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BIOELECTRIC EFFECTS OF HIGH-ENERGY IRRADIATION ON NERVE

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INTRODUCTION

There is little in the literature concerning the action of high-energy radiation on the bioelectric properties of nerve. Most papers deal with the exposure of nerve to x rays (Audiat, 1932; Audiat and Piffault, 1934; Audiat et al. 1934; Bachofer, 1957; Bachofer and Gautereaux, 1959, 1960a, b; Gerstner, 1956; Gerstner et al., 1955; Janzen and Warren, 1942) or β rays (Gasteiger, 1951, 1952, 1959; Redfield et al., 1922). The goal of this investigation was to determine the dose of high-energy radiation that would inhibit the excitatory process of frog's sciatic nerve. Synchrocyclotron-produced 910-Mev α particles, and 455-Mev deuterons were employed as irradiation beams.

The effects of high-energy α particles and deuterons have medical implications because of the increasing application of cyclotron beams to sterotaxic radiosurgery in the central nervous system (Tobias et al., 1952, 1958; Born et al., 1959). In space exploration and in projects involving long-time exposure, such as lunar colonization, the biological effects of high-energy particles might be a limiting factor. Evaluation of this hazard has been speculative. A practical way to study this problem is to engage existing cyclotron facilities for biological research.

METHODS

Biological Material

Frogs (Rana pipiens) were housed under low-temperature conditions (10°C) for about a week prior to experimentation. They were sacrificed by decapitation followed by spinal cord pithing. Both sciatic nerves were excised from more than 200 frogs and placed in Ringer's solution (Mitchell, 1948). One nerve of each pair was irradiated, while its companion functioned as a control.

Electrical Recording

To determine neural activity, a nerve was placed on Ag-AgCl electrodes in a moist chamber (Fig. 1) through which circulated a mixture of 95% oxygen and 5% carbon dioxide saturated with water vapor after passage through three gas-washing cylinders. Monophasic rectangular stimuli 0.1 msec in duration were delivered from a Grass stimulator (Model S4) through an isolation unit to the nerve at 60 pulses per second. Recording electrodes detecting the propagated neural impulse ran to a push-pull, ac preamplifier (Grass Model P5), which then fed the signal into a Tektronix oscilloscope (Model 532) with a high-gain differential input amplifier (Tektronix type 53/54 D). In conduction velocity studies a fast-rise dual-trace input stage amplifier (Tektronix type 53/54 C) was employed. The displayed action potentials were photographed by a Fairchild polaroid oscilloscope camera (Model F286).

Cyclotron Irradiation

The Lawrence Radiation Laboratory's 184-inch frequency-modulated cyclotron was available as a source of 910-Mev α particles and 455-Mev deuterons (Tobias et al., 1952, 1958). By appropriate magnetic focusing techniques, these high-energy nuclei were made to travel in parallel,

approximately monoenergetic beams. An ionizing chamber placed in front of the bombarded nerve was used to monitor the delivered dose (Birge et al., 1956). The specifications of the 184-inch synchrocyclotron are summarized in Table I.

Under most experimental conditions, the dose rate received by nerves was 2 krad per minute (1 krad = 10^5 ergs absorbed per gram, or 1.07×10^3 rep absorbed in tissue). High-energy nuclei were generated by the 184-inch synchrocyclotron in 500-microsecond pulses at a frequency of 64 pulses per second. In special experiments the effect of varying the dose rate of the cyclotron's beam from 0.5 to 8.0 krad per minute was tested to determine if this was a significant factor in altering neural activity. The linear energy transfer (also referred to as stopping power and rate of energy loss) of α particles was 15 Mev-cm^2 per g (Born et al., 1959), i.e., approximately the same linear energy transfer of secondary electrons as from a 250-kev x-ray machine.

RESULTS

Bioelectric Studies

In exploratory experiments nerves mounted in a moist chamber were placed in the horizontal path of high-energy particles generated by the 184-inch synchrocyclotron. Irradiation of the nerve was beyond the stimulating electrodes (maximum beam diameter was 44 mm). After every 10 krad, the cyclotron's beam was interrupted, and the action potential of the nerve being irradiated was recorded photographically until there was no electrical activity. Large doses of α particles were required to block excitation. It is now known that there is a serious difficulty with this type of procedure because a greater

dose than minimal was received by the nerve to eliminate its electrophysiological response.

To determine the effect of high-energy particles on neural activity, it was deemed prudent to follow the time course of the survival of bioelectric activity after exposure to some specific dose of irradiation. For this purpose the following method was adopted. After oscillograms of the pre-irradiated neural activity of both isolated sciatic nerves of a frog had been obtained, one nerve of the pair was bombarded in the cyclotron beam while contained in a plastic vial filled with Ringer's solution. Following irradiation, the neural activities of the exposed and control nerve were again monitored after transferral to a moist chamber (Fig. 1). This routine was repeated at 2-hour intervals for a minimum of 24 hours. Control nerves maintained in Ringer-filled vials were treated in an identical manner.

In Fig. 2 are shown three rows of oscillograms of the action potentials of the right (upper photographs) and left (lower photographs) sciatic nerves of a frog. Preirradiation action potentials were recorded, and the right sciatic nerve was subjected to 72 krad of 910-Mev α-particles. The left sciatic nerve functioned as a control. Immediately after α-particle irradiation (oscillograms above "0 hr" in Fig. 2), a transformation in the action potential complex of the exposed nerve was apparent. Oscillograms recorded at 2, 4, 6, 8, 10, and 12 hours after irradiation trace the deleterious effects of α-particles. At 14 hours postirradiation, there was complete cessation of the bioelectric activity of the α-bombarded nerve, while the action potential of the control nerve was still present.

The spike potential changes for the irradiated and control nerve illustrated in Fig. 2 are summarized in Fig. 3. On the ordinate of Fig. 3 (and also on the ordinates of Figs. 4, 5, and 6) is plotted the percentage

of the initial spike potential, i.e., the ratio of the amplitude of the spike potential at some t hours after irradiation over the preirradiated spike potential amplitude, multiplied by 100.

In Fig. 4 is presented a sample of the data obtained for alterations in the neural activity resulting from α-particle irradiation. It is clear that large doses of high-energy α-particles (greater than 300 krad) eliminate neural excitability rapidly. With lower doses of high-energy α-particle irradiation, the survival of neural activity is progressively extended. It would appear from Fig. 4 that at 6 hours postirradiation there is considerable enhancement of the neural output. That all this enhancement is a direct consequence of irradiation seems doubtful, because when the irradiated nerve of a pair demonstrated an enhanced neural output, so did its nonirradiated control (Fig. 5). However, bombarded nerves with enhanced activity were usually 5 to 10% higher in their neural output than their controls. The nonirradiated nerves manifested the enhancement phenomena most during the winter season.

The time course for the abolition of neural activity was also studied as a function of deuteron dose. A sample of the findings for the degeneration of the spike potential due to different doses of deuterons is presented in Fig. 6. Deuteron experiments, which were carried out in the spring and summer seasons, showed only a small enhancement of neural output.

The relative inhibitory effects of α-particle and deuteron irradiation on excitability are exemplified in Fig. 7. The time for the complete extinction of spike amplitude is a logarithmic function of the absorbed dose, within certain limits. Below 30 krad for α-particles and 60 krad for deuterons, no demonstrable suppression of the spike potential of sciatic nerve due to irradiation can be reported. Irradiated nerves after more than 24 hours showed

deterioration of spike potential activity, but the degree of impairment was mimicked by the nonirradiated controls. The slope of the α-particle dose-survival line is double that of the deuteron line (Fig. 7). This α-particle/deuteron slope ratio is taken as evidence that α-particles have twice the relative biological effectiveness of deuterons.

