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**EFFECTS OF PULSED
GAMMA-NEUTRON IRRADIATION
ON THE EEG AND BEHAVIOR
OF THE MONKEY**

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FOREWORD
(Nontechnical summary)

The objective of this study was to correlate electroencephalographic changes and behavioral impairment in rhesus monkeys after a whole-body exposure to a 2500-rad pulse of mixed gamma-neutron radiation. The cortical EEG was used as the index and the monkeys were trained to perform a visual discrimination task. A method for analyzing the EEG quantitatively was implemented to facilitate comparison of EEG changes with behavioral changes. In addition, systemic blood pressure was measured to investigate the possible relationship between cardiovascular changes and EEG changes. Shifts in values of the EEG measures, indicating an alteration to high amplitude slow waves, occurred in about the same time period as the behavioral deterioration of the early transient incapacitation (ETI) period. Cardiovascular changes were not as closely related to behavioral changes. In the recovery period following the ETI, performance of the monkeys returned to near normal levels of accuracy and then usually deteriorated in the last part of the session. There was no clear relationship between EEG measures and accuracy of response in this period following ETI.

ABSTRACT

Cortical EEG recording leads were implanted in seven rhesus monkeys (Macaca mulatta). The monkeys were then trained to perform a visual discrimination task. After the animals had been trained to acceptable levels of performance, blood pressure measuring devices were surgically implanted. Two weeks after surgery the monkeys were irradiated with a single 2500-rad whole-body pulse of mixed gamma-neutron radiation from the AFRRI-TRIGA reactor. EEG, behavioral, and cardiovascular parameters were continuously monitored and recorded on magnetic tape. The EEG was analyzed by a power spectral density procedure, and various measures, including first and second moments of the spectra, were obtained. Relationships between these EEG measures, behavioral changes, and cardiovascular alterations were then studied both preirradiation and postirradiation. Some degree of apparent relationship was found between changes in the EEG measures after irradiation and changes in performance, particularly during the early transient incapacitation (ETI) period. This relationship could not be well established in the period following ETI or between behavioral and cardiovascular changes. A consistent relationship between cardiovascular and EEG changes was not established.

I. INTRODUCTION

The role of the central nervous system (CNS) in radiation damage can be studied in two ways: (1) measurement of the effects of varying doses and types of radiation on the morphology, electrical activity and biochemical properties of the CNS elements and subsystems; and (2) correlation of such effects and various aspects of CNS function and behavior, e.g., sensory input, learning efficiency or capacity, performance efficiency, memory, or motor functions.

Much of the earlier work on effects of radiation on the CNS concentrated on microscopic cellular changes. For example, Arnold² demonstrated acute cellular damage (cell destruction, loss of cytoplasm) in the hypothalamus of monkeys after 3000-14,000 R of 23 MeV x rays. At doses of 1500-3000 R, damage to the hypothalamus was more restricted to the supraoptic and paraventricular nuclei. Arnold et al.,^{3,4} using 23 MeV x rays, reported complete destruction of the brain in the beam path at doses of 7000-14,000 R. A delayed radionecrosis of the internal capsule and deep cortical white matter in the beam path was found at doses of 1500-3000 R. The authors stated that this necrosis was not related to vascular damage. Ibrahim et al.¹⁸ exposed heads of monkeys to 2000 R (either 250 kVp x rays or ⁶⁰Co) and concluded, in contrast to Arnold et al., that "The sites at which lesions develop in the CNS would seem to be determined by the regions of the vasculature in which hemodynamic crises occur." Innes and Carsten,¹⁹ however, reported that irradiation of the spinal cords of rats with 3500 R x rays produced lesions in the cord which could not be related to vascular damage.

The combination of electroencephalographic recording and biochemical analyses with neuropathological observations provides much more sensitive indices of radiation damage.³⁶ If anatomical studies are made in conjunction with functional observations,^{25,26,30} valuable correlations between structural alterations and function can be obtained.

The present study concentrated on the psychologic and physiologic indices of radiation damage, in particular electrical activity of the CNS. Considerable evidence has accumulated indicating that the electrical activity of the CNS is disturbed by ionizing radiation. For example, Brooks⁵ found that 1000 R of whole-body gamma radiation at a dose rate of 1000 R/minute caused slowing of the EEG wave form in anesthetized monkeys. Caster et al.⁸ reported that after 700 R of total body x irradiation in rats there was a decrease in both low frequency (1.5-7 Hz) and high frequency (14-30 Hz) EEG activity relative to the 8- to 12-Hz band 3-12 hours after irradiation. There was a significant decrease in brain DNA in this same time interval. Caveness et al.⁹⁻¹² and Carsten⁷ indicated that monkeys exposed to 3500 R of 250 kVp x rays (right side of head only) at a dose rate of 350 R/minute showed EEG amplitude alterations as early as 24 hours after irradiation, a decrease in magnitude of the visual evoked response in the irradiated hemisphere, reaching its nadir in the 6th week postirradiation, and the appearance of high amplitude slow waves 18-22 weeks after irradiation. They were able to correlate evoked potential changes with reductions in dendritic ramifications in the cortex and appearance of EEG high amplitude slow waves accompanied by neuronal tissue destruction, myelin degeneration, and inflammatory and glial reactions. Innes and Carsten¹⁹ also reported hemiplegia and EEG abnormalities in monkeys

6-8 weeks after receiving 3500 rads of x rays to the right cerebral hemisphere.

Gangloff and Haley¹⁴ reported primarily subcortical (particularly hippocampal) responses to 200 and 400 R x irradiation in cats. Two points of special interest in their work were that (1) hippocampal spiking occurred only with whole-body or head irradiation, and not with the head shielded, suggesting a central nervous system effect; and (2) the initial cortical response at these dose levels was an arousal one (low voltage fast activity), with high voltage slow wave activity not appearing until the animal approached death. Monnier and Krupp²² also found that 400-600 R head only gamma irradiation to rabbits produced neocortical desynchrony and hippocampal hyperactivity. However, if the dose was increased to 900 R, high voltage slow cortical waves appeared. Nair et al.²³ found that 10,000 R of 250 kVp x rays at 295 R/minute to the heads of rats resulted in a marked EEG amplitude reduction, 24-48 hours postirradiation. Ross et al.²⁷ reported high amplitude slow waves in monkeys after 1500-6000 R of 250 kVp x rays (118 R/minute) to the head. These changes appeared within the 1st day postirradiation after 4500-6000 R, after 24 hours in the 3000 R group, and by the 4th day in the 1500-2000 R group. Absence of symptoms of radiation sickness such as vomiting, diarrhea, and hemorrhages in these head-irradiated monkeys led them to conclude that there is no causal relationship between CNS damage and those syndromes. Sams et al.^{28,29} reported hippocampal spiking in dogs whose heads were exposed to 10 or 100 rads of 250 kVp x rays at 21.7 R/minute. They could not relate the spiking activity to any behavioral changes, although they did report an increase in time spent in deep sleep after irradiation. In contrast, Herrmann et al.¹⁷ reported that monkeys generally spent more time asleep, but primarily in the lighter stages of

