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Authors

Tobias, Cornelius A.
Brustad, Tor.

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RADIOBIOLOGICAL STUDIES WITH ACCELERATED HEAVY IONS

Cornelius A. Tobias
Tor Brustad
November, 1958

RADIOBIOLOGICAL STUDIES WITH ACCELERATED HEAVY IONS

by

Cornelius A. Tobias and Tor Brustad*

Donner Laboratory of Biophysics and Medical Physics
Berkeley, California**

As far as we know, the primary cosmic rays consist of rapidly moving light nuclei: protons, helium ions, and nuclei with various atomic numbers, like carbon, oxygen and calcium. The particles arrive from all directions in space, and are mostly extrasolar in origin. Correlations with solar activity indicate, however, that varying fractions of the primary nuclei originate from the sun and that solar magnetic phenomena influence the terrestrial intensity of the extra solar component as well.

Because of the shielding and reflecting influence of the earth's magnetic field, we have detailed experimental information only for those components of the primary rays which have sufficient momentum to penetrate the earth's magnetic field. Up to the age of space flight we could only guess and extrapolate with respect to the frequency of "low" energy primaries (meaning mostly energy up to several hundred Mev per nucleon), which may actually have a more important contribution to biological effects than the better known high energy component.

* Research Fellow of the Norwegian Cancer Society and the ICA, Oslo, Norway

** This study is based on work performed under contracts between the University of California and the Atomic Energy Commission

Observations in the explorer satellites by Van Allen and associates (1) have given proof of a new component of rays extending from a few hundred miles altitude on up to at least 30,000 miles. It is of great current interest to find out the exact intensity and particulate composition. Electrons of about 6 Mev and/or protons up to 300 Mev might be the most frequent particles.

There is an interesting new theory which attempts to explain the presence of protons in the high radiation belt on the basis that these result from the radioactive decay of neutrons generated when primary cosmic rays interact with top layers of the atmosphere. The protons are then trapped and presumably focused by the earth's magnetic field. If this theory outlined by Singer at the present symposium (2) were true, then one would not expect light nuclei other than protons, and protons would become the greatest radiation hazard in the high radiation belt. The neutrons also produce decay electrons; these would then presumably also become part of the radiation belt.

Another theory that might explain the radiation belt would involve low energy particles originating from the sun, which would then become injected into the earth's magnetic field when ionized magnetic clouds pass near the earth. If this second model were true, we might expect to find some heavy ions as well.

In order to assess the biological hazards of cosmic rays in space flight, one may proceed in several steps. First, it is necessary to know the frequency, energy distribution and charge of the particles as completely as possible. For with a heterogenous group of particles, it is not sufficient to know the "dose" or the energy deposited in a

gram tissue. We also must know the distribution of "linear energy transfers" (LET), and thus have information of the frequency of ionization tracks with different ion densities. The LET is a function of the charge of the particles as well as their kinetic energy. By use of data taken in balloons and rockets near 100,000 feet altitude, we do have some knowledge of the distribution of heavy ion primaries (3)(4)(5) and also know that they have very large variations in intensity. Where knowledge is most important, at low energies which have a large contribution to dose with the heaviest ionization densities, space investigations have not as yet started. In the absence of detailed knowledge of similar information for the Van Allen radiation belt, we only know now in general terms that certain regions of space offer serious radiation hazard.

More exact knowledge of the hazard will be available when each type of cosmic ray particle has been tested for biological effects; knowledge of the full radiation spectrum will also allow detailed calculations for shielding of space ships.

Methods for Particle Acceleration

The usual way for assessment for biological hazards of a complex radiation spectrum is to produce and test the effect of each component separately then study the interaction of effects. When dose rates are low, as for some of the most penetrating components of cosmic rays, then biological hazard calculations are based on extrapolations of results obtained with high doses.

The components of the radiation belt which are known so far: electrons and protons can be studied in conventional accelerators. For example, electrons there is a 6 Mev linear medical accelerator at Stanford (6), and one for high energy at the Argonne National Laboratory (7). There

are several betatrons available as well. Protons up to 700 Mev deuterons to 450 Mev and alpha particles to 900 Mev have been used for biological studies at the Berkeley 184" synchocyclotron for the past nine years. Also recently similar studies were started at Chicago (8) and in Uppsala (9). Until recently the only heavy ion accelerator was the 60" cyclotron used by Birge et al (10)(11). For the past year a new heavy ion linear accelerator has been used in biological studies (12)(13) at Berkeley, and there is a similar one being completed at Yale University. The Berkeley HILAC (Figure 1) can accelerate alpha, carbon, nitrogen, oxygen, neon and argon particles to about 10.2 Mev per nucleon, so that, for example, neon would have a kinetic energy of 208 Mev. A few properties of the particles accelerated in the HILAC are given in Table I. The range penetration of these particles in tissue is only a few hundred microns, so they are suitable for irradiation studies of unicellular organisms and of thin layers of tissue.

radiation

If we wish to know the effect of whole body, or of deep irradiation in animals, it will be necessary in the future to produce higher energy beams of these particles. The methods have been worked out in principle: for example, it would be possible to extend the HILAC machine which is now about 100 feet long and gain energy in proportion to length. Or the injection of a beam of partially or fully stripped ions is feasible into high energy cyclotron or bevatron (14). Because these machines are large and complicated, any such undertaking would mean a major effort.

