twice the number of particles during solar minimum compared to the number observed during solar maximum. The difference is greater below 1 Bev.[24] Careful analysis[5] of the ratio of heavy particles to the number of protons between 1 Bev per nucleon and 2.5 Bev per nucleon shows no difference in composition between solar minimum and solar maximum. Since this low energy portion of the primary cosmic ray spectrum (below 1 Bev) is responsible for the most densely ionizing tracks, the exposure to heavy primaries can be expected to vary at least by a factor of 2, possibly a factor of 10 between solar minimum and solar maximum. Yagoda[25] has observed significant changes in the ratio of the number of medium weight to heavy galactic primary nuclei on successive days near solar cycle minimum. Preliminary results of satellite studies near solar maximum[11] have not shown this type of variation.

Based on Schaefer's criterion[17] of 10^4I.P./μT (ion pairs per micron of tissue) for a thindown "hit" Yagoda[26] observed an exposure rate of 27 heavy primary thindowns per cc of tissue per day extrapolated to the top of the atmosphere. Schaefer[15] has calculated exposure rates in terms of the numbers of thindown hits per man per day at various altitudes (or thickness of shield material in space).

The physical radiation pattern of heavy primary cosmic rays suggests that there are several aspects of this track producing radiation which may independently influence the biological effects produced. The uniquely high intensity of core (track producing) ionization characteristic of heavy ions may be responsible for biological effects distinguishable from effects produced by the uniquely wide radial spread or effective cross-section area of the heavy ion track. The number of delta rays per micron of particle path length may be equally important.

These factors interrelate in a complex manner. The intensity of core ionization increases for ions of increasing weight, reaching a maximum for each ion at the low energy end of its path. The form of this relationship is shown by the ordinate values for ions of various charge in Figure 1. In a similar way, the intensity of the delta ray aura of radiation around the core increases with ions of increasing charge reaching maximum values at higher energies than the peaks of the curves in Figure 1. The radial spread factor is not so sensitive to the charge of the ion, but increases chiefly with increasing velocity of the ion. By selecting emulsion sensitivity the number of delta rays and the intensity of core ionization can be read directly. Total ionization per path length must be derived for most tracks.

It is instructive to compare the number of ionizations per micron of ion path (LET or linear energy transfer) of various heavy ions in terms of the path length remaining to termination. Figure 1 is a modification of a graph prepared by Foelsche[6] for heavy ions. Curves for protons and alpha particles have been added to the original graph. These additional curves were plotted from data presented in references.[9,12,14] The ordinate expresses total ionization including both central core ionization and delta ray ionization.

The ionization produced by the delta rays and the central core are evenly divided in oxygen ions of 10 Mev/nucleon. Although the core ionization is not a constant per cent of the total marked increase in delta ray density for heavier particles of nearly relativistic velocity.

The lack of clear guidelines as to what aspect is of greatest significance stems from the paucity

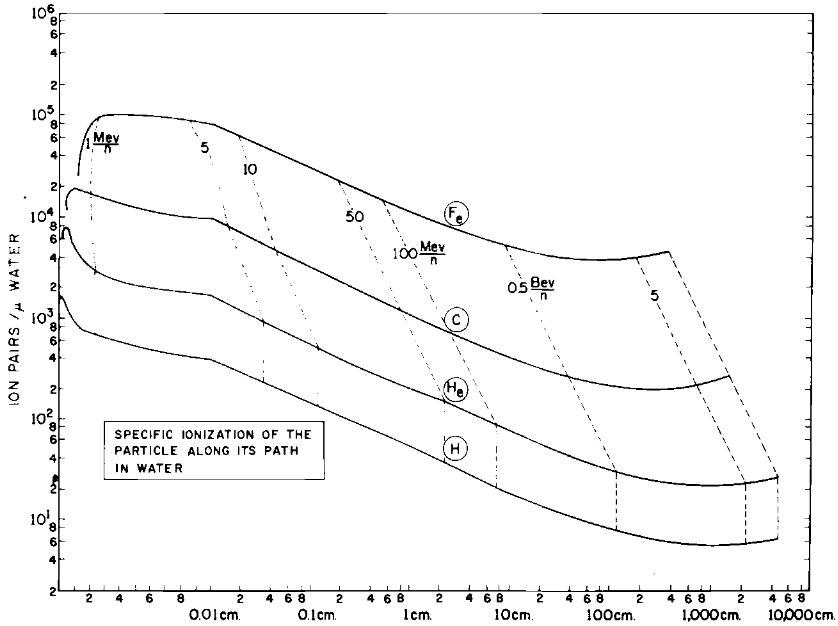

Fig. 1. Graph of ionization produced along the paths of four types of cosmic ray particles as they terminate in water. The dotted lines show corresponding energy levels along the path of each kind of particle.

ionization it tends to increase as the LET increases along a curve of Figure 1 going from right to left. The highest intensity of core ionization corresponds to the highest portions of the curves. Schaefer[7] postulated that this region of maximum LET may be the most biologically significant feature of heavy primary tracks and selected the ordinate value 10^4 I.P./μT in Figure 1 as the lower limit of LET for defining a heavy primary "hit."

