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Effects of Sublethal Doses of Ionizing Radiation on Repeated Acquisition in Rats

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WINSAUER, P. J. AND P. C. MELE. *Effects of sublethal doses of ionizing radiation on repeated acquisition in rats.* PHARMACOL BIOCHEM BEHAV 44(4) 809–814, 1993. – To extend previous research on the effects of ionizing radiation on learning, dose-effect data with ^{60}Co γ-rays were collected for individual rats responding under a repeated-acquisition procedure. Under this procedure, subjects acquired a different three-response chain each session by responding (nose push) on one of three transilluminated response keys in the presence of each of three sequentially ordered colors. The response chain was maintained under a second-order fixed ratio (FR) 2 schedule of food presentation. An error produced a 5-s timeout but did not reset the three-response chain. Acquisition of each response chain was defined by a decrease in errors as the session progressed (i.e., within-session error reduction). Each session ended after 200 reinforcements or 90 min, whichever occurred first. When day-to-day acquisition for all four subjects reached a steady state, the effects of three or four doses of γ-rays were assessed. In general, radiation doses of 1, 3, 4.5, and 8 Gy of gamma radiation delivered at a dose rate of 2.5 Gy/min produced a dose-dependent decrease in the overall response rate for 24–72 h after exposure in all four subjects. Radiation exposure also produced an increase in percent errors but only at doses that substantially decreased overall rate of responding. Unlike the effects on response rate, which were relatively consistent over a 72-h period, the effects on accuracy were greater at 72 h than at 24 h in three of four subjects. The results indicate that the repeated-acquisition procedure may be particularly useful for quantifying the effects of ionizing radiation on acquisition behavior or learning and that γ-rays can differentially affect behavioral measures of rate and accuracy over a 72-h period following exposure.

Repeated acquisition Operant behavior γ-rays Rats

FEW studies have examined the effects of ionizing radiation on learning, or the acquisition of behavior. Moreover, these studies, which involved both monkeys and rats, have produced widely differing results ranging from improved to disrupted learning [see (15) for review]. In the studies involving monkeys, for example, the reported inconsistencies can often be attributed to different tasks or doses and types of radiation or simply to the lack of data in general. However, in the rat studies where the effects of radiation have in general been tested on only one type of learning (i.e., maze learning), the inconsistencies in the data are still marked. Two reports (3,9), for example, found that rats exposed to either 4.8 Gy of whole-body X-rays or 24.2 Gy of cranial X-rays actually performed better on a maze task than nonirradiated control rats. Although the effects in these studies have been explained in various ways (e.g., irradiated subjects may be less distractible), the failure to find convincing evidence that ionizing radiation affects the acquisition of behavior in a consistent manner is somewhat surprising.

One possible explanation may be related to the fact that there are large individual differences in rates of acquiring behaviors. This aspect of learning, along with the well-established finding (11) that subjects reacquire specific tasks at a faster rate (i.e., subjects "learn to learn"), have consistently posed problems for the study of learning and those variables affecting it. For these reasons, as Anger and Setzer (1) state in their article examining the effects of a pesticide on learning, certain types of learning such as maze learning may not be the most appropriate baseline for the evaluation of toxic agents because it can be a one-time learning phenomenon and is not repeatable in the same subject [cf. (17)]. The important distinction between testing the effects of a toxic agent on learning and testing the effects of a toxic agent on retention of learning was demonstrated in a radiation study by Urmer and Brown (24). They found that sublethal doses of ionizing radiation in rats produced no disruptive effects on the retention of response patterns acquired preirradiation but did produce a decrement in the capacity of subjects to reorganize the

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For ease of comparison with previous research, all the radiation doses cited (either roengten or rad) have been converted to Gray (Gy). The conversion factor for roengten to rad is 0.966 to account for the difference between air and muscle. Rad can be converted to Gray by multiplying the dose by 1/100.

preirradiation response pattern into a new response pattern postirradiation.

