We undertook a series of experiments in an attempt to simulate electrone, x-ray, and nuclear particle work with high Z particles at the Berkeley Linac and Berkeley Cyclotron. Acceleration of heavy ions to energies of several hundred MeV/nucleon is required. Studies of the effects of accelerated helium ions on the mammalian retina are in progress. Low energy (8 MeV/nucleon) organ ions are being used for an assessment of the effects of these heavy particles on cells in cultured cerebellar explants.

**INTRODUCTION**

For the past twenty-five years some of us interested in manned exploration of space have been concerned about space flight radiation hazards, and in particular the importance of high Z particles of the galactic cosmic rays impinging the body. We have some understanding of the high Z fluxes (e.g., see 1, 2, 3) expected during solar minima during interplanetary travel, and have been aware of the potential hazards from heavy particles such as iron intersecting the non-regenerating tissues such as nervous tissue (4,5). However, it was not until the light flash phenomenon noted by astronauts on Apollo 11 that our previous work with high Z particles at the Berkeley Linac and Berkeley Cyclotron accelerated its pace in order to not only elucidate and characterize the phenomenon of light flashes seen by astronauts, but also to assess the importance of these particles to the health of astronauts on missions of long duration, e.g., Mars.

This paper will emphasize the mechanism for light flashes seen by astronauts, and our studies on high Z particles impinging on nervous tissue in vivo and in culture. We will describe briefly experiments conducted since April 1970, which include neutron radiations from 1 MeV to 60 MeV, pion exposures, and finally helium ion beam exposures of the human retina. Some of these experiments have been discussed previously by us (6, 7, 8) with corroborative experiments by Fremlin (9) and Chermak and co-workers (10). In addition, we will describe experiments on rabbit eyes using helium ions and, eventually, carbon ion beams. Our investigations are designed to extend the information on bioelectric response after irradiation of the eye. Past studies have been high dose and acute experiments from which we cannot evaluate the effect as a function of particle linear energy transfer (11-15).

**HYPOTHESES REGARDING LIGHT FLASH PHENOMENON**

When in the course of the historic Apollo 11 flight astronauts Neil Armstrong, Edwin Aldrin, and Michael Collins first experienced sensations of streaks and flashes of light, it was speculated that these visual phenomena could be caused by any one of the following:

1. Mechanical stimulation such as pressure phosphenes.
2. Electrical stimulation of the visual apparatus.
3. Induced currents from magnetic field changes.
4. X-ray stimulation of the visual apparatus.
5. Psychological states -- illusions.
7. Cosmic ray interaction in the eye or along the visual pathway.

In order to understand the mechanism of interaction whereby light flashes were seen by astronauts, we undertook a series of experiments in an attempt to simulate electrical, x-ray, and nuclear particle phosphenes. In addition, we worked with the Apollo 14 astronauts and members of the investigative team at the Manned Spacecraft Center to clarify the description of this phenomenon with regard to shape, brightness, duration of occurrence relative to the earth's electromagnetic shield, and frequency of events.

The flashes seen were in the main, pinpoints of light similar to momentary discrete colorless star-like flashes, or streaks of a few degrees aperture. The phenomena were in general colorless, and occurred at a frequency of one-half to two per minute. There is a consistency in observation among the Apollo 11, 12, 13, and 14 crew members as to the above general characteristics; however, there is also considerable (and not unexpected) variability in terms of predominant direction and ease of visualization. Shortly after the report of Apollo 11, we speculated that these events were from interaction of charged particles with the retina, or some other part of the central nervous system involved in visual sensations, as one of us had predicted a number of years ago (4). We excluded from consideration electrical, magnetic, pressure, and psychological states as explanations for these phenomena because flashes and streaks of light are not common to the other modes of stimulating the visual apparatus. The consistency of reporting, lack of color and plausibility of alternate explanation excluded psychological states as a reasonable course to pursue.