It is also possible to obtain some heavy recoils as secondaries from high energy proton, meson or neutron beams. These would be products of spallation or fission reactions or meson initiated nuclear stars.

Usually the heavy recoils are a small part of a complex background radiation and some method, e.g. magnetic analysis would be required to study them separately. Products of spallation or of fission may be studied within the animal body also. For example, there is a study available of effects of thermal neutron induced fission of U^{235} (15) where the effects are assumed to be due in part to heavy fission recoil nuclei.

The Nature of Heavy Ion Tracks of cosmic rays

It is well known that the heavy ions produce very wide tracks in electron sensitive photographic emulsions. An example is shown in Figure 2. Actually the picture in the emulsion does not show the detailed nature of the track. It consists of a number of electrons which were knocked out of the atoms and some of which (the delta rays) travel considerable distance from the core of the track and produce some ion pairs themselves. The central core, perhaps one micron in diameter, has also many positive ions. Most of the energy loss to tissue occurs in the core, and as the particles travel slower this linear energy loss increases. As a matter of fact, the picture one obtains of a track in a photographic emulsion depends on the electron sensitivity of the emulsion. In K_{-2} emulsion which is sensitive only to energy loss greater than 4 Mev per micron, Heckman (16) and Barkas (17) obtained the picture of the "core" of the accelerated tracks, densest near the end of the thindown.

In living tissue, like in photographic film, heavy ion effects depend on the "electron sensitivity" of the cells. In the most sensitive material one can expect effects over the entire width of the track, but it is also possible that only the very "hot" core of the tracks do the damage. Actually within the heaviest core the dose is about 1000 - 3000 rad,

(delivered within 10^{-14} seconds), while in the periphery it is only 1 - 5% of this figure. How misleading the appearance of the tracks can be is illustrated in Figure 3. This shows four years' accumulated ground level cosmic ray background in G5 emulsion and also the effect of a single one roentgen exposure to 250 kv X-rays. The latter almost completely blackens the photographic plate.

Biological Experiments with Heavy Ions

For assessment of the effects of heavy ions two types of experiments are necessary. Using single cells first, it is necessary to know the biological effectiveness or RBE of the particles as a function of their ionization density, LET and their delta ray distribution. Secondly we must know how many neighboring cells a single particle can affect. It is clear that the effect of heavy primaries will be most critical in parts of the body where the "redundancy" of the cells is low, that is, where a few neighboring cells control the function of many others in the body.

Experiments with the Heavy Ion Linear Accelerator

Knowledge of the effects on single cells, viruses and enzymes is now gained quite rapidly with the HILAC, which has been in continuous operation for the last year. Donald Fluke and Tor Brustad (12)(13) thus far have developed three kinds of exposure devices for heavy ions. Protein molecules, dried viruses and cells are exposed in vacuo on a disk with 12 samples, each of which may be moved into the beam by remote control. A remote control absorber wheel regulates the residual range of the particles, and the beam current is measured directly. From the vacuum chamber the beam is passed through a thin window aluminum foil and a

shallow ionization chamber to a space with controlled atmosphere, suitable to expose wet biological specimens, e.g. unicellular organisms. Finally, through a suitable aperture and window the beam may be brought outside and used to irradiate an animal. Figure 4 shows the absorber wheel in the controlled atmosphere chamber.

The present studies with molecules and microorganisms are being performed with a view to obtaining information of the shape of survival curves, of the relative biological effectiveness of the heavy ions and whether or not the mode of action of these radiations is the same as that of X-rays. This latter point is studied by the use of environmental modifiers.

For several different enzymes (including lysozyme, ribonuclease, peptidase and xanthine oxidase) as well as for bacteriophage T_1 , dried bacteria and resting wet haploid yeast cells the survival curves are exponential functions of dose: this may be interpreted to mean that a single ionizing particle is able to cause inactivation or lethal effect. The efficiency of producing this lethal effect may be interpreted in terms of the apparent cross section that the biological specimen exhibits to the bombarding particles. It is well-known that the ionization density of the particles is the significant factor for their action: in more precise terms, their linear energy transfer (LET). Cells cannot distinguish different radiations from each other - they do respond to different LET.

