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# X RAY-INDUCED TRANSIENT CHANGES IN NERVE CHARACTERISTICS

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## FOREWORD
(Nontechnical summary)

Perception of ionizing radiation has been demonstrated in a variety of experimental animal species; furthermore, medical practitioners have reported instances of radiation therapy patients who could "sense" when the x-ray beam was on. The objective of the currently reported research was to characterize changes taking place in nervous tissue during and immediately after irradiation which might explain the mechanisms by which perception of ionizing radiation occurs.

Frog sciatic nerves were given repeated 10- to 90-second exposures of 300 kVp x rays at 2750 or 1450 rads/minute. Before, during, and after irradiation the nerves were submaximally electrically stimulated (10 times per second) and the resulting nerve conduction velocity and compound nerve action potentials (NAP) analyzed.

A transient increase in amplitude of the NAP's was detectable within 3 seconds of the onset of irradiation; within a very short time following termination of exposure, NAP amplitudes returned to values not markedly different from those measured before irradiation. After doses of approximately 4000 rads, transient increases in nerve conduction velocity were also detectable. The increased NAP amplitudes and increased conduction velocity were accentuated while a nerve was subjected to additional identical exposures, implying that damage remained from the previous exposures that was not clearly evident without the added stress of subsequent irradiation.

It is suggested that increased NAP amplitude and conduction velocity are the result of a lowered threshold for stimulation (increased excitability) and an increased

initial rate of change of sodium conductance across the nerve membrane. Further, the increased excitability resulting in NAP enhancement is a plausible mechanism for perception and is not inconsistent with observations.

## ABSTRACT

The immediate effects of x rays on nerve excitation and conduction characteristics were studied. Excised sciatic nerves of frogs (Rana catesbeiana) were given a series of 10- to 90-second 300 kVp x irradiations at 2750 or 1450 rads/minute. Before, during, and after irradiation the nerves were submaximally excited by identical electrical stimuli 10 times per second, and the resulting monophasic compound nerve action potentials (NAP) and nerve conduction velocity were analyzed. A transient increase in amplitude of the NAP was detectable within 3 seconds of the beginning of irradiation; NAP amplitudes returned to stable, near preirradiation values shortly after termination of each exposure. Doses of approximately 4000 rads resulted in easily detectable transient increases in nerve conduction velocity. It is suggested that these changes are a result of a lowered threshold for electrical stimulation (increased excitability) and an increased initial rate of change of sodium conductance across the nerve membrane. Further, the increased NAP amplitudes and conduction velocities were accentuated as a nerve was repeatedly irradiated implying that damage remained from previous exposures which was not clearly evident without the added stress of subsequent irradiation.

# I. INTRODUCTION

Most end points for characterizing the effects of ionizing radiations on biological systems (organism morbidity or death, cell death, epilation, mutation, etc.) require minutes to years to develop to a detectable degree. Consequently the experimenter is obliged to speculate as to the chain of events that occurred between the initial energy absorption and the detected end point. By choosing effects which develop earlier, this chain may be shortened and the number of intervening events to be speculated upon decreased. In particular, the response of excised nerve to electrical stimulation can be measured at frequencies high enough (10 $sec^{-1}$) to yield time resolution of better than 1 second.

Previous investigators[2,6] have tested the effects of high doses of ionizing radiations on excised nerves from various invertebrate and vertebrate species. They report increases in conduction velocity, spike amplitude, and sensitivity to electrical stimulation at doses between 20,000 and 60,000 rads. Dawson and his associates[7-10] studied x radiation-induced excitability changes in isolated frog sciatic nerves. They detected[9] small increases in sensitivity to electrical stimulation at dose rates as low as 500-700 rads/minute. Further, they estimated by extrapolation from a 5-minute exposure at 2000 rads/minute that the increase begins when less than 100 rads have been accumulated and that return to preirradiation values occurs in about 15 minutes after termination of the exposure.

The experiments reported here were designed to extend the understanding of the immediate effects of x rays on nerve by improving the time resolution between irradiation and response. Nervous response to electrical stimulation at the

highest practical sampling frequency was continuously recorded before, during, and after irradiation.