sleep, after a 5000-rad pulse of mixed gamma-neutron radiation. Also in connection with sleep stages, Ono et al.²⁴ used the "EEG afterreaction" (appearance of regular slow waves in the hippocampus, frontal cortex, and brainstem reticular formation) as an indicator of paradoxical sleep. Following ⁶⁰Co irradiation to the head of rabbits (200-10,000 R at 37-96 R/minute) there were (1) increases in latency of appearance of the afterreaction with increases in dose; (2) disappearance of the afterreaction with doses of 3000 R or more; and (3) a rise in the threshold of septal stimulation induced afterreaction with increases in dose. Tsuya,³² using rabbits and gamma irradiation to the head (96-37 R/minute), found flattening and slowing of the EEG after doses of 5000-15,000 R, more moderate flattening and slowing after 1000-3000 R (hippocampus and amygdala affected more than cortex), and a slight "lowering" of EEG in the 200-500 R group within 3 hours after irradiation. Uzzell and Sheer³⁴ exposed cats to either 500 R whole-body gamma radiation or 2000-3000 R head only gamma radiation. They found a transitory loss of 40 Hz activity in olfactory bulbs in the 2000-3000 R head only irradiated group, but a nontransitory loss of 40 Hz activity over the 7-day observation period in the 500 R whole-body irradiated cats. They related these EEG results to changes in norepinephrine and serotonin levels in the olfactory bulbs. Garcia et al.¹⁵ reported an EEG arousal reaction in sleeping rats within 1 second after exposure to 250 kVp x-ray doses delivered at rates as low as 0.1 to 0.2 R/second. They presumed that this response was due to activation of peripheral receptors.

In one of the few papers dealing with effects of radiation on both EEG and behavior, Adey and Schoenbrun¹ reported the following. (1) Doses of 100-400 R of 250 kVp x irradiation (50 R/minute, delivered weekly over a 6-week period for a total of 600 or

2400 R and directed to the heads of cats) produced hypersynchrony at 5-6 Hz in the hippocampus and entorhinal cortex and a depression of locomotor activity but had no effect on learned behavior. (2) Whole head irradiation by 1000-1500 R also produced hypersynchrony and spiking in the hippocampus promptly after irradiation. These symptoms diminished and then returned 18 days later coincident with anorexia and performance decrements. (3) Unilateral irradiation of one hippocampal arch with 1000 R resulted in a decrease in motor activity and hypersynchrony in the hippocampal EEG at 5-6 Hz, but such effects diminished with accumulated doses over 10,000 R. Performance accuracy was not affected at any dose. (4) Bilateral hippocampal irradiation with 2500, 5000, or 10,000 R of x irradiation produced increases in response latencies and shifts in the peak of the EEG "power" spectrum to lower frequencies. Food intake of these cats was not altered nor were there signs of radiation sickness as there were following their whole head exposures. The latter finding contrasts with the lack of radiation sickness of whole head irradiated monkeys reported by Ross et al.²⁷ In another behavioral study the visual acuity of monkeys after 3500 rads of 250 kVp x rays at 350 rads/minute to both occipital lobes was examined by Graham et al.¹⁶ Significant decrements in acuity appeared 119 days after exposure. Blindness occurred 149-195 days after exposure. Yanson³⁵ irradiated rabbits in which a conditioned response had been developed with 500 R of 180 kVp x rays delivered to the head only, total body, or body only. The conditioned response disappeared 15-20 minutes after both head only and total body irradiation, whereas impairment of the reflex did not occur until 1 to 2 days in the body only irradiated group. EEG changes were not

seen in the latter group, although erratic wave forms and amplitude decreases were seen in the first two groups.

The above studies indicate that a fair amount is known about CNS electrical responses to x rays in particular in a variety of species, but relatively little work has been done with high doses of gamma-neutron radiation. In addition, little information is available concerning the effects of high radiation doses on behavioral-neurophysiological interactions in trained animals. Therefore the purpose of the present study is to provide data relating effects of pulsed gamma-neutron radiation on cortical electrical activity, task performance, and certain pertinent cardiovascular measures.

II. MATERIALS AND METHODS

Seven male rhesus monkeys (Macaca mulatta), approximately 2 years old, were placed in primate chairs for a 3- to 5-day adaptation period. EEG electrodes (Carmeci et al.⁶) were surgically implanted on the dura over paired frontal, parietal, and occipital areas under general anesthesia. A miniature Winchester plug, to which the EEG leads were attached, was also implanted on the skull. After surgery, the monkey was replaced in the primate chair (Figure 1) and allowed to recover for 1 week before training started.

Training took place in a ventilated, sound-shielded room in which the monkey remained for the entire experiment. The monkey was placed in its chair inside a white painted plywood training box provided with a 15-watt house light. One side was hinged to serve as a door and an opening was provided for television monitoring. Electrodes for applying electrical shock in case of errors were connected to the monkey's tail and lower back. A stimulus presentation console with a single visual

stimulus presentation aperture was mounted on the chair frame at eye level in front of the monkey. A lever operated, solenoid controlled, variable tension response switch was mounted on the chair frame at midrib level in front of the animal. A series of colored lights appeared in a random time sequence in the display console. The monkey was trained to press the lever if the light was green ("go" cue) and to not press the lever if the light was red, yellow, or white ("no go" cues). Errors were punished by electrical shock.

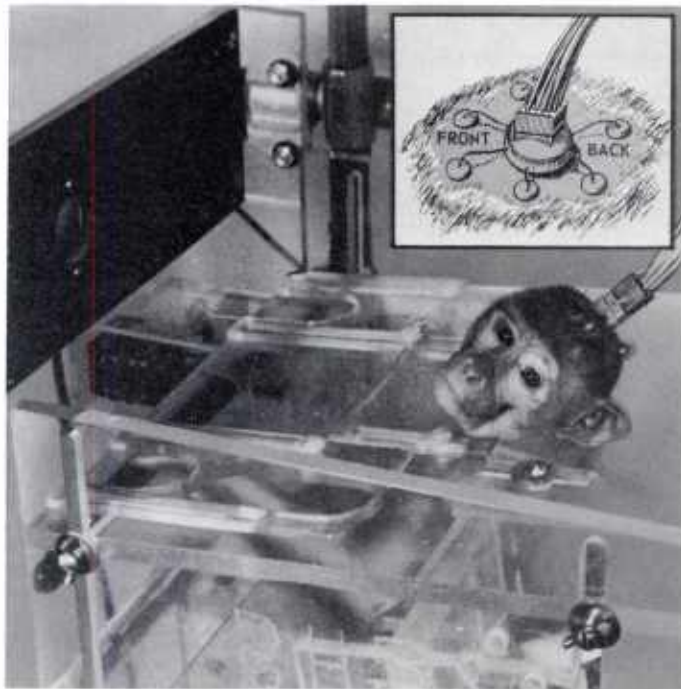


Figure 1. Monkey in the primate training chair. Note the console mounted at eye level with its single display unit, the bar at arm level for responding, and the EEG recording cable plugged into the receptacle cemented to the skull. The inset shows a detail of the electrodes in position with leads going to the central connector. The shaded area represents dental cement covering the electrodes and anchoring the connector to the skull.