Direct cortical stimulation has, of course, been known since classic experiments of Penfield and this remains a possible explanation through the action of cosmic ray particles rather than direct electrical stimulation (16). We had previously examined characteristics of x-ray, magnetic, and electrical phosphenes...
which, in general, can be described as nondescript graying or lightening of the otherwise darkened field (17). Electrical phosphenes are easily generated by merely applying three volts from small batteries across the head, and x-ray phosphenes can be experienced by dark adapting and standing in front of an x-ray beam at dose rates and doses lower than that experienced in a routine chest x-ray (6, 18).

In order to examine the hypothesis that explanation 7 above applied to light flashes seen by astronauts, we launched a series of experiments with pions, neutrons at various energies up to 640 MeV and, most recently, individual helium cone ions impinging on an observer's dark adapted retina. During the course of our attempts to simulate cosmic rays using high energy neutron beams impinging on the carbon, nitrogen, and oxygen atoms of the eye, Fazzio and others (33) theorized that these light flashes in space were from Cerenkov emission of primary cosmic ray particles. Our investigations include both relativistic and non-relativistic particle exposures, and we show in this paper that the most plausible explanation for the light flashes seen by astronauts is direct ionization or electronic excitation, rather than the Cerenkov effect, because our high atomic number exposures indicate that observation of light flashes from single particles occurs frequently when the linear energy transfer (LET) is greater than 10 keV/micrometer though we expect that events might be occasionally seen at even lower LET. In interplanetary space most of the fast galactic carbon particles and heavier ($Z > 6$) at several 100 MeV/nucleon cause visible events when these cross the retina. We expect that "slow" particles at several MeV/nucleon can also cause a light sensation even at $Z = 1$.

**NUCLEAR PARTICLE EXPERIMENTS**

**Human Experiments:**

The experiments to be outlined below involve human observers in neutron and charged particle beams for which there is some precedence in that the patients are irradiated at very high doses and high dose rates for ablation of pituitary and cancer radiotherapy, and by neutrons for therapy or whole body activation analysis (19). However, for experiments described below special precautions and detailed protocols were prepared to limit exposures to a safe range. We operated with close adherence to already well established human use committee procedures existing at the University of California and the University of Washington. The utmost care was made to keep doses at minimal levels, and no investigator during any experiment received more than 30 mrem to the eyes or other sensitive organs. The subjects are volunteer, mature scientists who have technical familiarity with radiation physics and radiation biology. In addition to the responsible medical group which reviews the experiments, the individuals in charge of each accelerator facility agreed to the protocol in advance. Health Physicists in charge carried out independent measurements and were present during each experiment with a veto power. The principal investigators who were exposed are a part of a group of scientists who receive periodic eye examinations. The first series of eye examinations have been completed on the individual with the greatest exposure, and no abnormalities over a previous examination have been noted.

**High Energy Neutron Exposure:**

Our first experiments (6) were designed to simulate cosmic particles of carbon, nitrogen, and oxygen by producing recoil carbon, nitrogen, oxygen and nuclear fragments in the eye. Two human subjects were exposed to a beam of fast neutrons with energies between 20 and 640 MeV produced by a 0.64 GeV proton beam impinging on a 12 cm thick beryllium target (Fig. 1a,b). Most of the neutrons were at energies near 300 MeV, and only 2% or less of the dose came from slow neutrons and gamma rays. The flux, continuously monitored, was $1.4 \times 10^4$ neutrons cm$^{-2}$ sec$^{-1}$. On four exposures (total 8.5 mrem) of duration between 1 and 3.5 seconds, one subject saw pinpoint flashes coinciding with the presence of the beam, and the other subject during a 3 second (2.6 mrem) exposure saw between 25 and 50 bright pinpoint flashes which were described as being similar to driving into a light snowfall at night. The events were colorless, and had some shape similar to a tadpole or "comma". The events that we saw could have been caused by neutrons, proton recoils, nuclear spallation products, and even carbon, nitrogen, and oxygen recoils atoms in the eye or other parts of the visual apparatus including the cerebral cortex for the front exposure. X-rays could not account for the phenomena as the dose rate for x-rays was much lower than that necessary for the stimulation of x-ray phosphene, which, in any event, are different in character than the pinpoints of light seen (6). This experiment did not exclude Cerenkov as the mechanism because some protons and pions had energies greater than 470 MeV, and some Cerenkov emission would be expected. Experiments described below were done to exclude Cerenkov as the basic mechanism.