Other factors, such as the energy distribution pattern as evidenced by the radial spread or effective cross-section area of the track, may be equally important. Within the energy limits of Figure 1, increasing values on the abscissa correspond to an increasing radial spread. However, it is not clear whether the greater distance from the core that higher energy delta rays reach are more significant biologically than the of experimental data. The cosmic radiation experienced at altitude is a mixture including particles ranging through a spectrum of charges, each arriving in a spectrum of energies. One approach for resolving what charge-energy combination of these space particles are most significant is to identify an individual particle in terms of charge and energy and relate this to the specific biological effect produced by it. Unfortunately simple nuclear emulsion techniques do not identify both the charge and energy of a track. Identification of the approximate charge of an ion assuming it is close to relativistic velocity (energy $>$ 0.5 Bev) can be readily accomplished by counting the number of delta rays produced per unit of track length. Accurate determination of energy is much more difficult for most tracks.

Attention in the past has been concentrated on the biological effects of heavy primary particles corresponding to the charge-energy region defined by the portions of the curves in Figure 1 which lie above the ordinate 10^4 ion pairs per micron tissue. The monitoring techniques generally used for biological specimens do not permit identification of particles in terms of this factor. The technique used in recent studies by the Bioastronautics Branch of the School of Aerospace Medicine originally suggested by Dr. Yagoda, was developed primarily to locate the path of a heavy primary traversal through a biological sample. This technique identifies particles characteristic of a different region defined by the boxed area of Figure 2. The vertical line DE represents the minimum energy which a particle must have to be counted. A track must penetrate both emulsions to be scored. At lower energy the ion cannot penetrate the track plate assembly. The horizontal line EF corresponds to the minimum delta ray count corresponding to a relativistic atom of charge 19. The only portion of this box which includes ions producing total ionization in excess of 10^4 ion pairs per micron of tissue is the hatched sector in the upper left corner of the box.

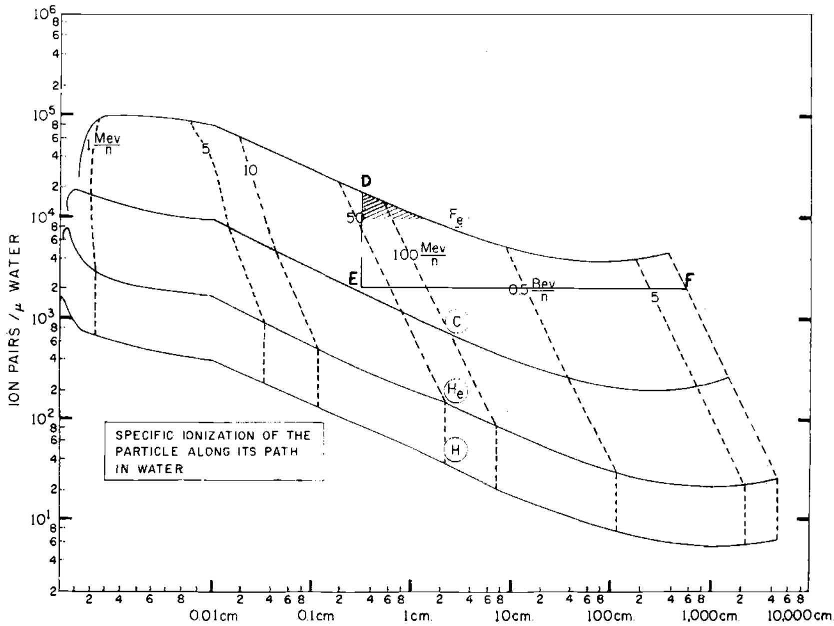

Fig. 2. Graph of ionization in water versus residual range for four types of particles. The area bounded by DE, EF, and the Fe curve includes the particle types and energies measured in monitored experiments.