The significant data obtained so far are presented in Figure 5. The cross section, or effectiveness within a single ionizing track, increases as the ionization gets heavy in each case. For wet cells, somewhere

in the vicinity of a LET of $2.10^9 \text{ evg}^{-1} \text{ cm}^2$, however, the cross section levels off, indicating that when the ionization becomes very dense, some of it is wasted. In the range studied, the cross section of phage and enzymes keeps rising.

In terms of dose, or amount of energy absorbed in a unit mass of matter, "relative biological effectiveness" of 120 Mev carbon ions is about twice that of X-rays; with increasing LET the RBE apparently starts to drop rapidly.

Measuring the actual cross section, it would appear that if the core of a heavy ion track (slow carbon or heavier ion) passes through the nucleus of the cell, eventual killing of the cell and its progeny will result.

Extension of such studies to other strains of microorganisms and to human cells is bound to bring a more detailed understanding. Already preliminary data indicates that for diploid yeast cells the RBE might be 3 or 4 and that due to the different shape of survival curves the effectiveness of heavy ions at low doses might even be greater. This certainly seems to hold true for some chromosome aberrations in plant cells (*tradescantia*) when these are exposed to heavy ions. Work is also in progress on production of mutations in *neurospora*, (Judd, University of Texas) and on human cells in tissue culture.

It would be of great interest to know quantitatively the effect of heavy ion beams on mammalian tissues. In this field we can only report a beginning of an effort, and definitive results will not be available for some time. Systematic studies have started with 10 Mev carbon nuclei on the skin of C57 black mice. Herman Chase and his collaborators

are carrying out the biological phases. With exposures of 330 rads to 2790 rads, the degree of damage to the skin, that is production of hyperphasia, sloughing and scar is much greater than with a comparable dose of X-rays. The carbon ions are also more effective than X-rays in producing greying of the hair. Some surface irradiations of mouse corneal epithelium have also been made. This tissue should be ideal for heavy ion beam studies since it consists of a few parallel layers of cells.

Experiments with the Berkeley Synchocyclotron

At the 184" synchocyclotron studies have been carried out for about eight years with protons in the 0-700 Mev energy range, deuterons in the 0-450 Mev range and with helium ions which have up to 900 Mev (18)(19). For each type of biological effect one should carry out separate experiments to ascertain the specific biological effects; in general it was found that over most of their range these particles affected animal tissues in a similar manner as do X-rays, and the relative biological effectiveness as compared to 250 kv X-rays is close to one.

Since studies have been carried out for several years with animals, and there is a human therapeutical program also in progress, reasonably elaborate facilities are available for producing localized radiation damage.

The group in Donner Laboratory has been interested in the effect of radiations on the central nervous system. It seems to us that radiation effects manifest themselves most in two kinds of tissues: either those that have a high rate of mitotic cell division, like epithelial cells, bone marrow and some tissues of the reproductive system, or those that regenerate very slowly, like nerve tissue. In fact, it is

believed that low intensity heavy cosmic ray primaries might exert their greatest deteriorating effect in the central nervous system. Considerable irradiation work is being done on the brain and spinal chord. In order to observe pathological and physiological changes in the animal within a reasonable time, it is necessary to deliver large single doses. So far, six general factors are apparent.

1. For observing irreversible necrotising damage in a given small region of the C. N. S. within a given time period, one must exceed a "threshold dose." This concept is indicated by the findings in Figure 6 where the dose-time relationship of the onset of irreversible damage in the third cranial nerve is plotted from deuterons, the work having been carried out in dogs. For damage within one year, the dose should be about 12,000 rad.

2. Irreversible damage is a function of dose as well as the volume of the irradiated region. In rats irradiated in the brain with varying dose levels and apertures, the onset of necrosis or of lethality is inversely related to the "integral dose." This is illustrated in Figure 7.

3. White matter and hypothalamus appears to be more sensitive to protons, deuterons and alpha rays than grey matter in the sense that lesions appear later in the latter region. The "hypothalamic radiation syndrome" leads to shortening of life span, and a number of symptoms accompany the lethal effect, which are characteristic of the failure of hypothalamic function. For physiologic effect due to a given hypothalamic radiation lesion, it is necessary, however, to irradiate bilaterally with a large dose of several thousand rad.

4. With Professor Lyons* an investigation of direct radiation effects on peripheral nerve trunks was made. An exposed segment of the sciatic nerve of the rat was exposed to deuterons. More than 10,000 rad were necessary over 6 mm of nerve to obtain late degeneration.