## II. MATERIALS AND METHODS

The experiments were performed on excised sciatic nerves of Rana catesbeiana obtained from Oshkosh, Wisconsin. Due presumably to the malnutrition and subsequent massive bacterial infection described by Gibbs et al.,[4] the initial 2-week survival in the laboratory after receipt of these approximately 450 g frogs rarely exceeded 40 percent. Therefore, the frogs were treated by stomach tube with 40 mg oxytetracycline hydrochloride (Cosa-Terramycin fortified soluble powder, veterinary; Pfizer) in 2 ml water twice a day for 5 consecutive days immediately on receipt, and then maintained without drug therapy for at least 4 weeks in moist cages at room temperature (20-25$^{o}$C) with R. pipiens, upon which the R. catesbeiana fed ad libitum. Animals thus treated had 5-week survival after receipt consistently in excess of 90 percent and were used for all the experiments reported here.

The nerves were dissected free 1 or 20 hours before irradiation and were kept in Ringer's solution of 111 mM NaCl, 2.5 mM KCl, 1.82 mM $CaCl_2$, 0.30 mM $NaH_2PO_4$, and 1.7 mM $Na_2HPO_4$, adjusted to a final pH of 7.30 ± .04 by addition of $NaH_2PO_4$ or $Na_2HPO_4$.

Specimens were x irradiated with a General Electric 300-Maxitron operated at 300 kVp and 20 mA, and with a target to specimen distance of 25 cm. Two different dose rates were used. These were obtained by different filtrations. With the inherent filtration (4.7 mm Be) the half value layer (HVL) was 2 mm Al and the dose rate was 2750 rads/minute; with an added filtration of 1.5 mm Al the HVL was

6 mm Al and the dose rate was 1450 rads/minute. A thin-walled (0.25 mm air-equivalent plastic) 3 $cm^3$ ionization chamber[1] provided data from which these dose rates were computed.

Nerves were irradiated at the ambient temperature of the x-ray facility, approximately 22°C, in either a moist air or a light liquid petrolatum-filled Lucite chamber. The nerve was strung across platinum alloy electrodes, with a single ground electrode halfway between the stimulating and recording pairs; then the nerve was crushed with forceps between the recording electrodes to produce monophasic action potentials (Figure 1).

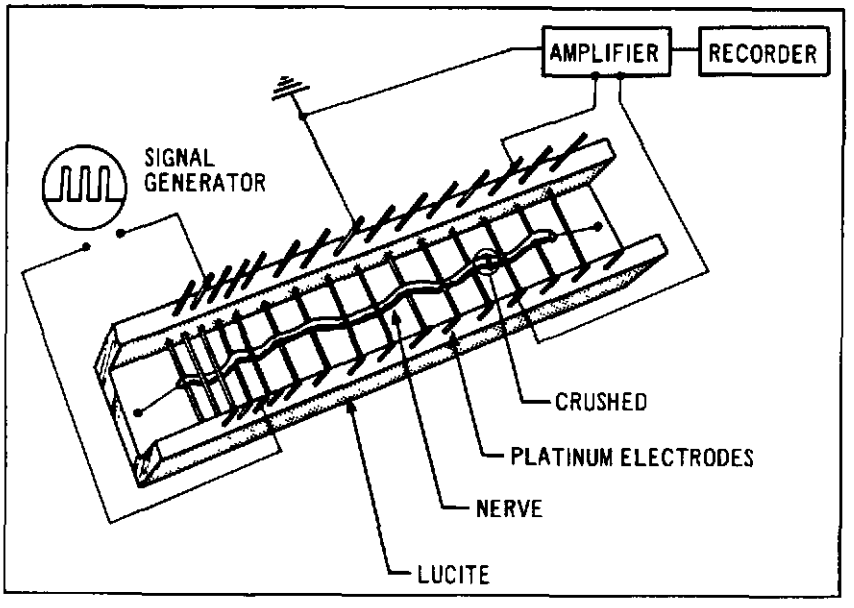


Figure 1. Drawing of nerve in exposure box with signal generator (stimulator), amplifier and recorder schematically represented

Identical rectangular electrical stimuli of 100 or 200 μsec duration and repetition frequency of 8 or 10 stimuli/second generated by a Grass Model S4GR stimulator, were isolated from electrical ground with a General Radio 578A transformer and applied to the stimulating electrodes. The differential inputs of a

battery-operated Lexington Instrument Company Type A103 neurological amplifier were connected to the recording electrodes and the third wire neutral input was connected to the chamber ground electrode. The amplitude of the stimuli was adjusted until the resulting action potentials averaged approximately 50 $\mu$V, which was about five times the maximum instantaneous peak to peak noise of the nerve-electrode-amplifier system. At this level of stimulation about 1 percent of the $\alpha$ fibers were excited (supramaximally stimulated nerves yielded action potentials of about 5 mV), and radiation-induced changes in nerve sensitivity sufficient to permit an additional 1 percent of the fibers to respond would produce an action potential increase on the order of 100 percent.