A manual procedure was used initially to teach the monkey to press the lever when the green light appeared. If he did not press the lever within 2 seconds of the onset of the green light, a brief electrical shock was given. After reaching proficiency on this phase of the task, sequencing of stimuli was placed under automatic control. Subsequent training was conducted in isolation. The isolation cubicle was illuminated 1 minute prior to the start of the program to serve as a cue to the monkey and to provide lighting for the television camera. Initial automatic training began with only the "go" (green) stimulus being presented. After achievement of a stable 90 percent correct performance on this phase, the first "no go" light (red) was introduced on the following day's session. On reaching a criterion of 90 percent correct performance for both green and red stimuli, the monkey was confronted with a third stimulus, the "no go" yellow, and training proceeded as with the red and green. A fourth stimulus, the "no go" white, was entered subsequent to reaching an adequate performance level on the previous three. Each stimulus was presented for 2 seconds. The monkey was shocked for failure to respond to green and for responding to any negative light stimulus. A response to green extinguished that stimulus but a "no go" stimulus remained on for the full 2 seconds regardless of response. Stimulus presentations averaged approximately six per minute over a 90-minute session, 50 percent being "go" (green) cues and 50 percent equally divided among the three "no go" lights. Shock for omission or commission error was automatically delivered for 100 milliseconds, with intensity varied manually depending on the training stage and shock response of the monkey.

As the monkey's proficiency rose, the shock intensity was increased gradually to a maximum (8 mA) at which it was maintained during all subsequent training and test sessions. This was done to avoid disrupting the early learning process with high shock levels and to prevent lapses of performance accuracy after learning the task by providing sufficiently intense punishment for errors. In addition, the high shock level provides, in this motivational system, maximum incentive for correct performance after irradiation, although even this incentive is ineffective in the early transient incapacitation (ETI) period which most monkeys pass through a few minutes after the pulse.

Daily sessions of 1-1/2 hours were held at the same time in the morning until each monkey achieved a level of 90 percent or better correct response to all cues for 3 consecutive days. The mean time to reach this level of performance was 25 days. At this time, the last four monkeys in this series were removed from the chairs, and catheters for blood pressure measurement were implanted under general anesthesia in the abdominal aorta via the femoral artery and in the vena cava via the femoral vein.³³

Behavioral and EEG base lines were selected from one of the sessions conducted on each of the 3 days immediately preceding the day of exposure. Prior to each of these sessions, the monkey was removed from the testing chamber, transported to the reactor exposure room area, allowed to remain for several minutes, and then returned to the testing chamber. An additional 1/2-hour session was given at the same time (3:00 p.m.) on each of these days, and the EEG was periodically sampled overnight. Testing time and recording equipment for the exposure session were

identical with previous training and test sessions, only the location differed. The possible effect of the latter factor on performance was minimized by the adaptation transportations described above and by placing the animal in the exposure room in a plywood box identical with his training box.

The monkeys were positioned in Exposure Room No. 1 of the AFRRI-TRIGA reactor to receive a dose calculated from previous dosimetry of 2500 rads of pulsed gamma-neutron radiation. The gamma-neutron ratio, free-in-air, was about 60 to 40. The midline tissue dose (MTD) was obtained by determining the tissue kerma, free-in-air, at the midline exposure volume and multiplying this value by an experimentally derived factor (0.85). Dosimetry on these animals indicated a mean dose of 2529 rads with a range from 2300 to 2800 rads. The entrance dose at the monkey's surface was 112 percent of the free-in-air dose, at specimen midline it was 85 percent of the free-in-air dose, and at exit it was 54 percent of the free-in-air dose.

On the day of irradiation the monkeys were placed in the reactor exposure room and recording leads were connected. After the exposure room door was closed the regular testing sequence started. The radiation pulse occurred 1/2 hour later with no interruption of the cue presentation program, which continued for another hour after the pulse.

To record the EEG, a low noise Microdot wire harness conducted the EEG signals from the animal to a switch panel where any combination of existing signals could be arranged and then fed in pairs to double-ended input preamplifiers. The EEG signal pairs used in this study were right frontal-right occipital, with one exception when the left frontal-left occipital pair was used because of noise problems in the right

frontal-right occipital leads. All signals were filtered at 0.1 Hz-1 MHz bandwidth and amplified 100 times at this stage, then routed to an Ampex DAS100 14-channel magnetic tape system with a bandwidth setting of 1-50 Hz, amplified 50 times (peak to peak), and recorded on analog tape. The EEG signals were both preceded and followed by 3-minute calibration periods. Calibration consisted of consecutive 1-minute periods of zero input, 1 mV square waves (10/sec), and zero input. In addition, three sets of known test signals were recorded near the beginning, middle, and end of the 1-1/2-hour session. These signals consisted, respectively, of a complex sine wave with 3, 10, and 30 Hz components, a white noise (all frequencies within a bandwidth of 5 Hz to 20 KHz present at identical amplitudes), and a sawtooth signal, all of known root mean square amplitudes. These signals served the dual purpose of checking the timing accuracy of the digitizing procedures and verifying the accuracy of the spectral analysis computer program. A graphic time code and behavioral event codes were also recorded on additional channels. Simultaneous visible records were obtained on a Brush pen writer or monitored on oscilloscopes.

The analog data on magnetic tape were stored for later computer processing, at which time taped EEG signals were played back, amplified five times at a 1-50 Hz bandwidth, and transmitted to the Scientific Data Systems 920 computer for digitizing and analysis. Just prior to entering the analog to digital converter, the signals were again filtered through a Krohn-Hite filter with bandwidth set at 0.1-35 Hz. The EEG data were digitized at a rate of 100 samples per second and stored on digital tape.

The data to be analyzed for this study consisted of 10-second epochs of EEG signals immediately preceding onset of stimulus lights. These epochs were selected

from the Brush records with care being taken to exclude motion artifacts. In the base-line period (the day preceding irradiation) 10 epochs were selected preceding green stimuli ("go" cue) and 10 preceding nongreen stimuli ("no go" cues) scattered throughout the entire 1-1/2-hour session. Ten "go" and ten "no go" epochs preceding correct responses were picked in the 30-minute preirradiation period on the day of exposure. Epochs preceding any errors were also selected in these time periods, although errors were very few because of the high response accuracy. In the 1 hour after the pulse, all epochs preceding errors were selected, and at least 50 percent of all artifact-free epochs preceding correct responses were chosen for analysis. The starting times of these epochs were entered on card coding forms for keypunching. Cardiovascular and response latency data were measured on the Brush records. Response latency refers to the time from the light cue onset to the time the monkey makes its response.