**Pion Exposure:**

A short exposure was done with 1.37 BeV kinetic energy (1.5 BeV/C momentum) positive pions at the Berkeley Bevatron. The maximum flux was 200 pions cm$^{-2}$ sec$^{-1}$, and no phenomena were noted, although the subjects dark-adapted eyes were bathed in a beam for 6 seconds. Previous investigations with mu mesons using a cosmic ray telescope at ground level showed a statistically significant coincidence between subjects reports of some visual event and the arrival of mesons (20). Recently the mu meson observations were repeated with improved cosmic ray telescope techniques by Charman and Rollins (21).

**Observations in Commercial Flights at High Altitude:**

We took advantage of conference meetings over the past year to examine whether any phenomenon could be seen in the well dark adapted trained observer at 10,000 meters in commercial airliners. Two of these flights were at geomagnetic latitude 60° north, and 2 at 30° north. Since the cosmic ray particles at altitude are more numerous than ground level by an approximate factor of 60, well dark-adapted individuals observing for 30 minutes after 30 minutes of dark adaptation would be expected to note frequent phenomena if cosmic ray phosphenes were observable at ground level. We were unable to note any events, although two observers enthusiastically pursued this project.

**Low Energy Neutron Experiments:**

The negative results with pions and at high altitude are certainly not sufficient to exclude Cerenkov radiation, because the number of photons released by a relativistic particle passing through the retina is a function of the charge squared. In fact, negative results with singly charged particles are expected as insufficient photons are released during Cerenkov emissions with $Z = 1$. To show the effect of particle interaction, we performed some experiments at neutron energies near 1
Figure 1a. Schematic layout of the Berkeley 184" cyclotron as it was used for observing light flashes from high energy neutrons (0.64 BeV maximum energy).
Figure 1b. The neutron beam was passed either laterally or frontally through the eye regions of the dark adapted observers.
Helium Ion Retina Exposure-Human:

From these experiments we are left with the hypothesis that either proton recoils or alpha particles, or both, are the most likely candidates for direct ionization or electronic excitations in or near the sensitive part of the retina. A direct test of this conclusion from our previous experiments involved the use of accelerated helium ions available at our 184-inch cyclotron at Berkeley in a beam which was aimed carefully at various portions of the posterior globe of human subjects. The objectives of our experiments were to characterize any visual phenomenon as to brightness, character, and efficiency of detection. These experiments have been done on two subjects using helium ions with a maximum energy of about 240 MeV (8). We found that the human eye could detect individual helium ions with an efficiency of approximately 40%. When helium particles were allowed to cross laterally the central region of the retina of the left eye at random time intervals with an average rate of 10 per second, both subjects saw two to five flash events per second. These events included streaks with motion sense in the beam direction similar to the phenomena "seen" in the neutron beam. At lower rates of approximately one particle per second and high rates of 100 per second, it was difficult to discern more than one event. These streaks appeared to be light flashes traveling horizontally across the field of vision with a length of 2 to 4 cm at 1 meter distance. The experimental set-up for these irradiations is shown in the bioluminescent exposure region where monochromatic beams of about 90 MeV helium ions are used in the helium ion pituitary radiation therapy program at our laboratory (Fig. 3).

The beam entered from the side, and moved through a dark plastic mask, skin, zygomatic bone, soft tissues, and into the posterior globe. The total number of particles for one observer was 1150 and for the other 1500. The dose along the beam path, which is 4 mm in diameter, is less than 1 mrem. The length of the streaks observed was equivalent to one millimeter on the retina, or less.

Considering the thickness of the retina outer segment of approximately 10 microns and a curvature of the eye, the longest unbroken straight path through the retina is about 2 mm. We observed four classes of events:

1. **Stars** -- these were brief minute dim light flashes not dissimilar in character or intensity from "stars" seen by some observers on trauma to the head or at night when first beginning to dark adapt.

2. **Bright flashes** were definite bright pinpoints of light that appeared as a star in a cloudless night.