Data were collected in 10-, 15-, 20-, or 30-second consecutive groups of up to 240 action potentials each. A typical 8-minute experiment (nerve 2, 7/21/67, Figure 2) was thus divided into forty-eight 10-second groups and included a total of about 4800 action potentials. During the last group in minutes 1 through 7 the nerve was irradiated. In early experiments regular intervals between irradiations were chosen, leading to regular changes in nerve response. Since it is conceivable that a regular periodicity in nerve response could result artifactually as an intrinsic property of unirradiated nerve or the electronic apparatus, in subsequent experiments irregular intervals between irradiations were used.

The action potentials were amplified by $10^4$ with the Lexington amplifier and recorded in the FM mode on one channel of a seven-channel Ampex SP-300 1/2-inch magnetic tape recorder at 15 inches per second (ips). Computer control signals and analogs of the stimulus current and voltage were recorded simultaneously on

remaining channels. The analog data were then converted to digital form using the AFRRI Data Acquisition System (DAS); the analog tape was played back at 1-7/8 ips and sampled at the rate of 4000 $sec^{-1}$, yielding an effective sampling rate of 32,000 $sec^{-1}$. A synchronizing signal derived from the leading edge of each recorded stimulus voltage pulse initiated sampling for each action potential. In the analysis of the digital representations, the DAS measured for each action potential its maximum value (amplitude) as well as the number of samples between the synchronizing signal and the maximum (this number of samples is directly proportional to the time