Conduction velocities of propagated impulses have been computed from the time delay between two spike peaks on oscillograms and the distance between recording electrodes. Alterations from irradiation in conduction velocity, latent period, and stimulus strength do not appear strongly related to suppression of the spike amplitude, because when the propagated impulse was 90% abolished, conduction velocity was retarded by only 25 to 30% of its original value, and the stimulus strength and latency period were changed by 25 and 20% respectively.

From recent studies employing two Grass stimulators (Model S-4), it was found that the refractory period increases (after a small transient decrease) before reduction of conduction velocity, depression of action potential, prolongation of latency period, and alteration of stimulus strength. Thus, the refractory period is the earliest index of radiation damage that the author has noted.

Dose-Rate Studies

The influence of modifying the dose rate at which α particles were administered to isolated sciatic nerve was investigated. The cyclotron beam was adjusted to deliver high-energy particles at the rate of 0.5, 1.0, 2.0, 4.0, and 8.0 krad per minute in eight experiments. The survival of excitability was found to be independent of the intensity at which irradiation was absorbed, and dependent on the quantity of dose absorbed. The inhibition of neural activity resulting from irradiation was not reversible.

Radioactive Studies

The influence of α-particle irradiation on sodium ion permeability of sciatic nerve can be presented here only as a brief preliminary report. Nerve sheaths were left intact in order to prevent volume changes,

Long-life Na^{22} was used as a radioactive tracer in Ringer's solution (1 μC per ml of Na^{22}). The proximal ends of isolated nerves were ligated with 3-mil tantalum wire to allow manipulation of the nerves. To determine the time course for the penetration of radioactive sodium, the nerve was immersed in "hot" Ringer's solution, and the activity accumulated during this soaking period was estimated by removing the nerve from the Na^{22} Ringer's solution to a 4-ml vial of nonlabeled Ringer's. A scintillation spectrometer registered the radioactivity of the sample, and the nerve was restored to the Na^{22} Ringer's solution for additional radioactive tracer uptake. The Na^{22} that diffused from the nerve during the counting time could subsequently be estimated by recounting the vial of contaminated Ringer's solution.

Results from eight experiments have revealed that nerves given less than 150 krad of α-particle irradiation did not differ significantly from their nonirradiated controls in the kinetics of sodium ion penetration. In the dose range 150 to 200 krad, the rate of Na^{22} uptake for irradiated nerves was increased to only a small extent over controls (Fig. 8).

The technique for studying the emergence of Na^{22} from isolated sciatic nerve was similar to that described by Shanes (1954). Nerves were immersed in Na^{22} Ringer's solution for approximately 12 hours at 10°C, brought to room temperature (21°C), and irradiated in the beam of the 184-inch synchrocyclotron. The emergence of Na^{22} from the "loaded" nerves into frequently replaced vials of inactive Ringer's was measured with a satisfactory degree of accuracy (counting error was less than 1%) by a scintillation spectrometer.

Figure 9 illustrates that after an exposure to 200 krad of α-particle irradiation, the rate of movement of sodium ions from the irradiated nerve was slightly less than from its control. From eight experiments in which nerves were administered doses below 150 krad of α particles, there was no evidence of an alteration in the rates of loss of Na^{22} as a consequence of irradiation.

From these limited radioactive studies, it can be inferred that with α-particle irradiation in excess of 150 krad there is probably a rise in the sodium ion content of sciatic nerve due to an increase in the rate of sodium ion penetration coupled with a decrease in the rate of sodium ion loss.

In these experiments the studies on the rate of Na^{22} loss began 5 minutes after irradiation was completed, while Na^{22} uptake studies started 1 hour postirradiation.

DISCUSSION

The present findings indicate that irradiation of frog nerve with 30 krad or less of high-energy α particles or deuterons was below the minimal dose required to evoke an early impairment of neural activity. Such a result is in general agreement with other observations found in the literature. Schmitz and Schaefer (1933) reported no functional damage to frog sciatic nerve when exposed to 10 kr of x rays. For rat sciatic nerve, no apparent effect on neural conduction after exposure to 10 kr of x rays has been observed (Janzen and Warren, 1942). Similarly, Rothenberg (1950) on administering 50 kr of x rays to squid's stellar axon reported that when the preparation was electrically stimulated, good action potentials were present. From the data offered in this paper, it is reasonable to report that 30 krad of 910-Mev α particles represents a threshold dose for the destruction of bioelectrical

activity of the amphibian nerve. No explanation on the molecular level that would account for what determines the functional resistivity of nerve to ionizing radiation is yet found in the literature.

For prompt inhibition of bioelectric activity of frog (Rana pipiens) sciatic nerve, about 300 krad of α particles or deuterons was required (present paper). Using a frog muscle–nerve preparation, Audiat (1932) and Audiat et al. (1934) observed that administering 300 kr of x rays caused a loss of neural excitability. Gerstner (1955; Gerstner et al., 1956) stated that the sciatic nerve of bullfrog (Rana catesbiana) suffered a conduction block when exposed to about 300 kr of high-intensity x radiation. The neural alterations of mammalian nerve during x irradiation have been investigated by Bachofer (1957) and Bachofer and Gartereaux (1960a,b), and they established that approximately 500 kr will extinguish the amplitude of the spike potential of the ventral caudal nerve of the rat. Extirpation of axonal activity of the median and lateral single giant nerve fibers of the earthworn (Lumbricus terrestris) was shown to occur after 246 and 306 kr of x rays respectively (Bachofer and Gautereaux, 1959). The neural mechanisms affected by these massive doses of irradiation have not been established.

The sodium ion influx into squid giant axon immediately after x irradiation has been reported by Rothenberg (1950), using Na^{24}. After 125 kr, sodium influx was increased markedly. On exposure to 50 kr, the rise in sodium permeability was smaller, but significant. The Na^{22} experiments on frog nerves (described in this report) after α-particle irradiation are in harmony with the view that irradiation increases sodium ion permeability. However, the α-particle dose must be near 150 krad to express a sodium permeability increase.

Experiments have revealed that the relative biologic effectiveness

(RBE) of α particles is twice that of deuterons in inhibiting neural activity (Fig. 7). It is known (Zirkle, 1954) that the linear energy transfer (i.e., the stopping power or rate of energy loss) along a particle's track varies as the square of its charge. The linear energy transfer of an α particle is four times that of a deuteron of the same velocity. Since biological effects in general vary with the linear energy transfer, it would be expected that the relative biological effectiveness of α particles with respect to deuterons would approach four as a limit.

Membrane Model

In the following section a membrane model for nerve is outlined which suggests how the function of nerve is affected by radiation energy.

Direct evidence of neural membrane structure, in terms of lipid and protein components, must await a detailed study of lipids and lipid-protein systems. Whatever may be the ultimate interpretation of the molecular organization of the axon membrane, it is probably safe to say from electron microscope studies that the unit membrane includes two protein monolayers allied with a double layer of lipid molecules (Schmitt, 1959).

If it is assumed that the protein molecules of the neural membrane are helical in nature and form an oriented structural layer, certain insights into membrane properties are revealed. Consider for a beginning three helical protein molecules of macromolecular diameter which are closely packed. As a consequence a fourth element is created – an interstice or fault which for convenience will be referred to as a "channel." When three protein macromolecules 28.2 A in radius are most efficiently packed, an intermolecular channel about 4 A in radius is obtained (Fig. 10).