5. When synaptic transfer was involved, as in the irradiation of segments of the spinal chord, nerve tissue exhibited greater sensitivity. An extreme case of this is found in the work of Lipetz, who found that threshold light sensitivity of the frog retina was temporarily decreased by X-ray doses as small as 10r (20). This finding was extended to humans by Motokawa and collaborators (21) and elaborated by Russian investigators also (22). There is a possibility that the radiation affects visual pigment as well as synaptic transfer in the retina.

6. Electroencephalographic changes, particularly post irradiation irregularities in the EEG, some of which resemble epileptic seizures, have for a long time been observed in X irradiated animals (23). Recently Tisjlar* has observed this effect immediately after localized irradiation by a 1 x 2 mm column of high energy alpha particles. The rat brains received a dose of several thousand rad.

It is somewhat reassuring that irreversible macroscopic degenerative changes have only been noticed following large doses of nuclear particles. However, we know that the ionizing core of single heavy ions does produce up to several thousand rad local dose. Moreover, there is some evidence that degenerative changes occur sometimes several years following irradiation. Embryonic nerve tissue is very sensitive to radiation.

* Unpublished data

Because of the apparent high density of protons in the cosmic radiation belt, stress should be laid on further studies with cyclotron produced protons, deuterons and alpha rays. The Berkeley 184" cyclotron is available on a routine basis for such irradiation, and collaborating with a medical group under John H. Lawrence, even therapeutic investigations are being carried out with this machine (24). Figure 8 illustrates a mammary carcinoma patient receiving 900 Mev alpha particles to her pituitary. There is another cyclotron operating in Uppsala (9) with 230 Mev protons where such irradiations are now also possible.

As for heavier ions, the availability of the HILAC will keep workers in the field busy for some time. It is clear, however, that in the future systemic effects of the various species of heavy ions will become known only when heavy ion beams of up to some billion Bev per nucleon are available in the laboratory. The knowledge of how to build such machines is available at present.

Shielding

If humans wish to fly in or through the Van Allen radiation belt, some shielding would probably be desirable in a space ship. It is interesting to note that if the radiations are protons, then a low atomic weight material (e.g. water or rocket fuel) can stop them more effectively than lead, since the stopping power per electron is greater at low atomic number. Thus the shield need not be "dead weight," but may contain materials essential to rocket flight or to the well-being of the passengers. If an absorber just greater than the proton range is employed, then the radiation dose penetrating the shield would be less than 0.1% of the dose in the external beam, mostly due to neutrons and gamma rays. Figure 8 gives the proton range and "absorber thickness" needed to

TABLE I

SOME DATA CONCERNING THE
HEAVY ION LINEAR ACCELERATOR

Particles	Approximate Energy Mev	Mean Range in Aluminium mgcm^{-2} (theoretical)*	Values of Linear Energy Transfer in Water (Mev/gcm^{-2})	
			Full Energy (theoretical)*	Bragg Peak
He^4	40	172	189	1,600
C^{12}	120	57	1,700	7,100
N^{14}	140	47	2,310	
O^{16}	160	41	3,030	10,000
Ne^{20}	200	34	4,720	
A^{36}	360	19	15,300	

* Measured values are slightly different (to be published).

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LEGENDS TO FIGURESFigure 1

Photograph of the interior of the tank of the Berkeley heavy ion linear accelerator. The beam would proceed at the center of the "drift tubes" of the evacuated tank. For size comparison note the person standing at the far end. The authors are indebted to Edward Hubbard for this picture.

Figure 2

Track of a heavy primary cosmic ray particle in a photographic emulsion. The particle enters on the top and stops near the bottom. The heaviest ionization is in the lower, thin part of the track, a few microns from the end. Thickening of the track near the top is due to delta rays. The authors are indebted to J. Lofgren for this picture.

Figure 3

Photomicrograph of 4 years cosmic ray background at sea level (left) and of the effect of one roentgen of X-rays (right) on G5 emulsion. This is offered as an illustration that not all black parts of a nuclear track are necessarily equally hazardous. The authors are indebted to H. Heckman for this picture.

Figure 4

Detail of the apparatus used at the Berkeley MILAC, showing the beam port (hole near the top of the picture) and the absorber wheel. By this the particles can be partially absorbed. Specimens may be mounted in vacuum in controlled atmosphere or in air.

Figure 5

Experimental data indicating the "efficiency" or "cross section"

for killing or inactivation as function of the linear energy transfer (LET). Conventional X-rays, neutrons or alpha particles have LET smaller than $10^9 \text{ evg}^{-1} \text{ cm}^2$. The data at higher LET was obtained with accelerated carbon, oxygen and neon ions. Note, that for cells and phage the cross section levels off when the ionization becomes so dense that some of it is wasted.