To deal with some of the problems involved in studying learning and the effects of drugs on learning, for example, Thompson (21,22) adapted a repeated-acquisition technique and used each subject as its own control. The repeated acquisition of behavioral chains provided a baseline under which the effects of various drugs on learning could be examined repeatedly, and the use of each subject as its own control helped deal with the problem of intersubject variability. The results indicated that repeated-acquisition procedures provide a sensitive baseline for assessing the effects of drugs on learning in individual subjects and that learning was more sensitive to drug effects than a performance condition where learning was not required. Shrot et al. (18), for example, developed this procedure in rats to examine the effects of microwave radiation on learning. Although there were methodological differences (e.g., only a single condition and auditory cues vs. visual cues), they found that microwave radiation was highly disruptive to learning at certain power densities. Since then, other investigators have effectively used this procedure with a variety of species to examine the effects of many toxic agents [e.g., carbon monoxide (19), carbaryl (1), and lead (7)] on acquisition behavior.

To examine the effects of ionizing radiation on learning in individual rats, the present research used a repeated-acquisition task similar to that used by Thompson (21,22). More specifically, the subject's task was to acquire a different three-response chain each session by responding sequentially on three keys in the presence of three colors. Acquisition of each response chain was defined by a decrease in errors as the session progressed. Following baseline stabilization where acquisition for each subject reached a steady state, dose-effect data were obtained for three or four doses of ^{60}Co γ-rays.

METHOD

Subjects

Four adult male Sprague-Dawley rats (R-9, R-13, R-14, and R-16) maintained at approximately 80% of their free-feeding weights (373, 404, 373, and 393 g, respectively) served as subjects. Food was earned during the experimental session and, if necessary, was provided in the home cage after the session to maintain subjects at their 80% weight. All subjects were housed individually in plastic Microisolator cages containing sterilized hardwood-chip bedding. The housing room was maintained at 21 ± 1°C with 50 ± 10% relative humidity on a 12 L : 12 D cycle, which began at 6:00 a.m. each day. Acidified water (pH 2.5–3) was available in the home cage throughout the experiment to minimize the possibility of opportunistic bacterial infection. Each subject had an extensive history of repeated acquisition of three-response chains under fixed-ratio (FR) schedules.

Apparatus

Four identical modular test chambers (Coulbourn Instruments, Inc., Model E10-10TC) configured specifically for rodents were used. The front wall of each chamber contained a houselight, speaker, auditory feedback relay, pellet trough (10 cm above the floor and centered), and three response keys aligned horizontally (8 cm apart, center to center, and 4.5 cm above the floor). Each response key could be transilluminated by three Sylvannia 28ESB indicator lamps, one with a red plastic cap, one with a green, and one with a yellow. Response keys required a minimum force of 0.15 N for activation and produced an audible click of the feedback relay. Each chamber was enclosed within a sound-attenuating cubicle equipped with a fan for ventilation. White noise was continuously present in each chamber to mask extraneous sounds. The chambers were connected to a PDP11/73 computer (Digital Equipment Corp., Bedford, MA) programmed in SKED-11 software (State Systems, Inc., Kalamazoo, MI) and to cumulative recorders (Gerbrands Corp., Arlington, MA) located in a nearby room.

Procedure

Baseline. During each session, all three response keys were illuminated at the same time with one of three colors, either green, red, or yellow. The rodent's task was to respond (nose push) on the correct key in the presence of each sequentially illuminated set of colors (e.g., keys green, center correct; keys red, left correct; keys yellow, right correct; reinforcement). The same chain [in this case, center-left-right (CLR)] was repeated throughout a given session. The three-response chain was maintained by food presentation under an FR 2 schedule, that is, every second completion of the chain illuminated the pellet trough and produced a 45-mg pellet. A completion of the response chain that did not produce food was followed by a 0.4-s presentation of the pellet trough light. When the subject pressed an incorrect key (in the example, the left or right key when the green light was presented), the error was followed by a 5-s timeout. During the timeout, the key lights were turned off and responses had no programmed consequence. An error did not reset the three-response chain, that is, the stimuli were the same before and after the timeout.