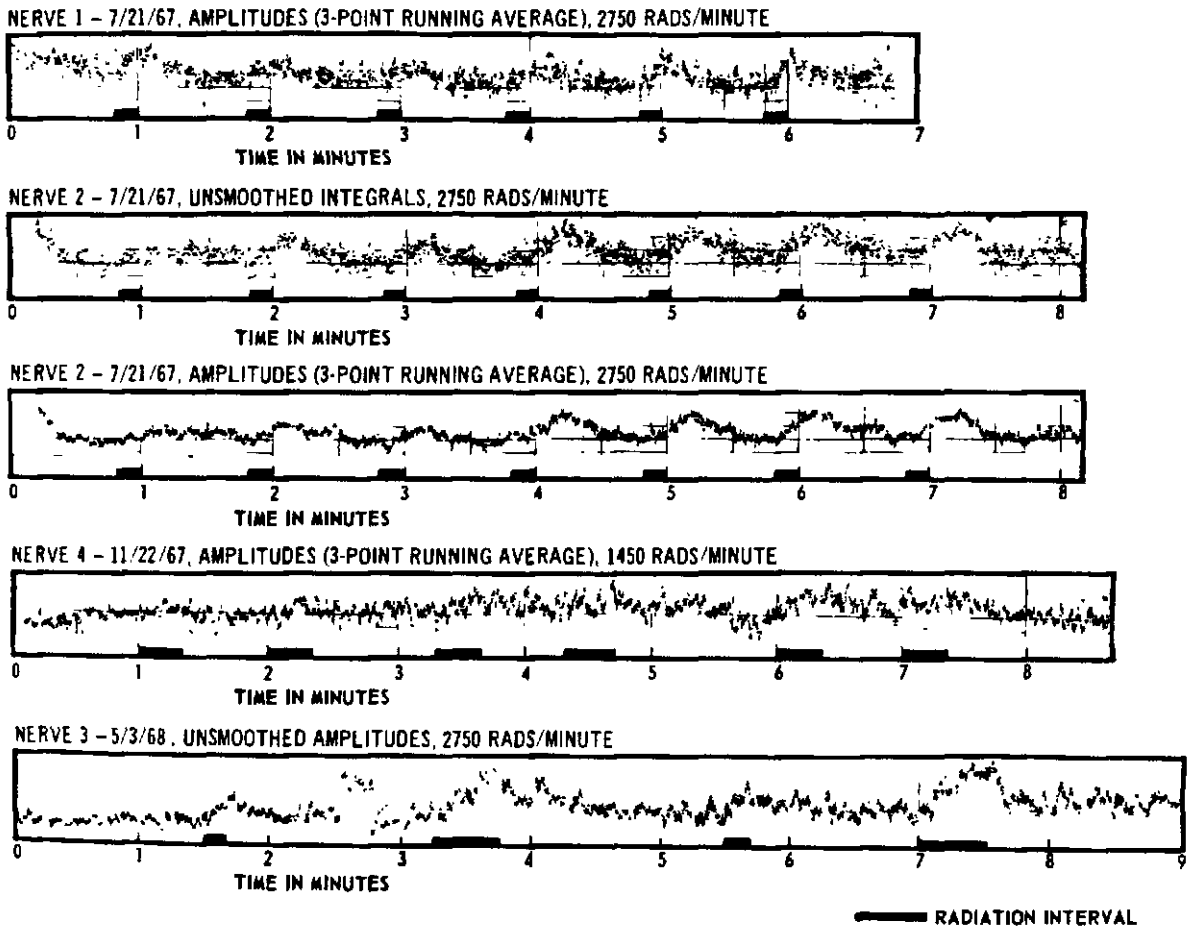


Figure 2. Amplitudes or integrals of compound action potentials before, during and after irradiation. (The apparent artifact at 2 minutes 40 seconds of nerve 3 -- 5/3/68 was caused by manual alteration of the stimulus magnitude.)

required for the action potential to propagate from the stimulating electrodes to the recording electrodes and is therefore inversely proportional to the conduction velocity). The DAS also computed the integral of each action potential.

Means and standard deviations of the three variables (amplitude, integral, propagation time) were computed for each group; the integrals and/or amplitudes in a group were displayed on the DAS oscilloscope -- a plot of nerve response versus time. These displays were photographed and the photographs for a complete experiment assembled (about 5000 response points in a typical 9-minute, 10 stimuli/second experiment). When point to point variance was so large that small trends were difficult to discern, a data smoothing program (3-point running average) was used. That is, each point $X_i$ was replaced by a corresponding point $X_i'$, where

$$X_i' = \sum_{j=-1}^{1} (X_{i+j})/3 \ .$$

## III. RESULTS

The amplitudes of monophasic submaximal action potentials of isolated frog sciatic nerves subjected to repeated identical electrical stimuli increased when the nerves were irradiated at sufficiently high doses and dose rates. (The lower dose rate, 1450 rads/minute, in this experiment did not always result in a detectable effect, but any detected effect was always of the same nature, i.e., the amplitudes increased in response to irradiation.) Usually at least a 10-second exposure was necessary before the resulting gradual increase in amplitudes was sufficiently large to be clearly distinguished from random perturbations in the preirradiation base line. However, the intersection of the slope of the increase with the base line shows

the increase beginning with a maximum lag of 3 seconds after the initiation of 1450 rads/minute (72 rads) and of 1 second at 2750 rads/minute (46 rads), in many cases there was no detectable lag. The rapid increase in amplitudes is clearly seen in both nerve 1, 9/5/68 (90-second exposures), Figure 3, and in nerve 2, 4/12/68 (10-second exposures), Figure 4.

The amplitudes usually continued to increase slightly for 5 to 15 seconds after a 10-second irradiation ended; the amplitudes then gradually decreased, returning to stable values. The time required for return was dose-dependent, as the 15-second exposures of nerve 4, 9/15/67 (Figure 4) returned in about 45 seconds and the 90-second exposure of 9/5/68 returned in about 3 minutes. The stable values to which the amplitudes returned were frequently different from the immediate preirradiation values, but were within the range of drift of unirradiated preparations.

Repeated exposures produced progressively greater rates of increase in amplitude and greater amplitudes, as well as longer periods before return to stable values. The response of nerve 2, 7/21/67 (Figure 2) illustrates this, as little effect can be detected from the first exposure but there are successively greater effects from each of the six subsequent exposures.