The electron sensitive emulsions clearly show the delta rays and core thickness as described above. If the ordinate in Figure 1 is changed from "specific ionization" to "number of delta rays" produced in nuclear emulsion, the curves will be of the same relative shape, except for the region below 0.3 cm. The curves of Figure 1 reveal large ambiguities in particle identification. For example, a slower, 40 Mev/n neon ion will produce the same specific ionization as an energetic 1 Bev/n iron particle. In order to make a positive identification of a given particle, its energy must be known. The energy may be readily determined if the particle comes to rest in the emulsion. Figure 1 indicates, however, that an unwieldy large block of emulsion is required to stop energetic particles. Another method involves the determination of the maximum radial spread of the delta rays. The energy of the ejected delta rays is proportional to the energy per nucleon of the incident cosmic ray particle.

The biological significance of a number of physical factors becomes much easier to relate when considered in terms of Figure 1. Note that the 0 to 0.01 cm segment of the abscissa is a linear scale, whereas all other portions of the graph are log-log. The diagonal dotted lines show the energy at which each particle produces the indicated intensity of ionization and the distance to termination. Based on the 10^4 ion pairs per micron tissue criterion for a cosmic radiation "hit" it is apparent that carbon particles reach this intense rate of ionization for a microscopic distance corresponding to the diameter of several cells. With particles of increasing charge, this distance reaches macroscopic dimensions.

Figure 1 helps to put into perspective the fact that particles of energy greater than 1 Bev per nucleon have a negligible chance of terminating as thindowns. They collide with other nuclei producing stars or spallation products. Particles of energy less than 100 Mev per nucleon have approximately a 90 per cent chance of terminating as thindowns. Thus the charge-energy region of interest concerns particles of energy less than 1 Bev/nucleon and of undetermined minimum charge.

If core density alone is a critical factor for producing biological effects, then relatively small changes in the low energy portion of the primary spectrum will cause major changes in the effective exposure rates.

If radial spread is of primary importance, then one would expect to observe unique biological effects produced by carbon nuclei of relativistic (1 Bev per nucleon or greater) energy. This corresponds to the region below the box in Figure 2. The general region of the box is characterized by a relatively high core radiation density, a relatively large number of delta rays, and a considerable delta ray spread. This combination may be as biologically significant as REL alone, but can be observed only in experiments conducted at high altitude. Many practical aspects of exposing biological materials at various latitudes in terms of the change in minimum energy observed due to geomagnetic cutoff and at increasing altitude have been discussed previously.[15,16] In the past year, several types of biological experiments were monitored using Ilford G-5 emulsion nuclear track plates. Exposure to space radiations were obtained on a rocket flight, medium and high altitude balloon flights, and satellite flights. The differences in heavy primary tracks observed on the plates indicate the differences to be expected from exposure of biological materials. Plates of Ilford G-5 emulsion were exposed on December 4, 1959 on the Little Joe Project Mercury test flight launched from Wallops Island at geomagnetic latitude 49 degrees N. Two tracks of charge greater than 18 were observed in the four readable 2 x 3 inch plates. The geomagnetic cutoff at that latitude limited exposure to primary particles of energy greater than 670 Mev/nucleon. The exposure time above 90,000 feet was close to 4.5 minutes. A maximum of approximately 15 minutes can be expected on ballistic type rocket flights.

By contrast, plates exposed on a balloon flight spent 11:40 hours at 130,000 feet altitude at 58 degrees geomagnetic latitude which was above the geomagnetic cutoff for galactic primaries. These plates should have received maximum exposure for the altitude flown. These plates showed an average of 143 ions per 2 x 3 inch track plate of Z equal to or greater than 23 (vanadium). Plates flown on a sister flight at the same latitude for 11:00 hours but between 130,000 and 140,000 feet graphically illustrate the effect of increasing the acceptable Zenith angle plus receiving lower energy heavy primaries which can penetrate the reduced amount of atmosphere. These plates averaged 166 ions per plate. The technique used did not permit evaluation of the energy of the particles so the charge was based on the assumption of relativistic velocity.

Plates exposed for 75 hours of polar orbital satellite flight on Discoverer XVIII launched on December 7, 1960, spent seven times as long aloft as the balloon flight plates. However, only 1/3 of this time was spent over the polar regions and nearly 2/3 in the equatorial zone which is geomagnetically shielded from low energy particles. The average total heavy primary count for a 2 x 3 inch plate was 31 ions of Z equal to or greater than 17. These results are shown in terms of particles per cm^2 in Table I.