The primary purpose of this study was to determine whether EEG patterns could be associated with animal behavior (performance) under a specific set of conditions. To accomplish this the mass of data collected on each animal had to be reduced to a manageable form, and measures which characterize an EEG spectrum were required. Power spectral density calculation was used to reduce 10-second EEG epochs to a plot of intensity versus frequency. Since the power density spectrum has the characteristics of a statistical distribution function (Jenkins and Watts,²⁰ p. 222), one might characterize the spectrum by its moments. The first moment is indicative of the location of the center of mass of a distribution function and the second moment is a measure of spread of a distribution. The implications in terms of EEG configuration

are that if the first moment center of mass measure (units in hertz) is low, then slow waves are predominant in the EEG. If the first moment is high, then higher frequencies are present in the EEG. If the second moment measure (units in hertz) is small, then the EEG shows a regular wave form synchronized around the frequency band indicated by the value of the first moment. If the second moment is large, then the EEG consists of a wider range of frequencies. The shape of the EEG spectrum is not symmetrical and often looks like Figure 2A. Since this is reminiscent of the log normal distribution, often encountered in biostatistical data, plotting the data on a log frequency scale would tend to make it symmetrical and would make the moments of the log frequency spectra easier to interpret. The median frequency is also considered since it gives the point that divides the area of the power spectral density function in half and has the same meaning regardless of the shape of the spectrum. A final measure that is used to characterize the power spectral density function is the total power which is the sum of all of the intensities without regard to frequency. It is an indication of the average amplitude of the EEG during the time of the epoch. If the power increases, then the amplitude of the EEG wave form increases. The power spectra were obtained by first calculating the autocorrelation function and then the smoothed power spectral density function using a weighted cosine transform. These terms are explained and the method of calculating the power spectral density function using the Parzen window for smoothing is described in Jenkins and Watts.²⁰ The method as described, using 10-second duration epochs and digitizing at 100 points per second with 200 lags in the autocorrelation calculation, resulted in a bandwidth of about 1/2 cycle per second, i. e., frequencies differing by 1/2 Hz can be distinguished.

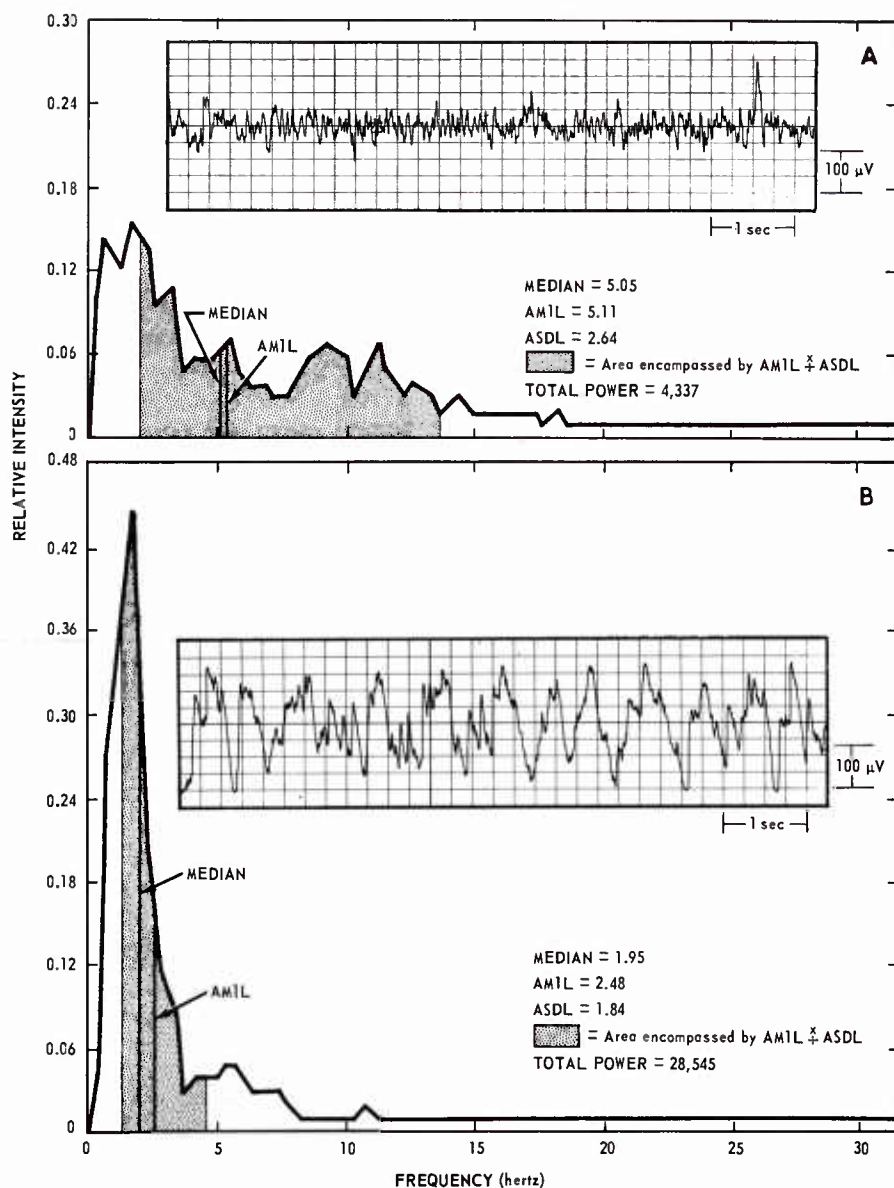


Figure 2. Samples of "raw" EEG epochs and their associated power spectral density plots. A. From a time period prior to irradiation. Three measures used to characterize the spectral density plot are illustrated. The median indicates the point at which 50 percent of the total power lies below and 50 percent above; AM1L is analogous to the mean of the power distribution and ASDL is a measure of spread. Note the multi-peaked nature of the distribution and the rather large spread indicated by ASDL in the shaded area. B. From the ETI period of incapacitation after irradiation. Note relative to the normal EEG in A that now most of the power is shifted into a large peak at around 1.5 Hz with corresponding downward shifts in the median and AM1L measures; ASDL is reduced; and the total power in the epoch has increased relative to preirradiation.