3. **Streaks** -- pencils of light which varied from dim, thin lines to globular, comma-tailed objects sufficiently bright that there is no mistake, but not so bright that they were distracting or alarming.

4. **Supernovae** -- these are bright single flashes of slightly more than momentary duration surrounded by a halo haze of less than half a degree aperture. Supernovae is a term coined by astronauts on Apollo 14 in trying to describe what we think is the same type of phenomenon.

These experiments definitely establish the fact that nonrelativistic helium ions could cause stimulation of the visual apparatus through interaction at the retina. We moved the beam in front of the retina (behind the lens) and into the optic nerve region, and in these two positions there was no response.

**APOLLO 14 ON-BORD EXPERIMENTS**

During Apollo 14 experiments were conducted by the three crew members to help characterize the light flash phenomena with regard to size, shape, brightness and the frequency of events. In addition, we endeavored to establish any relationship between the occurrence of these light flashes and the degree of dark adaptation of each observer. During preflight briefings with A. Shepard, S. Roosa, and E. Mitchell, methods were worked out for describing the types of events which we anticipated they would see based on our cyclotron experiments and discussions with other Apollo astronauts. The crew and investigators found this briefing helpful in that during the spaceflight the earth-based investigator had a common language for communicating and interrogating the crew who were acting as detectors. The initial observations by E. Mitchell and S. Roosa indicated that minimal or no dark adaptation was necessary before seeing the phenomenon. On the transearth coast a block of time was reserved. During this all three observers made careful observations with regard to shape, visual field position, and frequency of events. These observations were made in the dark after light adapting using a flashlight, and are summarized in Table 1. Four types of events include:

- **Flare** or star which indicates a momentary brief light flash of a few minutes are aperture.
- **Double** meaning two flashes across the visual field simultaneously suggestive of a particle
Figure 2a. Neutron spectra normalized so that the integral of $N(E)$ is equal to one for Californium-252 in the beam from 20 MeV deuterons of Beryllium. The experiment was performed with 22 MeV deuterons.

Figure 2b. Artists concept of starlike events initially seen in the high energy neutron beam.
Figure 3. Schematic layout of the manner in which individual accelerated helium ions were passed through the left eye of dark adapted observers. The 900 keV helium ion beam was moderated by absorbers to about 250 MeV kinetic energy, re-collimated and magnetically deflected. Each particle was individually monitored by means of a coincidence arrangement and a silicon detector.

| TABLE 1

Total Observed Events

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>In right eye</th>
<th>In left eye</th>
<th>In both eyes</th>
<th>Not reported</th>
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<tr>
<td>Lunar Module Pilot</td>
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<td>12</td>
<td>6</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Command Module Pilot</td>
<td>12</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Commander</td>
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<td>10</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTALS</td>
<td>48</td>
<td>28</td>
<td>12</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>
interacting with two portions of the retina as it passed through the head. 

Streak which varied in length from a few degrees to as long as half the visual field -- approximately 55° aperture. 

Supernovae -- those were bright stars which seemed to be surrounded by a halo of light or multiple smaller flashes. 

Clouds -- a few events were described as clouds based on preflight briefing descriptions of a phenomenon characterized as a summer electrical storm behind the clouds on the horizon. This was an unanticipated class of event.

Of the 48 events seen by the three observers during approximately 17 minutes observation period 28 were seen in the right eye and only 12 in the left eye, with one reported in both eyes and 7 without eye or field localization. Although the sensitivity of each human detector varied, when the occurrence of flashes are plotted in terms of the interval between successive events, the random nature of the events is indicated by the Poisson distribution of the time distribution of events.

The relationship between the occurrence of events and the degree of dark adaptation has not been established in space; however, initial observations suggest that there is relatively little dependence on the degree of dark adaptation. This would suggest that direct ionization or electronic excitation in or near the outer segment might be the causative mechanism, unless sufficient photons are released by the charged particles to overcome the threshold in the light adapted observer.

During postflight debriefing the astronauts augmented the observations recorded in spaceflight by more detailed discussion. Backlighted diagrams and shapes were used to gain size, shape, and intensity quantitation. This debriefing is the basis for some of the inferences we have made above. All the results of the Apollo 14 experiments are very similar to the helium ion earth-based experiments.