TABLE I. COMPARISON OF HEAVY PRIMARY EXPOSURES ON ROCKET, SATELLITE AND BALLOON FLIGHTS

Exposure Time		Flight	Number Observed	Observed Charge	No. Particles per CM^2
Hrs.	Min.				
00:	04½	Ballistic rocket	2	18 and 20	0.015
75:	00	Discoverer XVIII	31	17 – 22	0.83
11:	40	Balloon 130,000 ft.	143	23 – 26	3.81 Z=17–26 (6.30)
11:	00	Balloon 136,000 ft.	166	23 – 26	4.41 (7.31)

The plates exposed on this satellite flight were not as satisfactory for the study of heavy ions as were those from the balloon flights. A high proton flux was encountered during the flight which produced about 10^5 proton tracks/cm^2 in the plates. It was difficult to distinguish the delta ray tracks in such a high proton background. The determination of the charge of the heavies was therefore less accurate, and much more time consuming.

Solar flares, although they occur infrequently, present an even more serious difficulty for heavy ion studies. A flare occurred during the Discoverer XVII satellite flight launched November 12, 1960. The 100 micron Ilford G-5 nuclear emulsion from this flight was rendered opaque by the very high flux of protons making it impractical to distinguish heavy ion tracks.

OBSERVED BIOLOGICAL EFFECTS

Of the many different kinds of biological material exposed on high altitude cosmic radiation studies to date,[7] only one has produced clearly positive results. Chase[4] recommended the exposure of C-57 black mice scored for graying or depigmentation of hair. In such black-haired mice, the pigmentation of each hair results from the activity of 3 to 6 melanocytes. These pigment cells are highly radiosensitive, but are rarely if ever replaced when killed. Generally, such nonreplaceable cells are either strongly radiation resistant or are provided with a high degree of functional redundancy. Loss of just a few pigment cells produces a large "multiplication factor" producing a macroscopic effect from a microscopic cause. These specific cells are sufficiently numerous to make practical the detection of occasional cosmic ray heavy primaries.

A total of 185 mice and five guinea pigs have been exposed above 90,000 feet on 9 balloon flights and their appropriate ground controls evaluated by Dr. Herman B. Chase. The mice were exposed in the years 1953 through 1956. These animals were examined for graying. Four features were observed on these exposed animals, but not observed previously on ground controls nor among the ground control animals for these flights. These features included: 5 streaks, clustering of gray hairs, a statistical increase in the number of "white spots" per exposed animal, and removal of follicles with plucking. The senior author[23] has previously reviewed these observations in detail.

There is no longer any question that many of these streaks and white spots have been produced by heavy primary cosmic rays. Chase[1] has positively correlated graying phenomena with heavy primary tracks identified in nuclear emulsions individually mounted on the back of each mouse. By analyzing the length of time spent above 90,000 feet for the earlier group of high altitude mice, it was possible to obtain the value of 4,425 mouse hours total "exposure." This represents the total exposure accumulated by the group of mice in which the five streaks were observed. If the value of five streaks per 1,525 hours of exposure is representative, it required an average of 37.7 days exposure for one mouse to develop a streak. Many white spots are observed for every streak seen. Chase[2] observed 2 triads (3 contiguous follicles bearing gray hairs) among the 8 mice exposed in 1953. He reported[3] that most of the white spots counted from the 1954 flights comprised a group of hair growing from separate follicles, usually 2 and 3 follicles together. This same result was commonly observed among the mice exposed in 1955. The obvious implication of this observation, and of the observation of streaks *per se*, is that one heavy primary inactivated all melanocytes associated with the 2 or 3 adjacent affected follicles. This assumption is inconsistent with the radial spread pattern calculated by Schaefer,[13] which predicts a maximum radiation-effective radius of 6 microns. Each follicle is separated from its neighbor by approximately 100-120 microns; due to the geometry of hair growth, it is conceivable that a particle with a radial spread of 30 microns could influence adjacent follicles. The reason for this X5 discrepancy is not yet clear.

Langham[1] expresses the view of many radiobiologists in pointing out that human central nervous system tissue is the most likely to suffer sufficient track-inflicted damage to constitute a serious flight hazard. This tissue differs in a number of significant respects from the melanocytes of the skin. It is highly radioresistant, and has no multiplication factor to permit ready observation of damaged cells. It is equally irreplaceable although many cells in the central nervous system appear functionally redundant. Two promising approaches to the problem of determining the sensitivity of the central nervous system to track-producing radiation include monitored tissue culture studies and monitored animal flights. Passage of a heavy primary through the *in vitro* cells or the *in vivo* brains can be identified and the biological effects determined. Several attempts have been made to conduct both these experiments but technical difficulties have frustrated obtaining definitive results.