The final step of the spectral analysis program calculates total power which is the sum of intensities over all frequencies. The intensity at each frequency is divided by this total power, making the new sum equal to one and giving a relative intensity (I) at each frequency (W). The output of the spectral analysis program is in the form of 100 pairs of values: frequency (W) and relative intensity (I) from 0.1 to 40 Hz. The I values resemble proportions or percentages in the histogram interpretation of the spectrum. Thus we have the first moment

$$M1 = \sum_{j=0}^{40} I_j W_j$$

and the second moment

$$\text{Var } W = \sum I_j W_j^2 - (M1)^2$$

$$SD = \sqrt{\text{Var } W} .$$

Using the Parzen window, none of the I's can be negative.

The log moments were obtained by taking the logarithm of frequency and computing

$$M1L = \sum I_j (\log W_j)$$

$$\text{Var } L = \sum I_j (\log W_j)^2 - (M1L)^2$$

$$SDL = \sqrt{\text{Var } L} .$$

The required quantities were obtained by taking antilogs thus:

$$AM1L = \text{antilog } (M1L)$$

$$ASDL = \text{antilog } (SDL) .$$

Figure 2A and B illustrates the location of the AM1L and ASDL values on two power spectral density plots. That frequency (ω) at which the 50 percent point is located is called the median frequency (MED). If the median point was between two frequencies, linear interpolation was used to estimate the median.

The moment concepts were developed to permit quantification and summarization of the data on a large number of epochs in any given category for several animals. The basic comparisons were between preirradiation and postirradiation periods; between "go" and "no go" conditions; and between correct and incorrect responses. The EEG epochs were categorized to allow these comparisons to be made. A computer program was developed that lists the time; the category of epoch, e.g., preirradiation, "go", correct; the response latency for the 10-second epoch; and the value of power, M1, SD, MED, AM1L and ASDL, for each epoch. The values of heart rate (beats per minute) and blood pressure (millimeters of mercury) are listed as well for each epoch. The program further groups all of the epochs of a particular type, e.g., postirradiation, "go", correct, and for each condition gives average values of each EEG measure and physiological variable. A program option gives the summary for all monkeys while another gives a plot of each of the measures versus time.

III. RESULTS

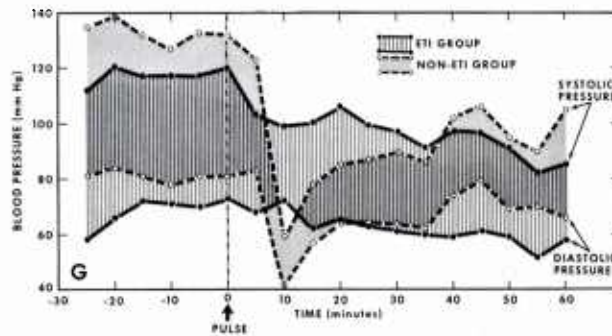
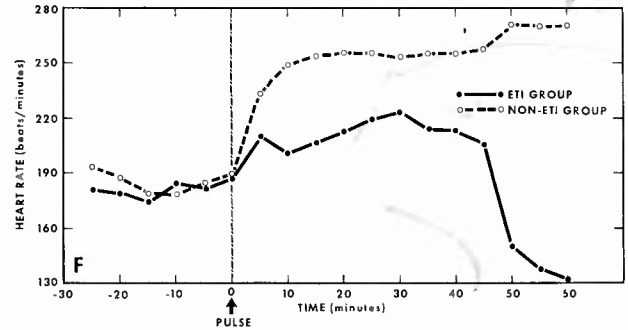
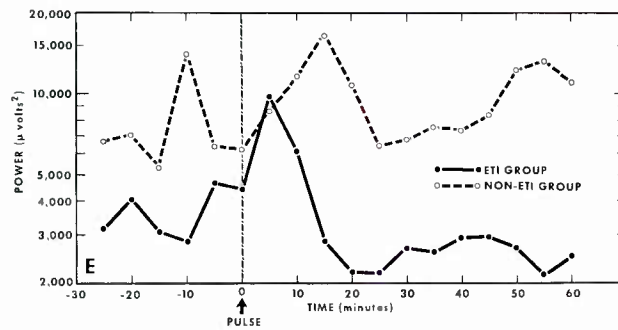
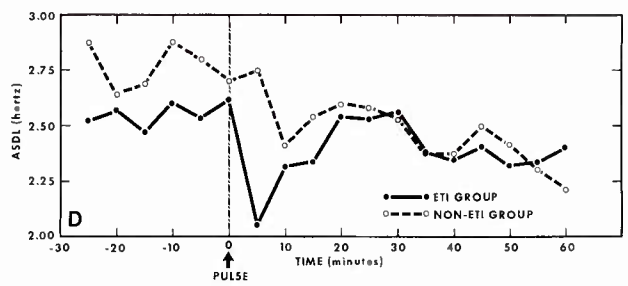
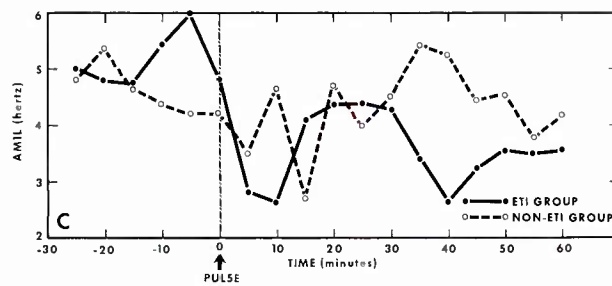
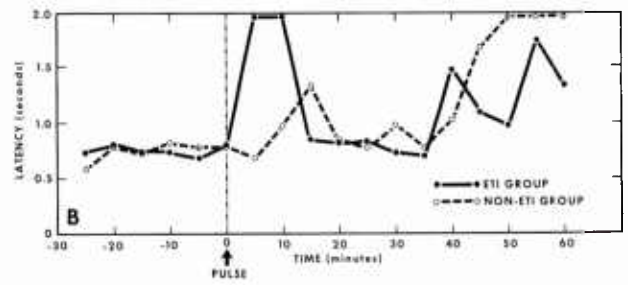
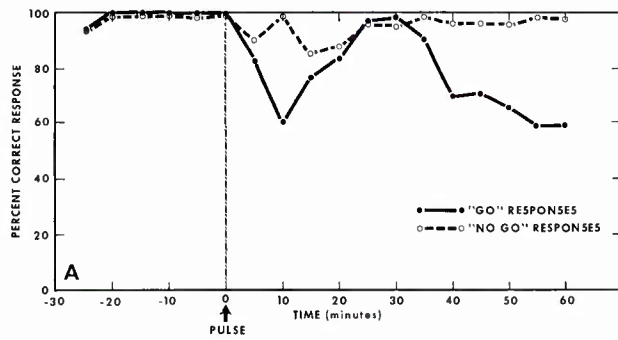
Figure 3A-G presents data averaged from all seven monkeys over 5-minute intervals. For each measure on each monkey an average value was determined for consecutive 5-minute intervals. The median value of each measure for all monkeys was then calculated per 5-minute interval as indicative values for a typical animal.