GALACTIC COSMIC PARTICLES AS THE CAUSATIVE MECHANISM

The experiments described above point unequivocally toward cosmic nuclei as the causative mechanism for light flashes seen by astronauts, particularly in view of the fact that the fluxes expected for nuclei of carbon and heavier (Z > 6) coincide with that observed. At distances greater than 30,000 miles from earth it is estimated that between 2 and 10 nuclei with Z > 6 intersect the human retina in a spacecraft configuration during a solar minimum (TFB). There is a remarkable consistency in the frequency of astronaut observed events of 1-2 per minute for the poorly dark adapted eye and the cosmic ray omnidirectional flux.

The significance of these results is that a new phenomena for stimulation of the visual apparatus has been noted. We should also note another important fact, that fast cosmic ray nuclei do penetrate and pass through the body of man flying in interplanetary space outside of the radiation shield of the earth. We have ascertained that on a 1000-day Mars mission several percent of the brain non-regenerating cell nuclei will be hit by charged particles. However, from counts of cosmic ray tracks in hemets of Apollo 12 astronauts (32) a conservative estimate for single nerve cell loss from cell nucleus hits is 0.1%. This low dose rate injury to non-regenerating tissues could lead to delayed death of several percent of cells, depending upon the injury cross section.

DELETERIOUS EFFECTS DUE TO PRIMARY COSMIC RAYS

The evaluation of biological effects due to primary particles poses special problems for the space scientist. Since individual particles might cause localized damage, some of us feel that the concepts of "space-time average dose" and "roentgen equivalent, man (REM)" do not apply. Instead it will be necessary to understand the effects of individual particles on cells and groups of cells in close proximity. Questions that arise may be grouped as follows:

A. Can the passage of a single heavy ion cause non-regenerating injury? What are the quantitative probabilities of obtaining such injury? For example, it seems possible that the passage of a single particle might cause permanent or transient, degeneration of the outer segments of rods everywhere along its track.

B. What is the significance of the accumulation of single particle initiated lesions to the health and performance of astronauts? This problem may be dissected into several classes of subproblems: 

-- We must classify the probability for destruction of "vital" centers, e.g., in the hypothalamus, and the significance of such effects;
-- We must ask whether or not accumulation of microinjuries, that might affect several percent of the cells of the brain could cause a decrease in performance, a slowing of reflexes and generally effect higher nervous system function;
-- We should inquire into the potential of heavy cosmic rays causing chronic degenerative diseases, such as life span shortening, degeneration of scotopic vision, cataract formation, and carcinogenesis. The group led by Curtis (22) has recently demonstrated that a single 500 Rad dose of deuterons to a portion of brain of mice leads to a measurable decrease of lifespan. There is also preliminary evidence (23) that proton irradiation of primate brain can lead to neurogenic tumors.

C. We should also ask what relationship, if any, exists between heavy particle lesions and chronic radiation effects from conventional radiations. In long term spaceflight radiation doses accumulate from low LET portions of cosmic rays and from nuclear power sources and propulsion units on board the spacecraft (24).

D. Is there a relationship between heavy particle lesions and other effects of space environment, e.g., weightlessness?

In quantitative studies of such phenomena, scientists are seriously hampered by the fact that at present there are no accelerators anywhere capable of producing accelerated heavy nuclei with range penetration and charge spectrum similar to that of primary cosmic rays. These investigators feel that until such machines are available our understanding of these radiation phenomena will be deficient at best.
We are pleased to report that attempts are being made to accelerate heavy particles in existing synchrotrons. During Summer 1971, attempts are being made to obtain accelerated nitrogen (7+) nuclei at several hundred MeV/nucleon at the Princeton Penn Accelerator and at the Berkeley Bevatron. Later, perhaps in 1972, it might become feasible to inject low energy heavy ion beams from the Berkeley Hilac into the Bevatron, thus greatly increasing the spectrum of fast heavy particles available for bio-experimentation.