It is of fundamental importance to establish whether discreet segments of the central nervous system are permanently incapacitated by a heavy primary track. In the light of repeated negative attempts[7,21] to observe pathological lesions in the brains of monitored animals it can be hopefully suspected that if such lesions occur they are relatively small ones. Recognizing the difficulty of selecting sacrifice times and the marked variability in radiosensitivity of various cell groups of the central nervous system, it is hazardous to draw conclusions at this time. Zeman, et al[27] reported that increasingly large doses of high energy deuterons were required to produce central nervous system lesions with successively smaller sized microbeam apertures. A 0.025 mm beam required an exposure of approximately 1 million rad to produce a lesion. The time required for this exposure was on the order of 1 second.

No untoward neurological symptoms have developed[1] following exposure of the pilot of the MANHIGH II flight to an altitude above 90,000 feet for over 16 hours. This further suggests that there is no significant neurological hazard from heavy primaries on short space flights. The facts to date leave the question of the hazard resulting from exposure lasting several months or years unresolved.

Efforts to identify genetic effects specifically attributable to identified heavy particles have also encountered formidable technical difficulties. Fortunately, this type of biological material can be exposed to the very short ranged heavy ions produced by a heavy ion linear accelerator. Such experiments should provide an opportunity to develop techniques suitable for space experiments and provide control data.

DISCUSSION

The graying effects reported by Chase demonstrate unique track effects from heavy primary particles. This fact raises the question, "which charge-energy combinations characteristic of the heavy primary spectrum produce the graying effects observed in mice?" The fact that tracks selected by criteria applicable only to the boxed region of Figure 2 correlated with the location of gray hair in mice suggests that primaries of this type may be biologically most significant.

Comparison of the results obtained from rockets, balloons and satellites makes it apparent that if one is interested specifically in the effects of track-producing heavy primary cosmic radiation, high altitude balloon flights are most satisfactory. Rockets provide limited exposure time and are usually launched at undesirably low geomagnetic latitudes. Balloon flights below 140,000 feet receive significantly reduced exposure which is biased to disproportionately reduce the incidence of the heaviest primaries. Polar satellite orbits limit the heavy primary radiation due to geomagnetic shielding during portions of each orbit, and accumulate Van Allen belt radiation which greatly complicates, if not precludes, the most convenient forms of track plate analysis.

The results of the Zeman et al[27] deuteron study leads to a conclusion contradictory with the Chase mouse graying results. One possible explanation is the 10,000,000,000:1 ratio in exposure time at the cellular level.

SUMMARY

The high correlation between the heavy primary tracks observed in monitoring track plates and the position of loci of graying in black mice reported by Chase suggests that heavy particles of higher energy and lower total specific ionization are responsible than was previously expected.

These results emphasize the need for developing techniques which are practical for monitoring biological specimens but which will identify more accurately both the charge and energy of galactic primary particles.

Comparison of heavy primary exposures observed in rocket, balloon, and satellite flights clearly indicates that for this type of experiment balloon flights at a minimum altitude of 140,000 feet provide the most desirable type of exposure.

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Therapy for Pruritus of Jaundice

When large amounts of bile enter the intestines, as with primary biliary cirrhosis or incomplete biliary obstruction, oral administration of MK-135, a bile acid-sequestering resin, relieves pruritus in jaundiced patients. The strongly basic anion exchange resin probably forms a nonabsorbable complex with bile acids in the intestines, causing the serum bile acid concentrations to decrease and pruritus to disappear. In patients with extensive or complete biliary obstruction, few or no bile acids enter the intestines and the resin has no effect. Because MK-135 does not alter the serum bilirubin value or serum alkaline phosphatase activity, the decrease in serum bile acid concentrations and relief of pruritus cannot be attributed to spontaneous or coincidental remission of the biliary obstruction.

Divided doses of 10 gm. of MK-135 fed daily to five jaundiced patients diminished high serum bile acid concentrations and relieved pruritus in each instance. In two patients, withholding the resin resulted in serum bile acid elevations and return of pruritus; refeeding the resin diminished serum bile acid concentrations and relieved itching.—JAMES B. CAREY, JR., M.D., and GALE WILLIAMS, University of Minnesota, Minneapolis. J.A.M.A., 176: 432-435, 1961. Abstracted in *Modern Medicine*, 1961.