Figure 3A presents the typical performance on both the "go" responses following a green light cue and on the "no go" response inhibition after a nongreen light cue. Prior to the pulse, the average performance was quite stable. An early transient incapacitation (ETI) appeared at about 10 minutes postpulse in the "go" responses and at about 15 minutes postpulse in the "no go" responses. Most monkeys returned to fairly accurate performance following the ETI period, although occasional errors occurred. It is particularly interesting that the peak decrement in response inhibition ("no go" conditions) occurred in the recovery period from the "go" response ETI, indicating a period of confusion when the monkey was responding to all stimuli. Most of the animals suffered a second performance decrement in the last part of the session, including two with severe decrements which brought the average performance down considerably. The continued high level of performance in the "no go" condition at this time reflects the fact that lack of response was correct for these cues. That is, lack of response due to incapacitation cannot be distinguished from inhibition of response in the normal animal. The primary value of the "no go" condition is in the recovery phase from the ETI when the animal is beginning to respond to cues, but fails to inhibit responses when a "no go" cue appears.

Figure 3B represents the median response latency with the animals separated into those showing a significant ETI within 15 minutes after the pulse and those not exhibiting such an ETI. A rise in latency can be seen 5-10 minutes postpulse in the ETI group and a delayed rise in the non-ETI group, followed by a short recovery and then a trend of gradually increasing latency for the remainder of the session. The drop in value of the median first moment, AM1L (Figure 3C), 5-15 minutes after the

Figure 3.

- A. Median percent correct response for successive 5-minute intervals for all seven monkeys for 30 minutes prior to the pulse and 60 minutes after the pulse. The solid line represents the performance on the "go" (before the green cue) condition, and the dashed line that on the "no go" (before the nongreen cue) condition. Standard errors are not indicated on this or subsequent plots in this figure since the statistical assumptions prerequisite for use of this measure have not yet been verified in this study.
- B. Median latency of response from cue onset for consecutive 5-minute intervals plotted separately for those monkeys (four) showing a significant ETI within 15 minutes after the pulse and for those monkeys (three) not showing such an ETI. All monkeys showed a secondary decrement toward the end of the session.
- C. Median AM1L values of EEG epochs plotted in successive 5-minute intervals for those monkeys showing an ETI soon after the pulse and for those not demonstrating such an ETI. See text for derivation of this and subsequent EEG measures.
- D. Median ASDL values of EEG epochs plotted at successive 5-minute intervals for the group of monkeys showing an ETI within 15 minutes after the pulse and those not demonstrating such an ETI.
- E. Median power values of EEG epochs for ETI and non-ETI groups of monkeys plotted in 5-minute increments. The peaks at minus 10 minutes and plus 15 minutes are due to aberrantly large values from a single monkey.
- F. Median heart rate in beats per minute plotted over 5-minute intervals for two monkeys showing an ETI and two monkeys not showing an ETI within 15 minutes after the pulse. Only four of the seven monkeys in this study were instrumented for cardiovascular measurements.
- G. Average systemic systolic and diastolic blood pressures plotted separately for two monkeys showing an ETI and two not showing an ETI soon after the pulse.



pulse, coincides closely with the latency changes in both ETI and non-ETI groups seen in Figure 3B. The trend toward lower values in the last part of the session follows the performance deterioration seen at this time. Note that the AM1L values after the pulse never reach the prepulse level, except for a brief period in the non-ETI group, indicating a downward shift in average frequency of the EEG. A similar correlation with performance changes is reflected in the ASDL measure shown in Figure 3D. The previous two measures have not, to our knowledge, been used before and provide a quantitative means of specifying changes in the power density spectrum. A measure that has been used by other investigators is the total power. The average of the logarithm of power is plotted in Figure 3E at 5-minute intervals for ETI and non-ETI groups. Once again, this measure follows changes in performance, with peaks appearing in close association with the latency changes of the two groups. Significance tests cannot yet be applied to determine whether the apparent differences in the curves are real. Taken together, the changes in the last three measures indicate that in the post-pulse period, and especially during ETI, the EEG was increasing in amplitude and becoming more synchronized at lower frequency values relative to preirradiation values.

The heart rate values in Figure 3F show an interesting apparent difference between ETI and non-ETI groups with the latter showing a larger increase in rate after the pulse. The sharp drop in the last three values for the ETI group is due to one animal which died shortly after the session. The average systemic blood pressure values of Figure 3G indicate that those animals that did not have an ETI exhibit a larger decrease in pressure after the pulse than those showing an ETI. However, the relative recovery of the non-ETI group is greater than that of the ETI group.

Table I presents medians of values for the indicated behavioral, EEG, and cardiovascular measures for each monkey over all epochs within a given category. Only those epochs preceding a green cue ("go" response cue) are considered. Latency of response shows a slight increase postirradiation in the correct category and reaches its maximum of 2 seconds in the omission category. Note that the median AM1L values drop from 4.42 to 4.27 to 2.96 Hz in the preirradiation correct, postirradiation correct, and postirradiation omission categories, respectively. ASDL values show the same trend, the two measures thus indicating that the EEG is shifting into a synchronous pattern at lower frequencies. The median values for power indicate relatively small differences between epochs appearing in the correct category preirradiation and postirradiation, but a sharp rise in power in the omission category.

Data for three of the EEG measures organized by behavioral category are presented in Table II. Each entry represents the ratio of average values of a given measure for all epochs in a given behavioral category for the indicated monkey. The ratio of a given measure consists of the mean value for epochs postirradiation divided by the mean value in that category of epochs in the preirradiation period. Thus a ratio with a value of less than one indicates a decrease in that measure and a value greater than one indicates an increase. Ratios were used rather than mean values so that data from all monkeys could be combined in spite of large individual preirradiation differences. The trend of the data was nearly always in the same direction. For example, considering the AM1L measure for the "go" epochs, five of the seven monkeys showed a drop relative to preirradiation values in the correct category and six of the seven decreased to even lower AM1L values in the omission category. This