The time required for the action potential to propagate from the stimulating electrodes to the recording electrodes decreased continually during irradiation and gradually stabilized near preirradiation values afterwards. Figure 3C shows the changes resulting from two 4125-rad exposures; the change in propagation time occurs at the same time as the change in action potential amplitudes (Figure 3A and B) and is on the order of 2-1/2 to 3-1/2 parts in 50 (5 to 7 percent) for each

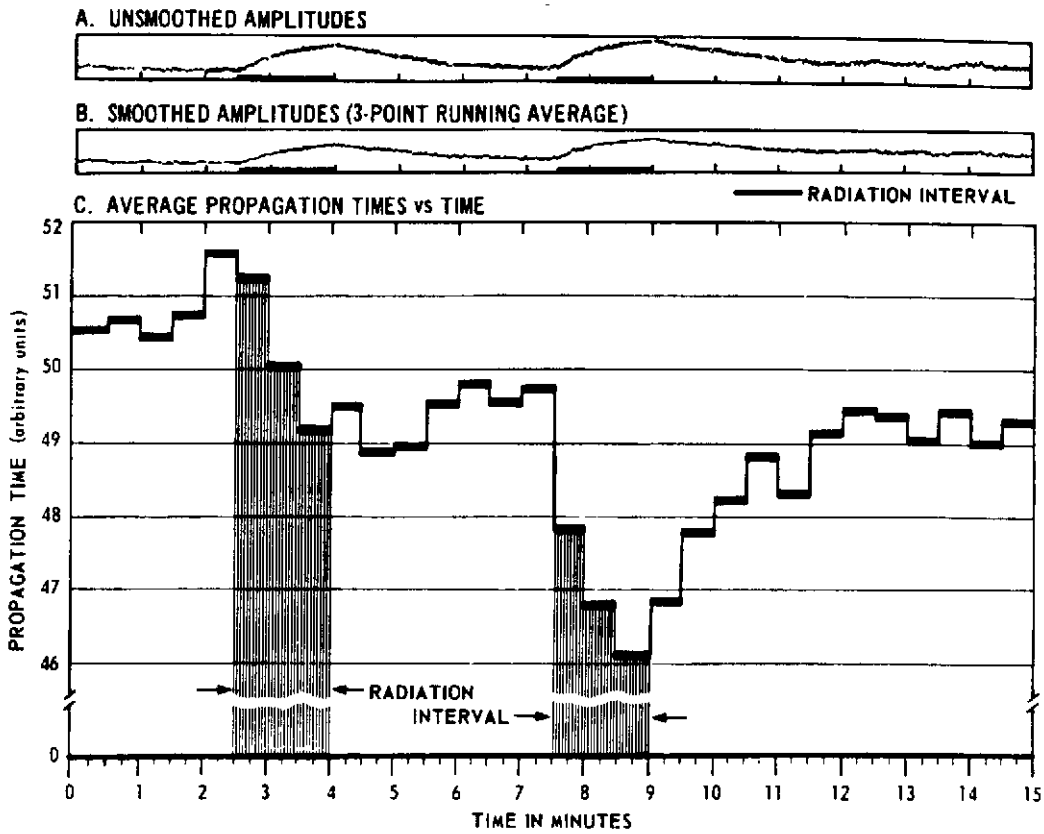


Figure 3. Nerve 1 -- 9/5/68, two 90-second exposures, dose rate = 2750 rads/minute. A and B illustrate the time course of the amplitude of the compound action potential during and after irradiation (B is the data of A displayed as a 3-point running average). C shows the concurrent decrease in propagation time, indicating increased conduction velocity during irradiation.