EXPERIMENTS IN PROGRESS

Retina:
It has already been shown by a number of investigators that single doses of X rays (25), neutrons (26) and of high energy helium ions (27) can cause irreversible degeneration of the outer segment of the rods in the mammalian retina. It is also known that histological degeneration is accompanied by profound degeneration of the electroretinogram (ERG) (25). As an example, in Figure 4 we reproduce the decrease of the amplitude of the b wave of ERG in felines, one week after exposure to a beam of 900 MeV helium ions. Unfortunately, the dose-effect relationship at low doses has not been established. Linearity between dose and effect would be a definite indication that we might expect a similar relationship when retina is exposed to heavy primary ions. In the work of Demirtschoglian (28) on frog eye, a linear relationship is apparent. More work is underway at our laboratory on this point using accelerated helium ions. Nitrogen ions will also be used as these become available.

Neurons in Culture:
For the last three years we have worked with cerebellar explants from new-born rats. It has been demonstrated that in roller tube type cultures it is possible to obtain monolayered cultures of a layer of Purkinje cells surrounded by granule cells and glia. The axons become myelinated in about ten days, functioning synapses develop, and such cultures have spontaneous electrical activity (29-31); the cultures have a life of at least eight weeks in the laboratory.

Since the thickness of the cerebellar cultures is only 20-30 micrometers, these cultures are suitable for irradiation by low energy heavy ions available from the Berkeley Hilac. In a pilot study, 8 MeV A(18+) nuclei were used. At doses of 1000 Rad and above it was possible to demonstrate progressive cellular degeneration in these cultures culminating in death and lysis of neurons and glial cells at from one to several weeks post irradiation. Some quantitative information was obtained on the appearance of glycogen granules in the cytoplasm of all cell types and of pyknotic nuclei in granule cells. These changes appeared to precede osmotic death of the cells. The Purkinje cells required several thousand rad for lethal effects at a period of one week post-irradiation. It is hoped that such experiments may eventually lead to a better description of chronic radiation effects of heavy ions at the cellular and subcellular level. The information should be of value for quantitation of a possible heavy ion hazard in space flights. However, such investigations are only of limited value to understand the entire neuro-radiation syndrome. The cultures do not possess blood vessels and circulation and are not suitable to assess blood-brain barrier alterations. Neither are they suitable for functional and performance studies involving the whole organism. Eventually it will be necessary to study the effects of accelerated heavy ions on the intact mammalian organism.

REFERENCES

Figure 4. The amplitude of the b wave of the electroretinogram reflects irreversible damage to the outer segment of retinal rods. These data were obtained with 900 MeV helium by Cornelius Gaffey (27).
26. Robertson, W.; Brookhaven National Laboratory; personal communication.

ACKNOWLEDGEMENTS

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DISCUSSION

ALLKOFER

What is the physical reason for the light streaks?

TOBIAS

We believe that direct interaction of the ionisation and excitation produced by the particles with molecules and membranes of the visual rods are responsible.

ALLKOFER

What is the reason for the difference between the right and left eyes in the events seen by the astronauts?

TOBIAS

We believe that an optical illusion exists whereby an event that appears far to the right is subjectively classified as being in the right eye.

ALLKOFER

Is this phenomenon dangerous?

TOBIAS

Research is in progress on pathological effects produced by heavy ions in retina and brain. It will be necessary to accelerate heavier particles than heretofore available; e.g. iron (Fe\textsuperscript{26}) before we have the full answer. It is possible that in long spaceflights (e.g. to planet Mars) or in long orbital missions, pathological effects may be encountered.

KASSUE

Did you use a $\pi^-$ beam for these experiments?

TOBIAS

We have not used a $\pi^-$ beam, only $\pi^+$ beams.

KASSUE

Is it intended to perform the same type of experiments as Bevalac at Berkeley?

TOBIAS

We have exposed three individuals (Prof. E.A. McMillan; Dr. Phillip Chapman, Scientist-Astronaut; and C.A. Tobias) to 4 Gev nitrogen 7 beams, with the particles slowed down so they stopped in the vicinity of the retina. Intense streaks were seen. A report is being prepared.