Table I. Median Values of EEG, Cardiovascular and Behavioral Measures

Preirradiation "go" correct						
Monkey #	Latency (sec)	AM1L (Hz)	ASDL (Hz)	Power	Heart rate (beats/min)	Blood pressure (mm Hg)
34	0.7	5.03	2.91	5,356	--	--
43	0.8	5.55	2.55	2,572	120	124/71
110*	0.7	2.95	2.68	3,174	156	137/88
180*	1.1	4.42	2.63	1,602	164	104/73
299	0.8	3.73	2.73	32,058	202	144/92
653*	0.5	5.49	2.72	3,794	--	--
802*	0.7	3.31	2.53	8,960	--	--
Median	0.7	4.42	2.68	3,794	160	130/81
Postirradiation "go" correct						
34	0.9	4.32	2.58	5,608	--	--
43	0.9	4.32	2.60	5,095	254	97/57
110*	1.0	3.78	2.52	52,053	240	120/66
180*	1.2	3.68	2.54	1,719	228	85/75
299	0.9	4.27	2.46	29,009	259	83/71
653*	0.7	4.99	2.49	4,880	--	--
802*	0.8	2.75	2.46	5,322	--	--
Median	0.9	4.27	2.52	5,322	247	91/69
Postirradiation "go" omission						
34	2.0	2.96	2.40	10,643	--	--
43	2.0	4.29	2.22	1,702	265	107/62
110*	2.0	1.88	1.71	19,350	211	61/38
180*	2.0	2.42	2.33	2,676	154	87/77
299	2.0	4.60	2.39	37,959	272	84/75
653*	2.0	3.46	2.08	24,208	--	--
802*	2.0	2.27	2.02	14,713	--	--
Median	2.0	2.96	2.22	14,713	238	86/69

* Showed ETI within 15 minutes after pulse

Table II. Postirradiation to Preirradiation Ratios
(ETI included) for AM1L, ASDL and
Power

Monkey #	AM1L			
	"go"		"no go"	
	Correct	Omission	Correct	Incorrect
34	.86	.59	.89	.85
43	.78	.77	.82	.56
110	1.28	.64	1.63	2.22
180	.83	.54	.71	.87
299	1.15	1.23	.85	--
653	.90	.63	.84	.47
802	.83	.69	.72	.94
Median	.86	.64	.84	.86
ASDL				
34	.89	.82	.95	.93
43	1.02	.87	.92	1.01
110	.94	.64	1.03	1.06
180	.96	.88	.93	1.04
299	.90	.88	.89	--
653	.91	.76	.86	.94
802	.97	.80	.86	.95
Median	.94	.82	.92	.98
Power				
34	1.05	1.99	1.05	.96
43	1.98	2.61	2.02	3.96
110	16.40	6.10	7.80	5.74
180	1.07	1.67	1.16	.94
299	.90	1.18	1.57	--
653	1.28	6.38	3.45	3.68
802	.59	1.64	1.72	.53
Median	1.07	1.99	1.72	2.32

indicates that the center of mass of the spectral density plot shifted to lower frequencies after irradiation, and particularly before omissions. Similarly, for the ASDL measure there is a general shift downward after irradiation, indicating less spread in the power spectra; that is, the EEG frequency spectrum has narrowed. The EEG epochs of three monkeys (Nos. 43, 110 and 653) showed moderate to large increases in power (average amplitude) relative to preirradiation values in the correct category and all monkeys showed large increases in power in the omission category, most of them increasing by a factor of 2 or more. The data for the "no go" correct epochs follow the same general trend as the data in the "go" correct epochs. The data are less consistent in the incorrect category, but these values should be taken with caution since they are based on very few samples.

In Tables I and II the data were considered without regard to whether or not the monkey showed a significant ETI. Table III presents the same measures in the postirradiation period as Table II, but monkeys are separated according to extent of the ETI. The criterion was arbitrarily established as follows: if the monkey spends 2 or less consecutive minutes at zero percent correct response to the "go" cue, he is not considered to have a significant ETI. Zero performance for 3 or more consecutive minutes is considered a significant ETI. It appears that there are no large differences in any of the measures between median values in the correct category for the ETI and non-ETI groups. In the omission category, there are larger differences in median values between the ETI and non-ETI groups. However, the values for the non-ETI group in the omission category show larger changes from pre-irradiation values than do values for the non-ETI group in the correct category.

Table III. Postirradiation to Preirradiation Ratios
in the ETI and Non-ETI Groups for the
Correct and Omission Categories

Postirradiation "go" correct				
Group	Monkey #	AM1L	ASDL	Power
Non-ETI	34	.86	.89	1.05
	43	.78	1.02	1.98
	299	1.15	.90	.90
	Median	.86	.90	1.05
ETI	110	1.28	.94	16.40
	180	.83	.96	1.07
	653	.90	.91	1.28
	802	.83	.97	.59
	Median	.87	.95	1.18
Postirradiation "go" omission				
Non-ETI	34	.59	.82	1.99
	43	.77	.87	2.61
	299	1.23	.88	1.18
	Median	.77	.87	1.99
ETI	110	.64	.64	6.10
	180	.54	.88	1.67
	653	.63	.76	6.38
	802	.69	.80	1.64
	Median	.64	.78	3.89

Table IV presents the data in a manner to completely separate the values for epochs appearing in the ETI period from those outside that period. Each entry represents the median of a set of ratios for the indicated monkey, category, and measure. Each ratio in the set was calculated by dividing the value of the measure (AM1L, ASDL, or power) of a given epoch in the postirradiation period by the average value

for that measure in the given category in the preirradiation period. Considering the AM1L measure under the omission category, it can be seen that in five of the seven monkeys there was a greater reduction in the ETI period than in the non-ETI period relative to preirradiation values. Also, in five of the seven monkeys the reduction in AM1L non-ETI omissions was greater than the reductions in the correct category. The ASDL measure shows the same trend as the AM1L measure. Power is greater during ETI omissions than during non-ETI omissions in five of the monkeys and is generally greater in both omission categories than in the correct category.

Table IV. Median Values of Postirradiation to Preirradiation Ratios for the "Go" Category

Monkey #	Correct			Omission					
	Non-ETI			ETI			Non-ETI		
	AM1L	ASDL	Power	AM1L	ASDL	Power	AM1L	ASDL	Power
34	.88	.87	1.00	.50	.86	2.74	.61	.80	1.33
43	.83	1.07	1.15	.72	.88	2.31	.66	.77	2.93
110	1.43	.92	8.52	.66	.61	6.60	.59	.88	1.61
180	.79	.99	1.03	.52	.91	1.69	.73	.88	1.32
299	1.01	.94	.81	1.09	.79	1.22	1.33	.91	.88
653	1.01	.92	.82	.45	.68	7.52	.64	.87	2.27
802	.79	.94	.50	.61	.70	1.28	.82	.76	1.49
Median	.88	.94	1.00	.61	.79	2.31	.66	.87	1.49

IV. DISCUSSION

These data provide support to the earlier work cited in regard to EEG changes following irradiation and also provide some interesting differences. With the higher doses and whole-body irradiation used here, the onset of a high amplitude slow wave EEG was generally more rapid. For example, as can be seen in Figure 3, such

changes in the EEG measures generally occurred within 10 minutes after the pulse. This is comparable to the time periods in which Brooks⁵ found EEG changes after whole-body gamma irradiation, and Tsuya³² after 5000-15,000 R gamma irradiation to the head. The appearance of EEG slow waves is in contrast to the arousal EEG found by Gangloff and Haley¹⁴ at 400 R total body x irradiation, by Monnier and Krupp²² with 400-600 R gamma irradiation to the head, and Caster et al.⁸ with 700 R total body x irradiation. However, when Monnier and Krupp increased the dose to 900 R, they did find slow waves appearing in the EEG. Similarly, Ross et al.²⁷ found a dose effect between the appearance of EEG slow waves and magnitude of dose. This was probably related to the differences in rapidity of development of neurological damage and extent of damage at the various dose levels. The differences in species and radiation sources make generalizations difficult, but there is a suggestion that low or moderate doses of radiation affect the nervous system differently than high (over 900 R) doses. The slow wave phenomena may be associated with the dendritic and other cortical disorganizations found by Caveness et al.⁹⁻¹² or with biochemical or cardiovascular dysfunctions related to the higher radiation doses.