(NOTE TO EDITOR: This material was presented at the Geneva Atoms for Peace Conference and will be in the proceedings of the United Nations. You may wish to check with them re copyright. It was in AEC Report UCRL-8242(1958)).

Figure 6

Time of appearance of palsy of the third cranial nerve in dogs following a single dose of high energy deuterons.

Figure 7

Relation of integral dose (volume x dose in rad) to time of lethal effect from nerve injuries in rats. High energy deuterons were used. (ABOVE NOTE TO EDITOR APPLIES HERE ALSO.)

Figure 8

Patient receiving pituitary irradiation with 900 Mev alpha particles at the Berkeley synchocyclotron. The apparatus was specially built for localized irradiation of small internal parts of head and brain. (Appeared in Radiation Biology and Medicine, Chapter 22.)

Figure 9

Range of high energy protons and "practical extrapolated range" of high energy electrons in water.

stop electrons, in the range of energies we believe to exist in the radiation belt.

The shield for the Van Allen radiation would also stop the low energy heavy cosmic ray primaries which perhaps constitute the most hazardous component. However, the high energy primary nuclei would interact with the atoms of the shield, and cause multiplication of the particles and an increase in ionization. For a reasonable size shield the penetrating component will cause a dose of 10 - 30 milliroentgens per day. It is doubtful that any practical amount of shielding can decrease the dose in the space ship below this level, which is near the present limit of permissible continuous exposure.