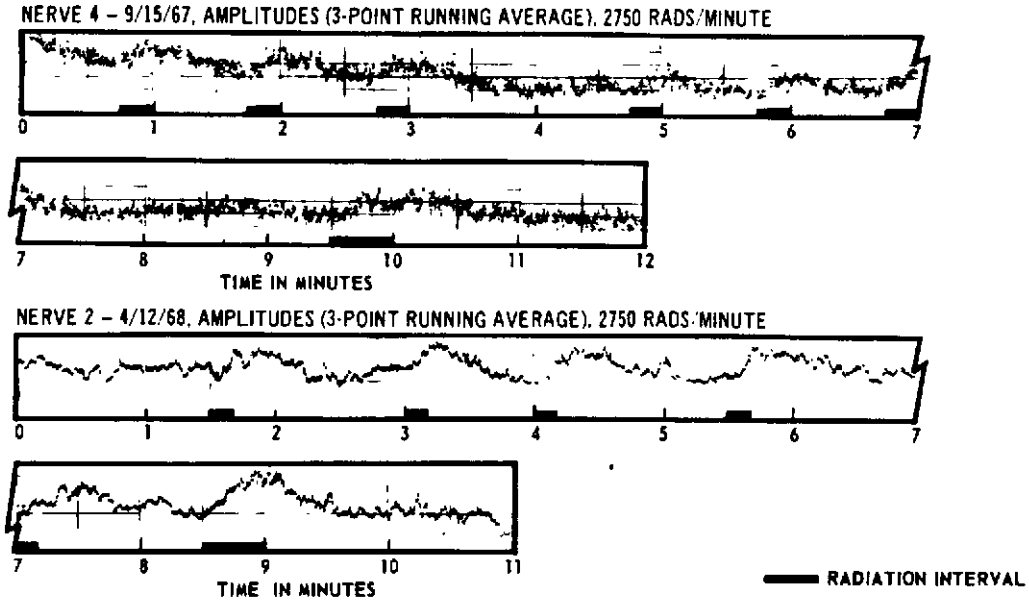


Figure 4. Amplitudes of compound action potentials before, during and after irradiation

exposure. The effect becomes more pronounced in the second exposure. In experiments with doses of 600 rads or less per irradiation the changes in propagation times were so small as to be barely resolvable; they were, however, large enough to suggest a need for the 4125-rad experiment.

The integrals of the submaximal action potentials were found to be linearly proportional to the amplitudes over a 4.5:1 range in amplitudes with correlation coefficients which varied from 0.85 to 0.97, thus demonstrating that within the ranges of amplitude variation examined, the compound action potential amplitude is an equivalent measure of the corresponding compound action potential integral, provided that only $\alpha$ fibers are excited.

## IV. DISCUSSION

The experiments described here confirm previous reports[6-10] that prompt, transient changes occur in the active properties of peripheral nerve exposed to x radiation. Time resolution has been improved; in none of the experiments of less than 1000 rads per irradiation would any of these transient changes have been clearly detected had testing of the nerves been delayed for more than 30 seconds after termination of the exposures. The minimum doses previously reported to produce changes in sensitivity to electrical stimulation[9] and increases in conduction velocity[2,6] are appreciably greater than the corresponding doses reported here.

The maximum observed lag (3 seconds at 1450 rads/minute or 1 second at 2750 rads/minute) between initiation of exposure and increased amplitude of the action potential confirms and extends the observation of Seymour and Dawson[9] that changes begin after less than 100 rads. Because the amplitudes usually continued

to increase for a short time after the exposure ended it is not necessary to interpret the lag between initiation of exposure and increased amplitude as a dose threshold; it is possible that the lag represents a delay time required for the manifestation to develop. Return to stable base-line values occurred in 20 to 45 seconds after 690-rad doses and 3 minutes after 4120 rads; Seymour and Dawson reported return to a similar base line required about 15 minutes after 10,000 rads. This demonstrates that the duration of aftereffects increases with dose.

Seymour and Dawson[9] found a negative correlation between sensitivity and membrane resting potentials, both gradually returning to preirradiation values after irradiation, and concluded that "At doses below 10 krads all the nerves showed complete restoration to their pre-irradiation state...." Their conclusion of complete restoration should be applied only to the sensitivity and resting membrane potentials as it is apparent that some damage remains and is detected in the heightened and longer lasting effects of subsequent irradiations with doses as low as 460 rads each.

The radiation-induced increased response (larger action potential) of a compound nerve to repeated submaximal stimulation may be explained in at least two ways. Either (1) more individual fibers respond, or (2) those fibers that respond do so with individually larger action potentials (spike potentials). In this study threshold decreases sufficient to recruit only another 1 percent of the fibers would approximately double the observed compound action potentials and, should all the $\alpha$ fibers be stimulated, an increase of as much as a factor of 100 might occur. The maximum increase observed in these experiments (Figure 3) is about 450 percent of preirradiation values.

The second explanation (larger individual spike potentials) is supported by the work at much higher doses of Bachofer and Gautereaux[2] and of Kaack[6] in which they report increases in spike amplitude to a maximum of 125 percent in earthworm giant nerve fibers and 115 percent in turtle postganglionic trunk respectively. An interpretation of the spike potential increase is that the rate of change of sodium conductance during depolarization is increased by radiation allowing more $Na^+$ to cross the membrane before inactivation sets in; this results in a larger spike potential (limited by the sodium equilibrium potential to a theoretical maximum of about 160 percent of the original spike potential) and increased conduction velocity by depolarizing contiguous areas of the membrane more rapidly.