It is known that models of membranes based on the concept of a continuous lipid layer are untenable because experiments reveal that biological

membranes are crossed by molecules of water and numerous compounds insoluble in fat. This is a property of a membrane with channels rather than a solution process in a lipid film. Comparison of rates of water entrance into cells under the influence of osmotic pressure gradients and simple diffusion gradients gives a rough indication of what may be the "equivalent channel size" (Koeffed-Johnson and Ussing, 1953; Prescott and Zeuthen, 1953). Values of channels range from 5 A in red blood cells to 16 A in squid axons (Nevis, 1957; Solomon et al., 1957). When frog nerve is placed in a medium labeled with deuterium, tritium, or O^{18}, the half time for equilibration is only 1 minute (Tobias and Nelson, 1959). Hence, the existence of a channel pathway through the ultrastructure of cell membranes to water and small ions seems likely. Specific information on the dimension of the channels in the membrane is of crucial importance in dealing with ionic penetration. Recently, Goldstein and Solomon (1960) have developed a new method to measure the equivalent channel size of red blood cell membranes. Assuming a membrane pierced by uniform cylindrical channels and the obedience of Poiseulle's law, they report the value of the mean equivalent channel radius as 4.2 A.

It has been suggested by Mullins (1956) that the number of shells of hydration associated with each ion in traversing the neural membrane is limited to the same minimum, say one. In physiologic solutions sodium ions are considered to be larger than potassium ions, because sodium ions orient more layers of hydration owing to the intense electric field created by the charge on the ion (Ling, 1952, 1957). Potassium ions, with a lower energy of hydration than sodium, have effectively fewer oriented shells of hydration and hence a higher mobility in an aqueous medium. Kortum and Bochris (1951) point out that for cations, water molecules on the first layer (primary hydration) are held so tightly that the primary hydration shell moves as a

unit with the ion. However, water molecules beyond the primary hydration layer are loosely oriented and exchange readily with surrounding water molecules. Hence, it is an acceptable hypothesis that ions with one layer of hydration migrate through neural membranes. From Fig. 11 it is seen that the radius of primary hydrated potassium is 4.05 A, which is larger than primary hydrated sodium (3.67 A in radius; Fig. 12). The crystal lattice radii are taken from Pauling (1945), and the width of concentric water shells of hydration is that of the diameter of a water molecule, 2.72 A (Buswell and Rodebush, 1956).

Before the implications of this membrane model are considered, two remarks should be injected. First, the intermolecular forces between protein elements of the membrane are no doubt subjected to lateral straining pressures produced by thermal motion (kinetic and vibrational) and cytoplasmic streaming. As a result, a channel is never of a fixed size, but statistically distributed, probably in a Gaussian fassion. The mode of the channel-size distribution of the resting membrane is assigned to the ion empirically known to have the highest relative membrane permeability, potassium (Fig. 13, resting state). The spread of the Gaussian distribution curve for the resting state (Fig. 13) is adjusted so that the area representing potassium ion channels is 25 times the area representing sodium ion channels, which is in harmony with Hodgkin and Katz's (1949) evidence that the relative permeability of potassium to sodium ions across the axonal membrane is 25 to 1. During excitation these relations are reversed, i.e., the permeability of potassium to sodium is 1 to 25. Hence, the mode of the distribution curve during activity is assigned to sodium (Fig. 13, conducting state).

Secondly, the concept that the neural membrane behaves as though it were a molecular sieve is not practical. Such a proposal does not offer an

explanation of how the cell discriminates between potassium and sodium ions, as indicated by permeability studies. A molecular-sieve model for the membrane permits a small ion to pass through any channel of greater size than itself. On this basis, sodium ions 3.67 A in radius should have free passage through channels that sterically just pass potassium ions 4.05 A in radius. Hence, a molecular-sieve model fails to explain selective ion permeability. This difficulty is removed if solvation (ionic interaction with the protein of the membrane) is "quantized." That is, when an ion enters a channel, all its hydration shells beyond the primary hydration level are solvated by the wall of the channel (Mullins, 1956). It is maintained that this process of solvation involves only whole shells of hydration. A 3.67-A sodium ion could not fit into a 4.05-A potassium ion channel because there is no level of hydration at which a sodium ion corresponds (in size) to a potassium ion channel. Such correspondence could occur only if some level of hydration (secondary, tertiary) for sodium did uniquely match some hydrated size of potassium. Similarly, potassium ions do not fit sodium-size channels. A comparison to Bohr's theory in which electrons exist in integral energy levels is only an analogy, but it may help one's thinking. For the membrane's channel wall, it is held that instead of an infinite number of solvation levels, there is only a restricted number with properties represented by functions of n, where n is an integer.

If the quantized view of membrane solvation is correct and ions penetrate the membrane with only the primary layer of hydration, then it will cost the living cell more in solvation energy to transport sodium (44.7 kcal/mole) than potassium (40.5 kcal/mole). On the evolutionary scale it would appear that the "cheaper" ion was selected to balance the intracellular negative charges.

The initial suggestion of a helical protein structure does not violate our knowledge about the architecture of proteins. In terms of our membrane model, the helical nature of protein provides a key to the interpretation of the excitation phenomena of axons. Protein membrane molecules are conceived to be in a contracted or coiled state, while the nerve is in the resting state. A threshold stimulus permits the constrained, helical macromolecule to become relaxed or uncocked, thus diminishing the radius of the macromolecule. Intermolecular attractive forces maintaining membrane structural order cause a decrease in the mode of the channel-size distribution after the coiled macromolecules uncock. If on stimulation the membrane macromolecules alter their radii from 28.2 A to 26.2 A, owing to a constrained-uncocked transformation, the new mode of the channel size distribution will be 3.67 A, the size of primary hydrated sodium ion (see Fig. 13, conducting state). It is naive to imagine that the helical protein molecules have characteristics of a mechanical spring. A coiled spring can be stretched a good deal before a decrease in radius is effected. The reduction of the radial dimension of the membrane's helical molecules is perhaps due to the action of London forces.

A pleasing consequence of this membrane model is the number of neural characteristics it can interpret. The all-or-none law for axons on the molecular level can be viewed as a consequence of the states which the membrane helical macromolecules can occupy; either a stimulus is sufficient to uncock the macromolecule, or it is not. If the stimulus is sufficient, the channel-size mode shifts from potassium to sodium. As a consequence ions follow their electrochemical gradient, thus generating a bioelectric impulse. Molecularly translated, the refractory period of a nerve is the time required to restore the helical macromolecule to the constrained state.

Hodgkin and Katz (1949) have presented evidence showing that, at rest, the ionic permeability of potassium is 25 times that of sodium. During excitation these ionic permeabilities are quickly reversed, so that sodium is 25 times as permeable as potassium. The burden of accounting for this sudden ionic shift has run down many an ingenious membrane hypothesis. The cocked-uncocked performance of helical molecules in the present membrane model not only supplies an adequate explanation for the cyclic permeability events triggered by excitation, but also offers a physical model to aid in understanding the time constants for the limbs of the action potential.

The character of the cocked protein molecule is such as to allow for a rapid change to the relaxed structural state, thus accounting for the small time constant of the ascending limb of the action potential. That a large time constant (of the descending limb of the action potential) is associated with reconstraint of the relaxed helical macromolecules suggests not only that the process is slow, but also that it requires energy. Since the ratio of heat produced during activity over that produced in recovery shows that the latter requires most of the energy, we have another observation that does not violate the model, but agrees with it.

Developing a membrane model has made the task of interpreting how radiation energy influences neural functioning relatively easy. Only an average energy of some tens of electron volts can be accepted by a molecule. Successive energy transfers occurring along the path of high-energy particles (kinetic energy in the thousand- or million-electron-volt range) exceed the acceptable energy level, and a defective molecule is the consequence. Radiation inhibition of neural excitation is construed as structural damage to protein molecules of the axon's membrane.