Fig. 1

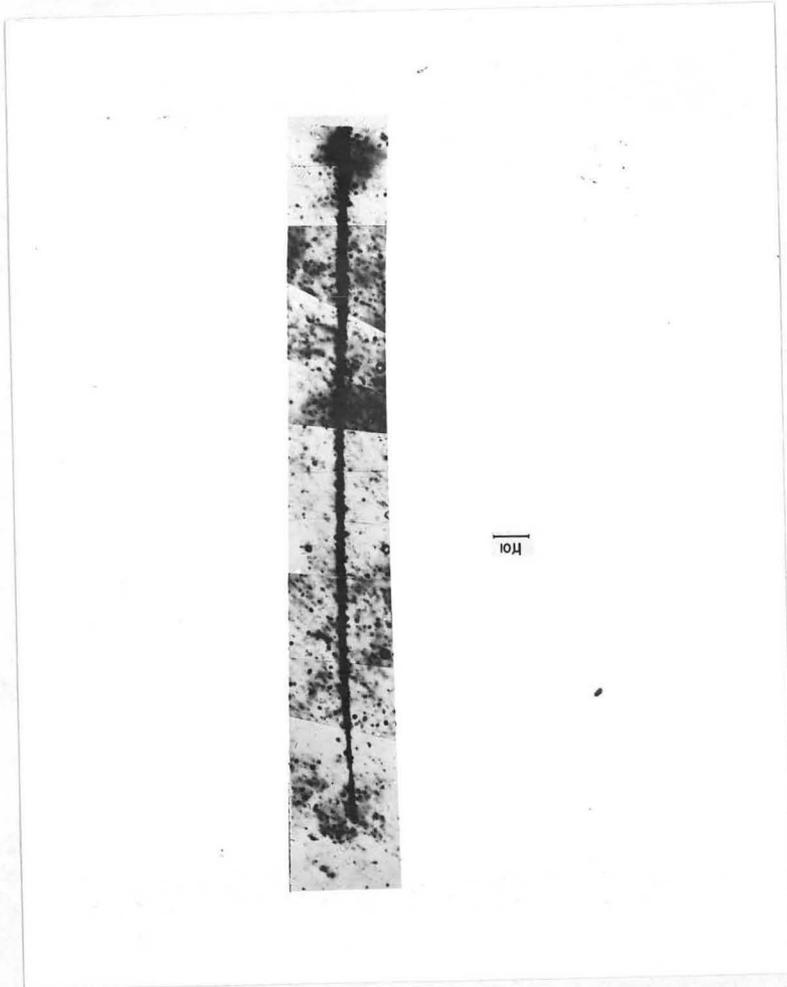


Fig. 2

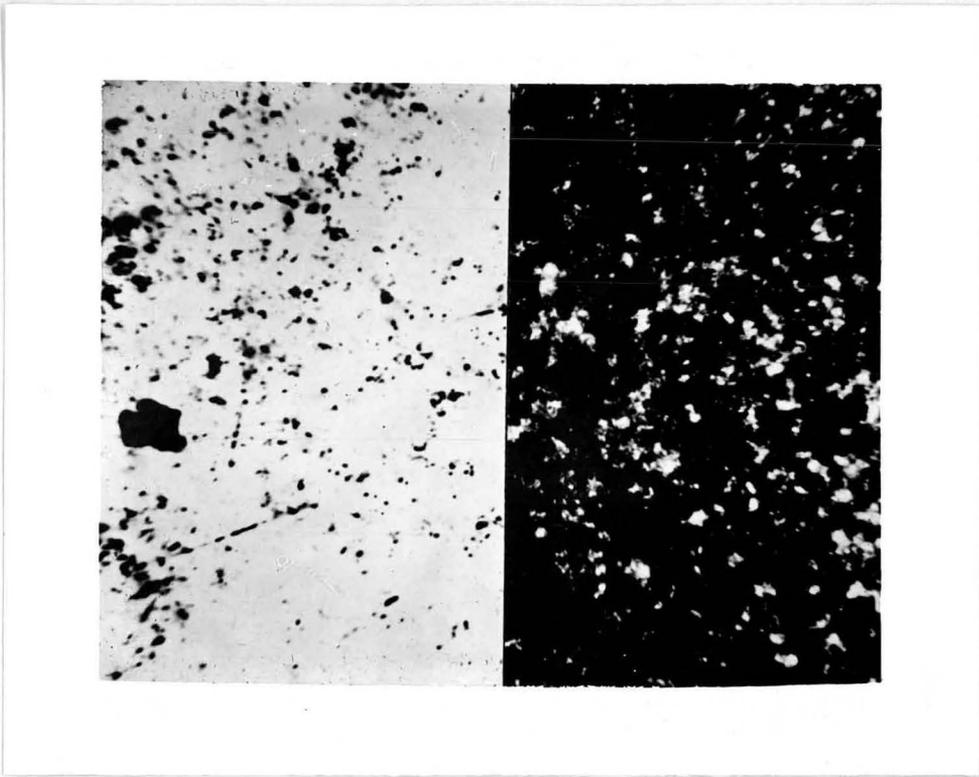


Fig. 3

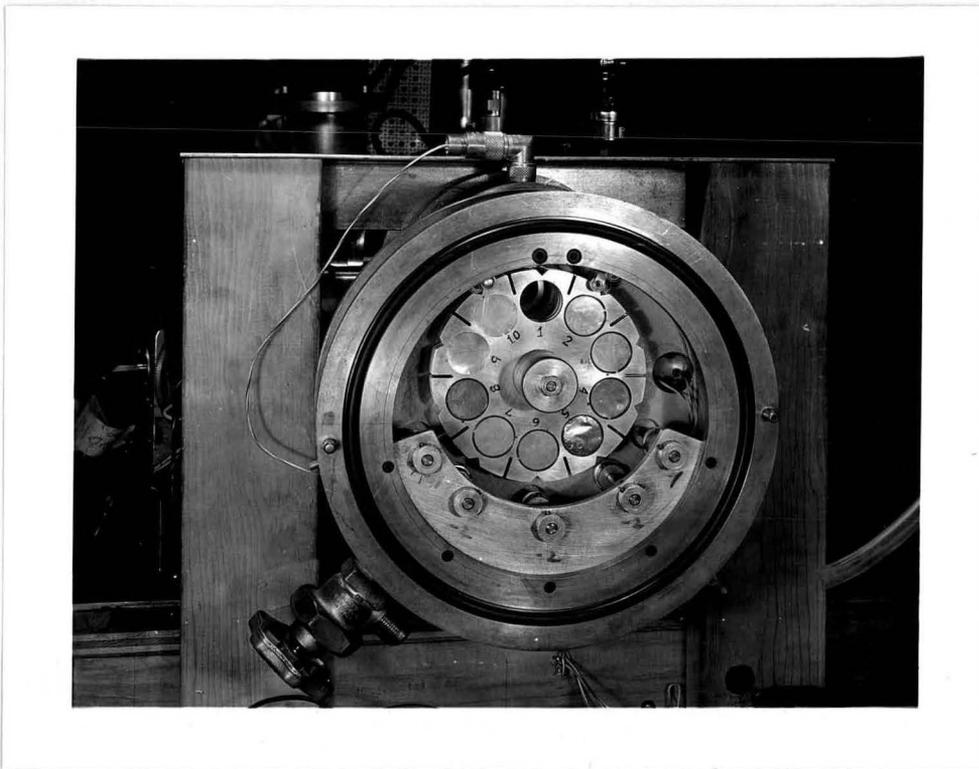


Fig. 4