The most likely situation appears to be that both mechanisms operate simultaneously. The hypothesis of decreased threshold for stimulation with more fibers firing can account for the rise to 450 percent of the preirradiation compound action potential but not the increased conduction velocity. The hypothesis of increased dynamic rate of change of sodium conductance during depolarization can account for increased conduction velocity but very little of the compound action potential increases observed.

It is interesting to speculate that similar prompt, transient effects may occur in other cells that maintain large steady-state transmembrane ionic concentration gradients, such as intestinal epithelium, erythrocytes, muscle, etc. Hug[5] has summarized muscle experiments that support this speculation.

From studies in the intact animal, Duchesne et al.[3] found neurosecretory changes in the hypothalamic centers and posterior hypophysis of the rat after

200-800 R of 200 kVp x rays. They postulated from their data that nervous structures connected with the hypothalamus may be stimulated by ionizing radiation. Their methods minimized irradiation to analysis time but did not absolutely preclude the possibility that substances formed in the irradiated portion of the body were transported by the blood to the head and resulted in the neurosecretory changes therein. However, the current observations that peripheral nerve excitability is altered within seconds of irradiation are consistent with their postulate. Further observations on the possible action of ionizing radiation in the capacity of a general, nonspecific nervous stimulant were discussed by Tsypin[11] based on studies in which he found an increase in the nervous activity of the depressor, vagus, and sympathetic nerves and intestinal branch of the splanchnic nerve of the rabbit during total body gamma ray irradiation at 1 R/sec for total exposures of a few hundred roentgens.

The observation that the amplitude of monophasic compound action potentials correlated between 0.85 and 0.97 with the respective compound action potential integrals when stimulus levels were sufficiently low that only $\alpha$ fibers were excited is important both for the pragmatic reason that many experimenters do not have access to equipment suitable for automatic integral measurement and for the reason that the high correlation implies that the shape of a compound action potential composed of only $\alpha$-fiber spikes is essentially unchanged except for a multiplicative constant as the number of fibers excited increases.

## V. SUMMARY

A. At dose rates of 2750 rads/minute and 1450 rads/minute of 300 kVp x rays, exposures in excess of 10 seconds duration produce the following effects in frog sciatic nerve excited submaximally by identical repeated electrical stimuli:

1. Prompt, transient increase in the amplitude of the compound action potential, detectable within 3 seconds or less after initiation of exposure and not detectable 15 seconds to 3 minutes after termination of exposure, depending on dose;

2. Dose-dependent transient increase in conduction velocity (about 5-7 percent after doses of 4125 rads); and

3. Accentuation of all effects (increased amplitudes, increased conduction velocity, decreased lag between initiation of exposure and detectable response, increased time for return to stable values) for subsequent exposures delivered to a nerve within a few minutes, implying existing damage not detected without the stress of subsequent exposures.

B. The observations are consistent with the hypothesis that both the threshold for stimulation is lowered and the initial rate of change of sodium conductance during depolarization is increased.

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13. ABSTRACT

The immediate effects of x rays on nerve excitation and conduction characteristics were studied. Excised sciatic nerves of frogs (Rana catesbeiana) were given a series of 10- to 90-second 300 kVp x irradiations at 2750 or 1450 rads/minute. Before, during, and after irradiation the nerves were submaximally excited by identical electrical stimuli 10 times per second, and the resulting monophasic compound nerve action potentials (NAP) and nerve conduction velocity were analyzed. A transient increase in amplitude of the NAP was detectable within 3 seconds of the beginning of irradiation; NAP amplitudes returned to stable, near preirradiation values shortly after termination of each exposure. Doses of approximately 4000 rads resulted in easily detectable transient increases in nerve conduction velocity. It is suggested that these changes are a result of a lowered threshold for electrical stimulation (increased excitability) and an increased initial rate of change of sodium conductance across the nerve membrane. Further, the increased NAP amplitudes and conduction velocities were accentuated as a nerve was repeatedly irradiated implying that damage remained from previous exposures which was not clearly evident without the added stress of subsequent irradiation.

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