Radioactive tracer studies of resting nerve (Rothenberg, 1950; also Radioactive Studies, in this paper) reveal that radiation causes an increase in sodium ion permeability, i.e., a shift in the mode channel size from potassium toward sodium (Fig. 13, resting state vs irradiation state). Bioelectric studies of single myelinate nerve fibers after irradiation (Gaffey, 1960) indicate that there is an increase in potassium ion permeability (revealed by a decrease in the slope of the falling limb of the action potential) and a decrease in sodium ion permeability (connoted by a decrease in the slope of the rising limb of the action potential). Deterioration of ionic permeability by the conducting nerve is viewed as a translation of the mode channel size from sodium toward potassium (Fig. 13, conducting state vs irradiation state). These early signs of neural impairment would be expected as a consequence of the partial loss of the ability of the membrane's helical molecules to fully coil and uncoil. The final degenerative steps due to radiation take place quickly and could be interpreted as a full loss of the ability of the helical molecules of the membrane to change state, perhaps as a result of loosening of their structure. This would cause a broadening and flattening of the channel distribution curve, which in essence eliminates selective ion permeability, thus causing a rapid loss of excitability.

In conclusion, it can be argued that certain doses of irradiation are threshold for neural injury as a result of the membrans's macromolecules being irreversibly impaired in their ability to change states.

SUMMARY

Isolated sciatic nerves from Rana pipiens were exposed to cyclotron-accelerated beams of 455-Mev deuterons and 910-Mev α particles. The degree of electrophysiological damage was found to depend on the dose of irradiation and the elapsed time from irradiation.

With massive doses of α particles or dueterons (greater than 300 krad) the action potential of the frog's sciatic nerve was promptly suppressed.

Within the range 30 to 300 krad for α particles and 60 to 300 krad for deuterons, the survival time of the action potential was a logarithmic function of the absorbed dose.

Alpha particles were found to have twice the relative biological effectiveness of deuterons in blocking excitation.

An increase in the refractory period was manifested before conduction velocity was reduced, action potential was depressed, latency period was prolonged, and stimulus strength altered in the high-energy-irradiated nerve.

Alpha-particle-irradiated nerves were shown not to increase in sodium ion permeability for doses less than 150 krad. From 150 to 200 krad the rate of Na^{22} penetration was slightly increased, whereas the rate of loss of Na^{22} from the nerve was decreased.

Variations in the exposure rate from 0.5 to 8.0 krad per minute failed to induce a dose-rate effect for α particles.

The inhibition of neural activity resulting from α-particle and deuteron irradiation was not reversible.

A model for the neural membrane was outlined, and the action of radiation was interpreted on the basis of this model.

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* This study is based on work performed under contracts with the U.S. Atomic Energy Commission.

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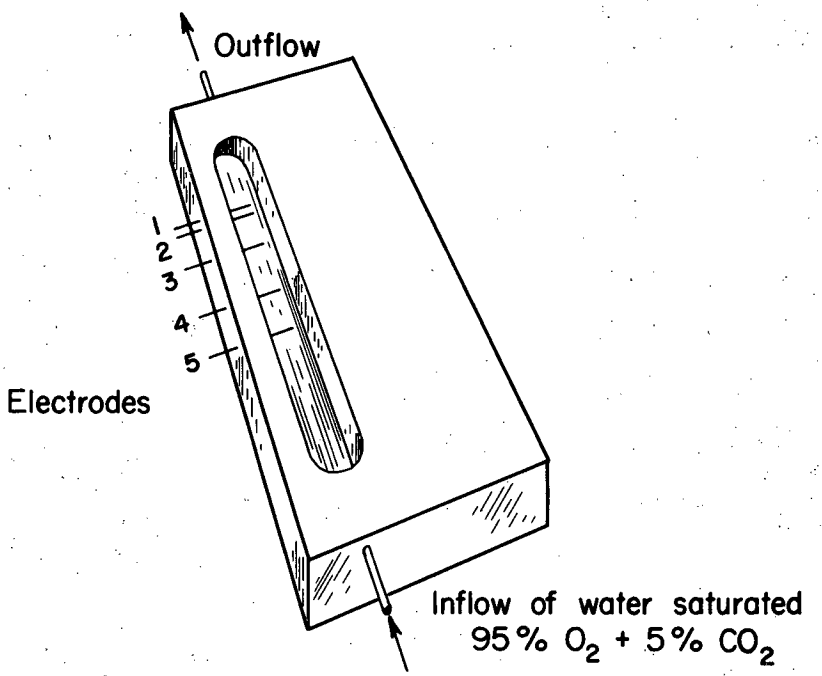
Table I. Summary of specifications of the 184-inch synchrocyclotron

	Beam particles	
	Deuterons	Alpha particles
Beam energy – maximum (Mev)	460	915
Beam intensity – average current (μa)	0.75	0.10
Beam intensity – peak current (μa)	120	16
Time required for acceleration (msec)	4.5	4.5
Number of revolutions during acceleration	110,000	110,000
Distance traveled during acceleration (miles)	550	550
Velocity at maximum energy (v/c)	0.59	0.59
Mass increase at maximum energy (% of rest mass)	24	24
Range of particles (in. of Al)	12	7
Range of particles (g/cm^2 of tissue)	44	22



MU-21179

Fig. 1. Lucite chamber for keeping a nerve moist during the study of propagated potentials. Electrodes 1 and 2 are stimulating electrodes; recordings can be made from electrodes 3 and 5 or 4 and 5. The distances from the first electrode are 3 mm, 15 mm, 30 mm, and 40 mm.