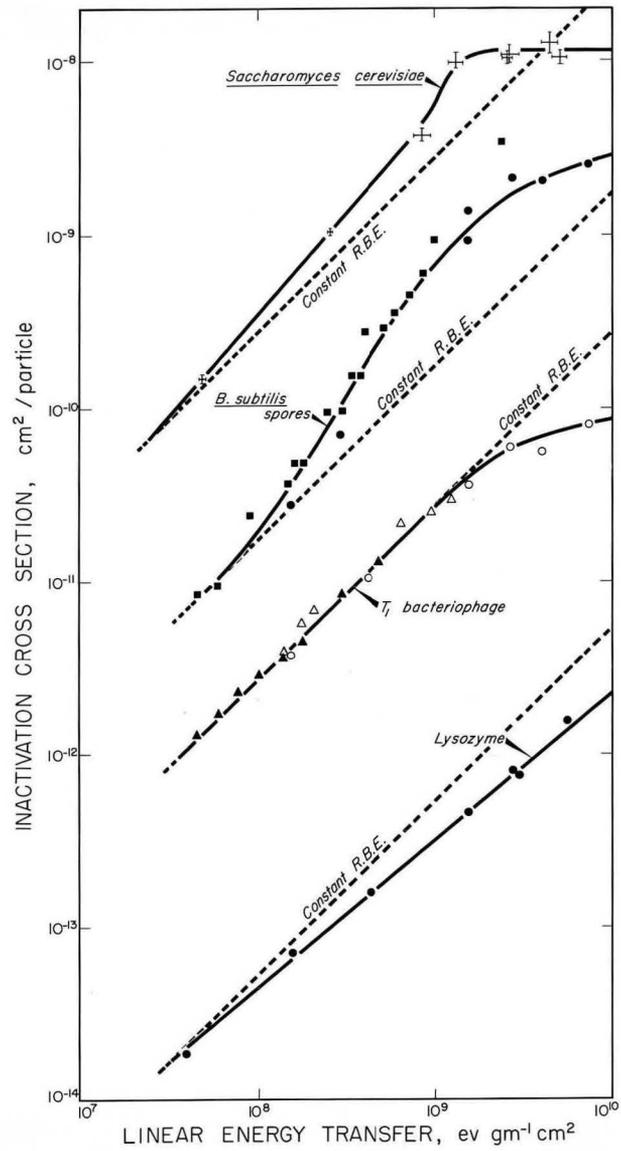


Fig. 5

NERVE DAMAGE AS A FUNCTION OF DOSE
AND TIME AFTER IRRADIATION

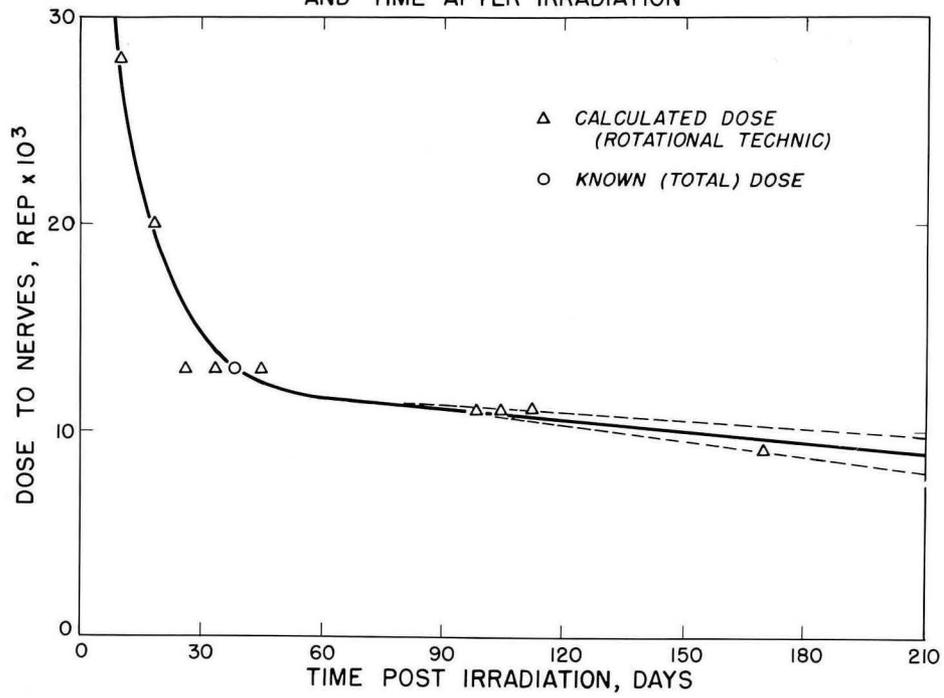


FIG. 6.