The finding of Adey and Schoenbrun¹ of a delayed decrement in performance after whole head irradiation but lack of decrement (except for increased response latency) with higher doses directed to the two hippocampi suggests that the performance decrement found in this study is related either to neural structures other than the hippocampus or to other physiological dysfunctions mediated by the brain. This suggestion must be tempered by the realization that species, task, and radiation sources differed in the two experiments.

There were two prime objectives of the present study: one was to find EEG correlates of the ETI period perhaps comparable to some of the EEG changes found in various stages of coma^{13,21,31} and the other was to begin a search for EEG changes associated with making correct or incorrect responses. In regard to the first objective, reference to Figure 3 shows that there is usually, coincident with the ETI period, a drop in AM1L and ASDL values and an increase in EEG power levels. In addition, the data of Table I indicated that while there was a general shift downward in values of AM1L and ASDL for EEG epochs preceding correct responses, the shift was even greater for those epochs preceding omissions. Most of these omissions occurred in the ETI period. As noted in the results section, median power levels were higher for omissions than for correct responses, indicating increased EEG amplitude in the former case. This general finding is substantiated again in Table II, using ratios and medians throughout and considering all the data postirradiation. Overall, in the "go" cue category (must make a response to avoid shock) the AM1L and ASDL values decrease in the omission category relative to the correct category, and power increases during omissions. The data in the "no go" category (must not make a response to avoid shock) are less consistent. This is primarily due to the few cases in this category. The data thus far considered provide support for the contention that changes in EEG measures can be used to characterize the ETI period.

Support for the second objective, to provide EEG indices of correct or incorrect responses, is not yet clear since most of the omissions occur in the ETI period. Therefore the values in Table III are organized to differentiate between monkeys showing a distinctive ETI and those that do not. There appear to be no particular

differences between the two groups of monkeys (with and without an ETI) in the correct category, but in the omission category, differences are evident. The influence of the ETI period in lowering the average frequency and raising the average amplitude of the EEG, as indicated by the AM1L, ASDL, and power values, is seen in Table IV where the omission category is separated into those epochs in the ETI period and those in the non-ETI period. Values in the ETI period are shifted to a greater degree than those in the correct category relative to the preirradiation values, those omissions in the non-ETI period are synchronized over lower frequencies and exhibit higher average amplitudes than are characteristic of the correct category. The shifts in EEG values noted here are not to be construed as anticipatory in the sense of a sudden change before a cue presentation. A more reasonable interpretation of these results is to postulate that if a cue light should appear when the EEG is in a high amplitude slow wave condition, the probability of an error is greater than if the cue light appeared when the EEG is closer to a normal wave form. This would seem to provide support for the second objective of differentiating by EEG measures between correct and incorrect responses, but such a conclusion is premature. This is due to the fact that the data for individual EEG epochs (not shown) indicate that not only are there AM1L values for correct responses as low as those for omissions in the ETI period, but in the period following ETI there are omission AM1L values as high as the pre-irradiation normal values. The same overlap holds for both ASDL and power values. This result is not too surprising since only cortical EEG is being considered in this report, and reports in the literature indicate that relationships between cortical and subcortical EEG's must be measured to provide indices of the correctness of a

response. The finding in most cases of a change in EEG spectral characteristics in the same time period as the behavioral ETI suggests that those changes may be a useful index of behavioral incapacitation. The differences in degree of EEG change in the ETI period and the period following ETI further suggest an objective rationale for separating the behavioral impairments after irradiation into a period of total incapacitation, the ETI period, and a period of performance decrement after the ETI.

A subsidiary objective of this experiment was to investigate the relationship of systemic blood pressure to EEG and behavioral change. These measures were obtained on only four of the monkeys. There was a consistent drop in blood pressure and pulse pressure shortly after irradiation and these measures never quite achieved preirradiation values thereafter. These results were consistent with the findings of Turbyfill et al.³³ Why that group of monkeys not showing an ETI within 15 minutes after the pulse should exhibit a greater drop in blood pressure than the group showing an ETI within that time period is not known. The non-ETI group did have a larger heart rate increase at this time and thus perhaps better maintained cardiac output. The lack of a close correlation between blood pressure changes and behavioral changes can be seen in Figure 3A and G where performance deteriorated badly 40 minutes after the pulse, but systemic blood pressure and pulse pressure stayed at lowered levels from ETI to the end of the session. Cardiovascular changes did not appear to follow EEG changes as can be seen in Figure 3C-G.

V. SUMMARY

In summary, a means of EEG analysis which allows quantitative measurement of EEG changes as a function of the ETI period has been devised. When this type of

analysis plus correlational techniques now being worked out are applied to subcortical EEG records as well as to the cortical signals, the probability rises that EEG indices of correct or incorrect response types can be found. In addition, refinements are being made in the cardiovascular measurements which may reveal cerebral blood flow changes associated with EEG and/or behavioral changes. The additional subcortical placements will also permit mapping the relative radiosensitivity of brain regions, thus providing clues to the mode of action of radiation on the central nervous system and to possible behavioral consequences of such regional radiosensitivity.

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13. ABSTRACT Cortical EEG recording leads were implanted in seven rhesus monkeys (<u>Macaca mulatta</u>). The monkeys were then trained to perform a visual discrimination task. After the animals had been trained to acceptable levels of performance, blood pressure measuring devices were surgically implanted. Two weeks after surgery the monkeys were irradiated with a single 2500-rad whole-body pulse of mixed gamma-neutron radiation from the AFRRI-TRIGA reactor. EEG, behavioral, and cardiovascular parameters were continuously monitored and recorded on magnetic tape. The EEG was analyzed by a power spectral density procedure, and various measures, including first and second moments of the spectra, were obtained. Relationships between these EEG measures, behavioral changes, and cardiovascular alterations were then studied both preirradiation and postirradiation. Some degree of apparent relationship was found between changes in the EEG measures after irradiation and changes in performance, particularly during the early transient incapacitation (ETI) period. This relationship could not be well established in the period following ETI or between behavioral and cardiovascular changes. A consistent relationship between cardiovascular and EEG changes was not established.			