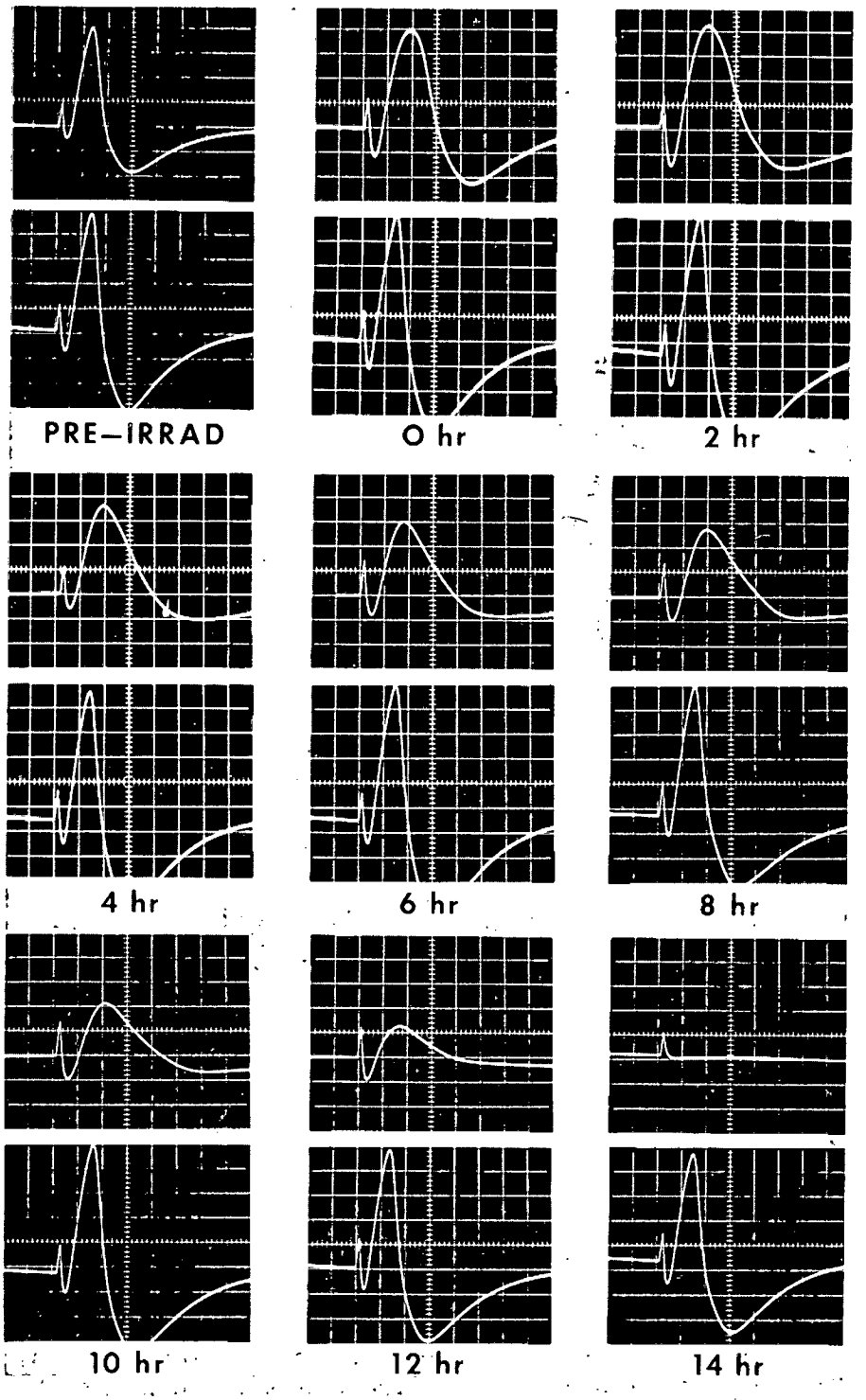


Fig. 2. A composite of action potentials from the right and left sciatic nerves of a frog before and after irradiation. The nerve producing the action potentials in the upper section of each row was exposed to 72 krad of 910-Mev α particles. The nerve producing the action potentials in the lower section of each row served as a control. Conduction block occurred in the bombarded nerve 14 hours following irradiation. On the ordinate, 1 unit is equivalent to 2.5 mv; on the abscissa 1 unit is equivalent to 1 msec.

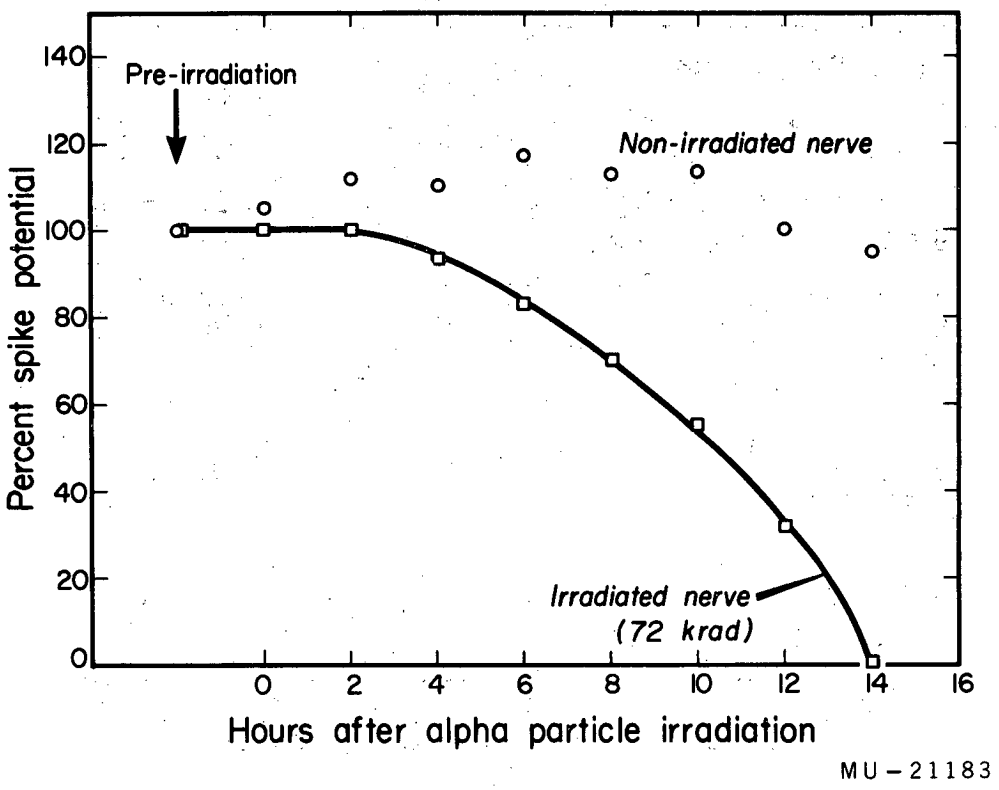


Fig. 3. The percent of the initial spike potential (%) plotted against postirradiation time for a nerve exposed to 72 krad of α particles and for its pair control. The oscillograms in Fig. 2 provided the data for the construction of this figure.

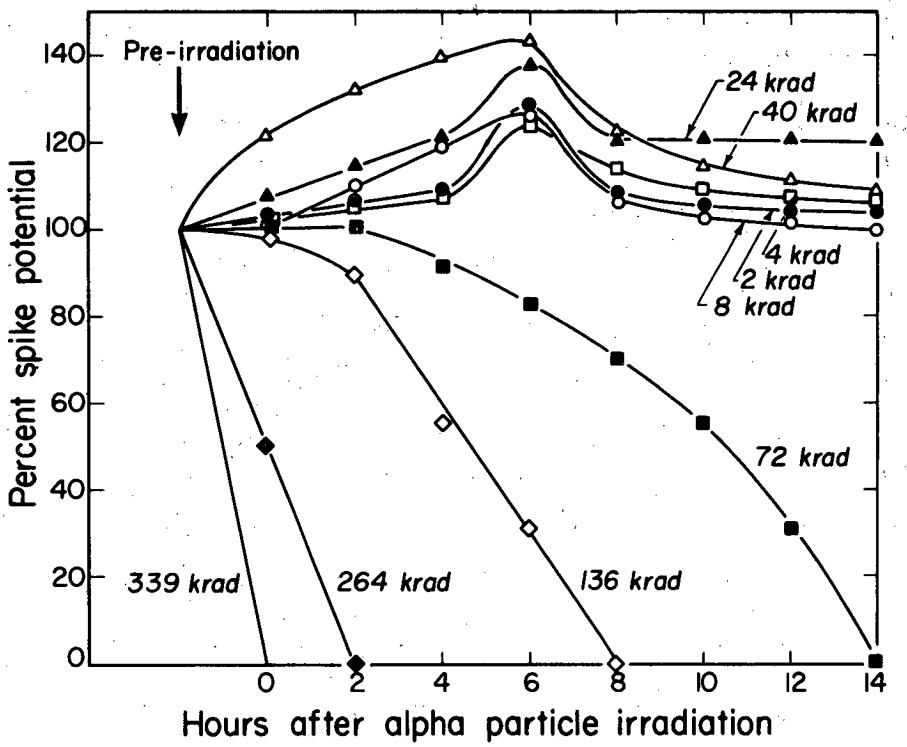


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Fig. 4. Percent of initial spike potential plotted against the time after irradiation by 910-Mev α particles for doses between 2 and 339 krad.