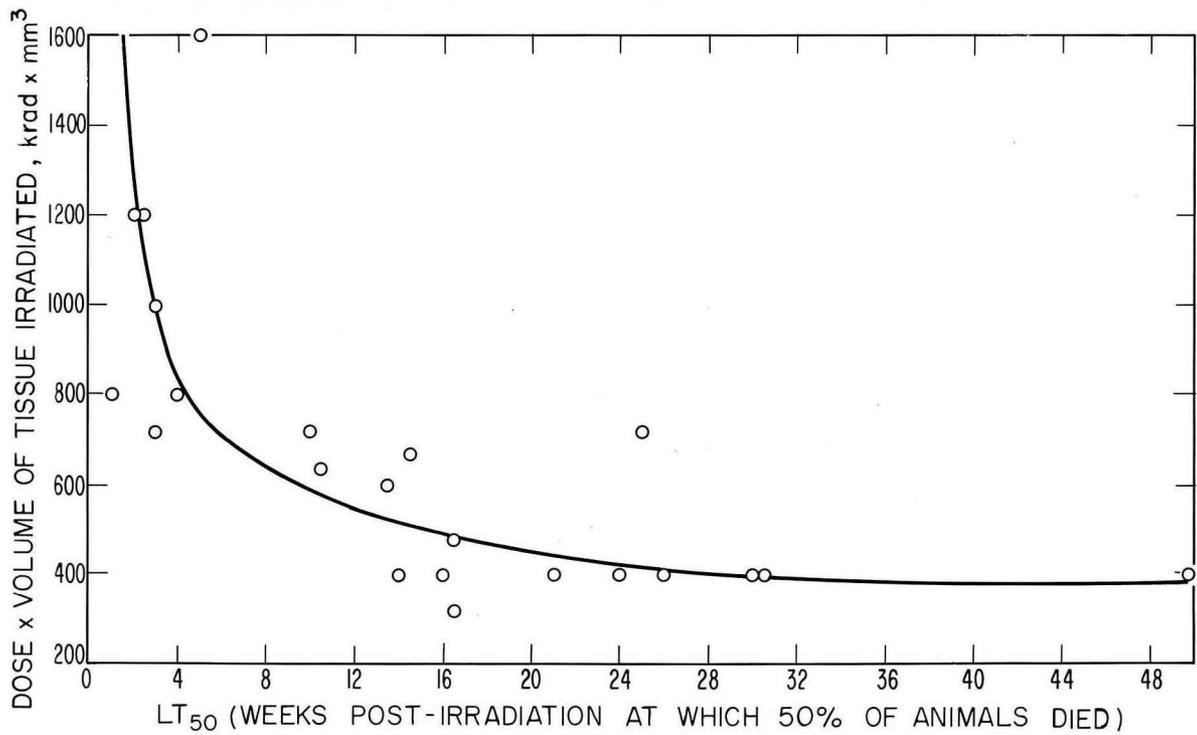


FIG. 7



Fig. 8

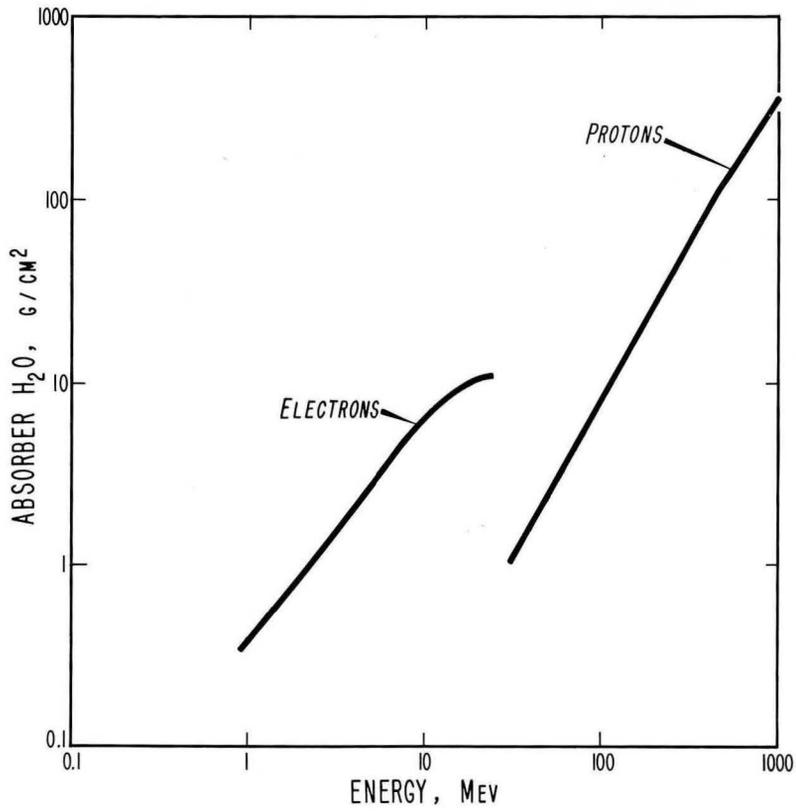


Fig. 9

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