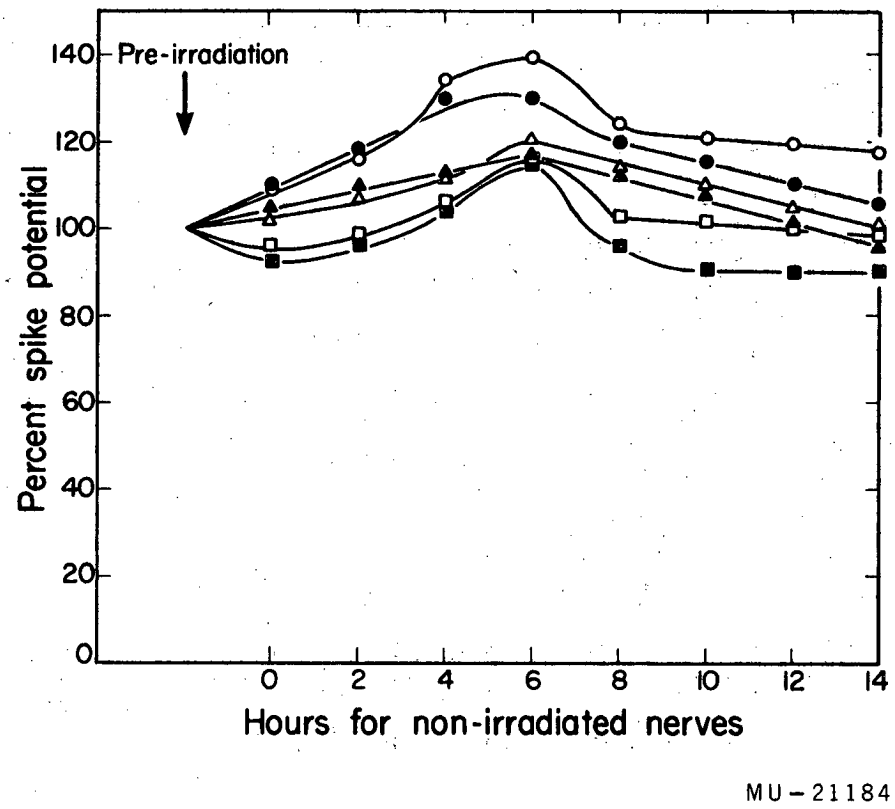

Fig. 5. Nonirradiated control nerves exhibit a variation in the amplitude of the spike potential when plotted as percentage of the initial spike potential.

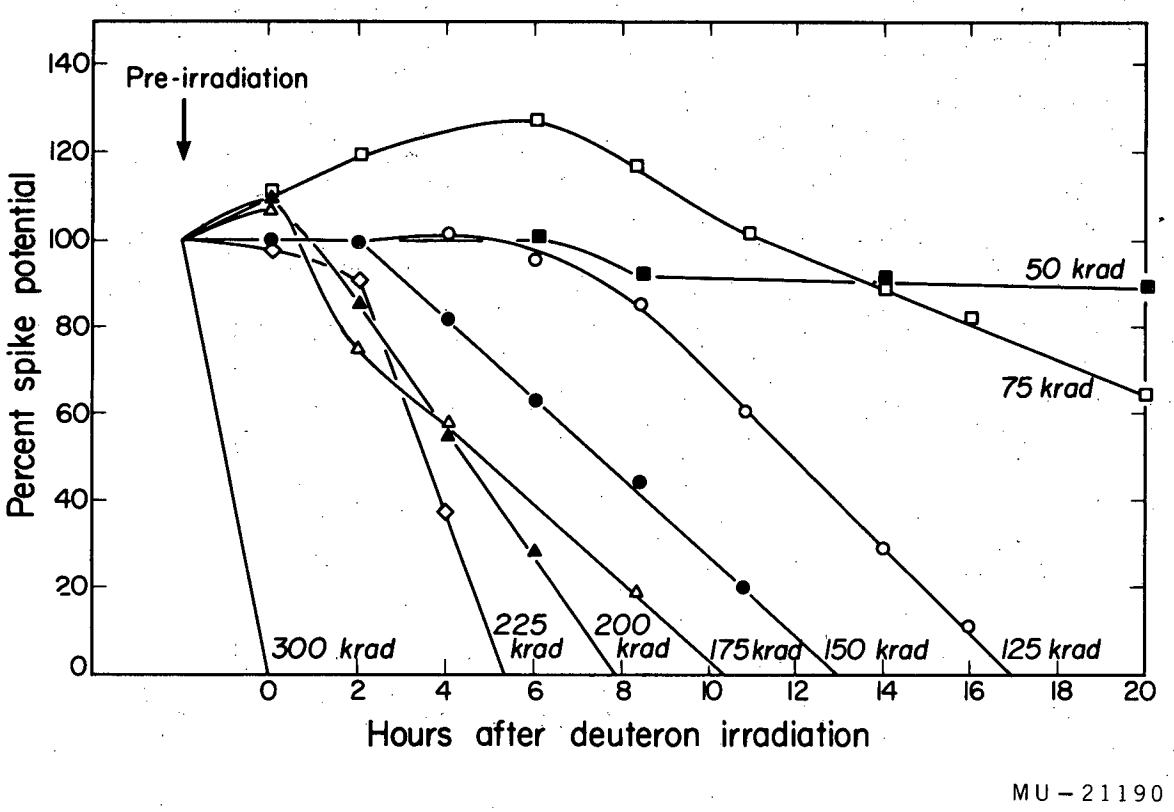

Fig. 6. The time course for the inhibition of the spike potential of nerves bombarded with 455-Mev deuterons in the dose range 50 to 300 krad. Alterations in the magnitude of the action potentials are given in terms of relative spike activity, i.e., percentage of the initial spike potential.

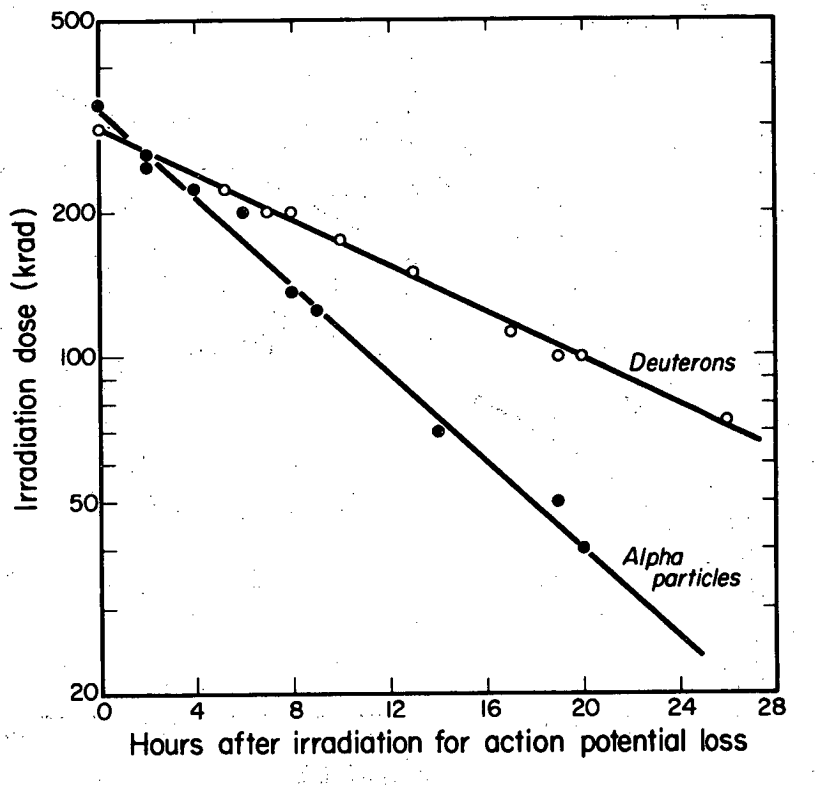

Fig. 7. The logarithm of the dose of irradiation (910-Mev α particles and 455-Mev deuterons) is plotted against the survival time of neural excitability. High-energy particles given in doses near 300 krad promptly inhibit the action potential of frog sciatic nerve. Above 100 krad each point on the diagram is the mean of two experiments; below 100 krad each point is the average of three experiments.

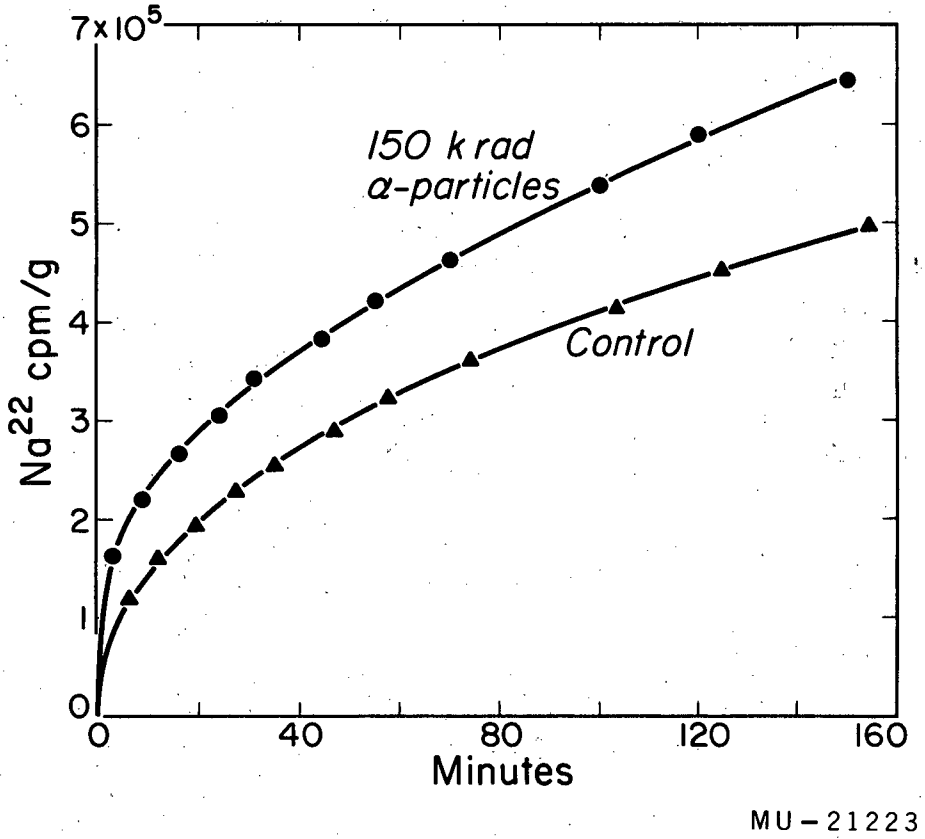

Fig. 8. The time course for the entry of radioactive tracer sodium into sciatic nerve exposed to a 150-krad dose of 910-Mev α particles, and its pair control. The experimental temperature was 21°C ± 1.5°C.

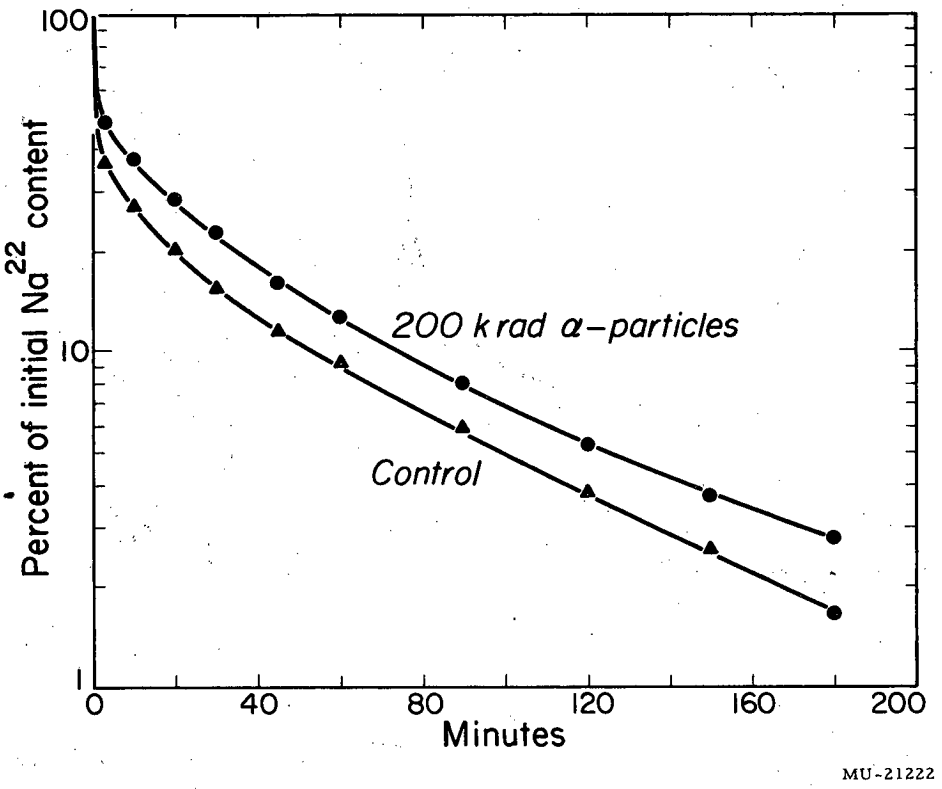

Fig. 9. Decline of the Na^{22} content (percent initial) of sheathed sciatic nerves by diffusion into Ringer's solution. Each of the experimental points on the 200-krad α-particles line is the average data from four experiments, as also are the points on the control line.

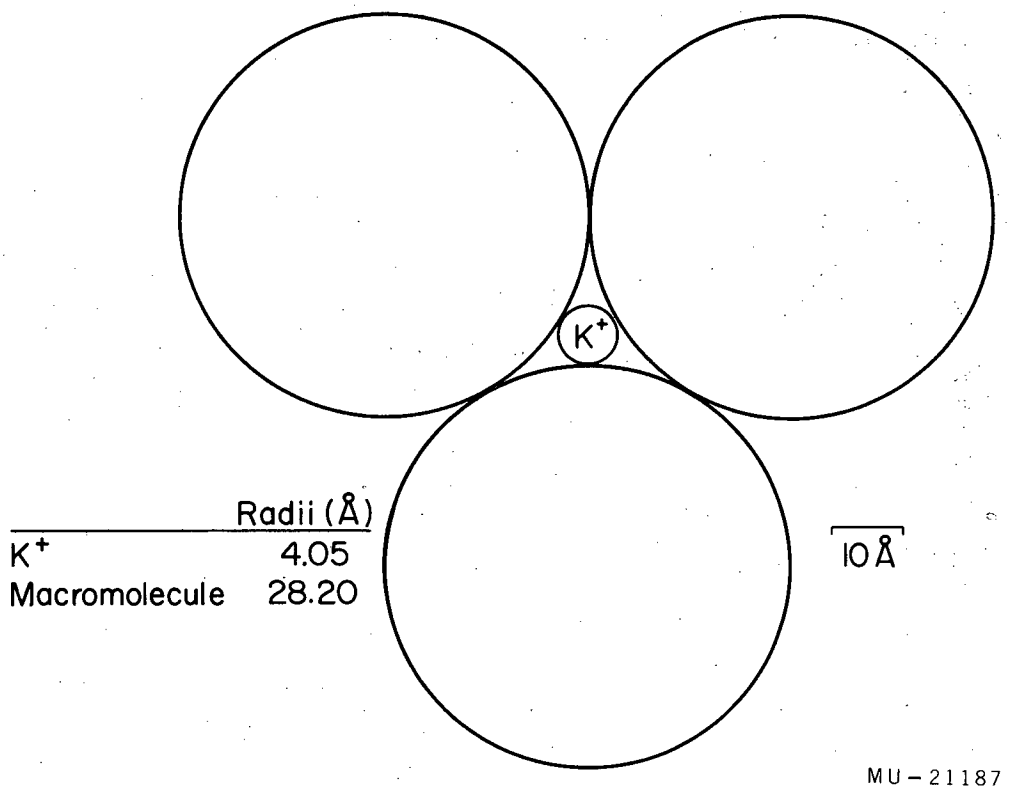

Fig. 10. Protein macromolecules are schematically represented as circles oriented hexagonally. At the junction of three macromolecules, an interstice is formed which in the three-dimensional model would be a channel. From this drawing (to scale) it can be seen that potassium with its primary layer of hydration fits the channel created by the macromolecules.

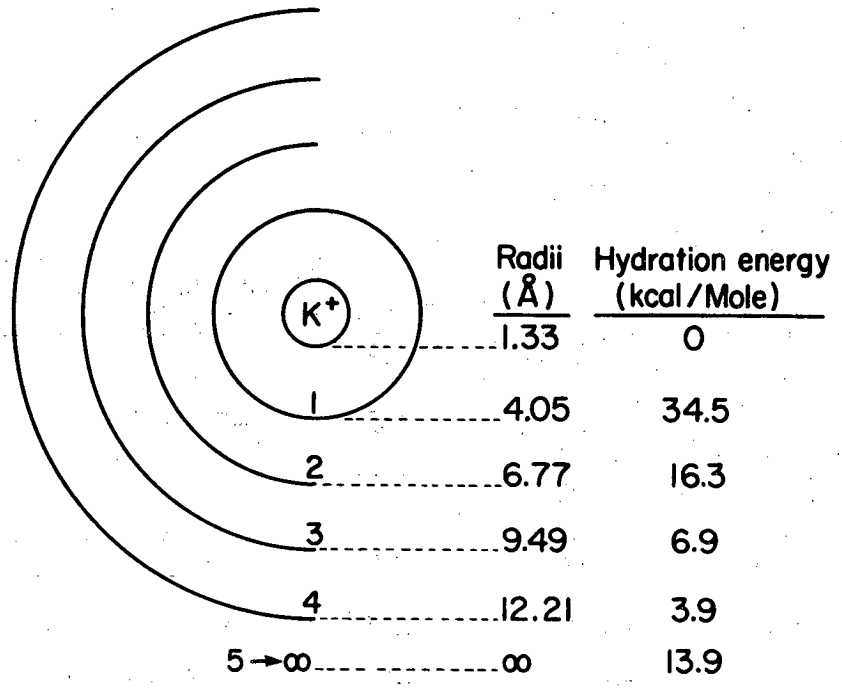

Fig. 11. Representation of the potassium ion with a crystalline radius of 1.33 A and the 1st, 2nd, 3rd, and 4th hydration shells. The diameter of a water layer is taken as 2.72 A. Hydration energies for a given hydration shell are computed on the basis that hydration energy exponentially decreases with the distance from the charge on the ion.

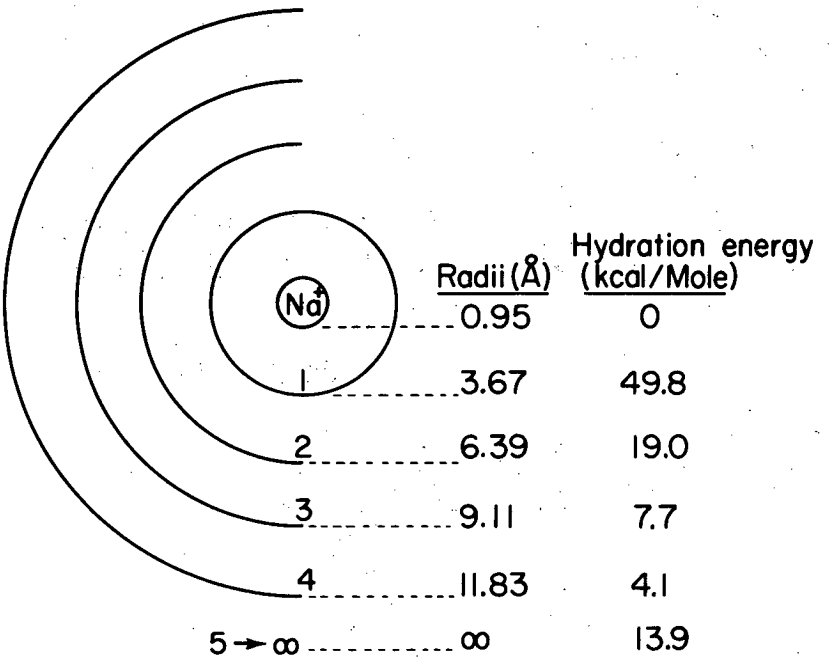

Fig. 12. Representation of the sodium ion with a crystalline radius of 0.95 A and the 1st, 2nd, 3rd, and 4th hydration shells.

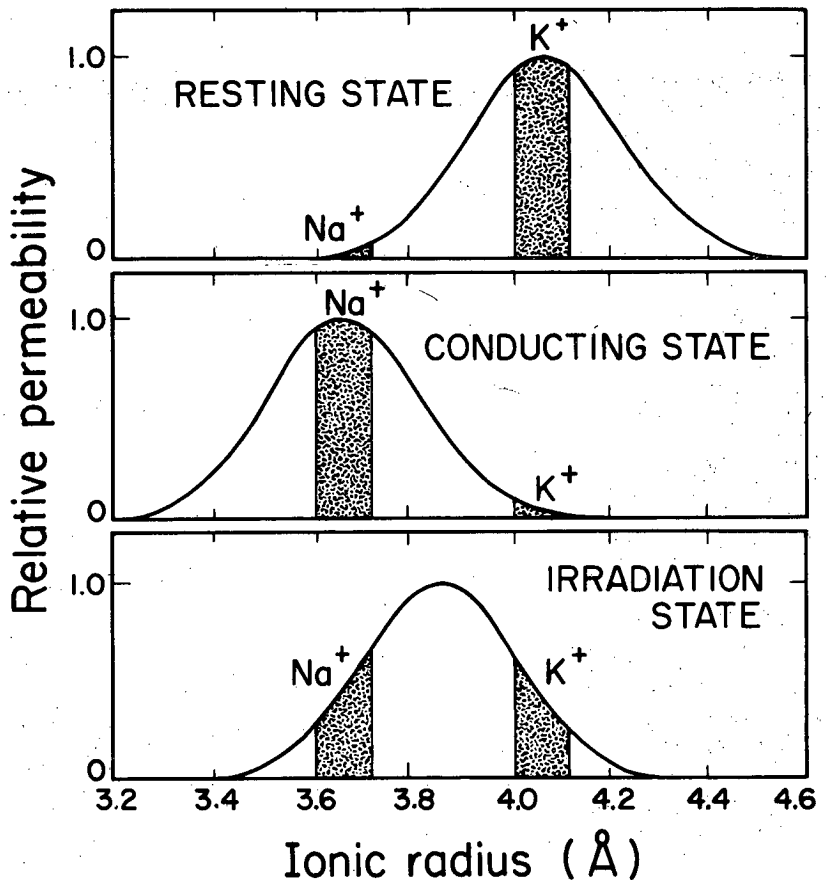

Fig. 13. The relative permeability of an ion (ordinate) is considered a physiologic term interchangeable with density of channel size. The ordinate on these diagrams could just as conveniently read "number of available channels per unit area of membrane." It is reasonable assumption that channel size (abscissa) is distributed according to a Gaussian curve. For neural membranes it is assumed the mode of the distribution curve is (a) in the resting state that of a potassium ion, (b) in the conducting state that of a sodium ion, and (c) in the irradiation state somewhere between (a) and (b).