To establish a steady state of repeated acquisition, the three-response chain was changed from session to session. A typical set of five chains was CLR, RCL, LRC, CRL, and RLC, with the order of the color presentations always green, red, yellow (reinforcement). The chains were carefully selected in several ways and there were restrictions on their ordering across sessions. More specifically, each sequence was scheduled with equal frequency and adjacent positions within a sequence for a given session were different. Occasionally, a correct sequence position for a given color was the same two sessions in a row.

Sessions were conducted Monday through Friday between 9:00 a.m. and 2:00 p.m. Each session was terminated after 200 reinforcements or 90 min, whichever occurred first. The data for each session were analyzed in terms of a) the overall response rate (total responses/min, excluding timeouts) and b) the overall accuracy, expressed as percent errors [(errors/total responses) × 100]. In addition to these measures based upon session totals, within-session changes in responding were monitored by a cumulative recorder and the computer. For example, acquisition of a response chain was indicated by within-session error reduction, that is, a decrease in the number of errors between food presentations as the session progressed.

Radiation testing. Following baseline stabilization, dose-effect data were obtained for multiple doses of gamma radiation. Subjects received bilateral, whole-body, midline tissue doses of 1, 3, 4.5, and 8 Gy of γ-rays administered at a fixed rate of 2.5 Gy/min from a ^{60}Cobalt source. These doses were selected from a range of doses previously found to have an effect on other schedule-controlled operant behaviors [e.g., fixed-interval (FI) and FR schedules (13)]. In general, doses of radiation were given in a mixed order except for the 8-Gy dose, which was administered last in three of four subjects. Subject R-16 received the 8-Gy dose as a third exposure and

was allowed 13 weeks of baseline recovery before being given a final 4.5-Gy exposure. The minimum time between exposures for doses less than 8 Gy was 4 weeks. This interval was chosen to allow for a) complete baseline recovery [cf. (13)] and b) the collection of sufficient control data prior to the next exposure.

For irradiation, subjects were placed in well-ventilated, clear plastic restraining tubes. A clear plastic stand, which held the tubes in a stacked position, allowed all four subjects to be exposed at one time, if desired. Dosimetry for bilateral irradiations was completed prior to the actual animal irradiations. Standard Task Group 21, Radiation Therapy Committee of the American Association of Physicists in Medicine (AAPM), protocol procedures (20) were used. A 50-cm^3 ionization chamber was used to obtain the free-in-air (FIA) tissue dose rate at the appropriate exposure position. A 0.5-cm^3 tissue-equivalent ion chamber was also used to obtain the tissue dose rate in the same position in a tissue-equivalent rat phantom. The tissue-to-air ratio (TAR) was calculated by dividing the nominal 0.5-cm^3 chamber reading by the 50-cm^3 chamber reading. The administered dose (midline tissue at the abdomen) to each animal was determined by the TAR value, the FIA value, duration of the irradiation, and other factors such as temperature and pressure. Each irradiation was conducted on a Monday and required approximately 20 min. This time included the actual exposure and the time necessary for transporting rats to and from the exposure area. Sham irradiations, which also included transport, consisted of subjects' being placed in the restraining tubes for a comparable amount of time.

RESULTS

Under baseline conditions, stable responding in the repeated-acquisition task was obtained in each of the four subjects. Stability was reflected in the consistent levels of overall response rate and accuracy for each subject from session to session. Acquisition of response chains was characterized by a steady state in terms of stable within-session error reduction, that is, the number of errors decreased as each session progressed.

Figure 1 shows the overall response rate and percent errors for each subject during control sessions and sessions at 24 and 72 h following γ-ray irradiation. Although all subjects were tested daily after radiation exposure, the data from these two sessions most clearly illustrate the effects obtained. In general, the effects at 48 h after exposure were comparable to those at 24 h; and in three of four cases, those at 96 h were comparable to those at 72 h. For the sessions presented, a dose of radiation was considered to have an effect to the extent that the postirradiation data fell outside the control range. As shown in the upper panel, despite relatively large individual differences in the control ranges, radiation exposure dose dependently decreased the overall response rate in each of the four subjects during both the 24- and 72-h sessions. Although there was an instance in which the effect of radiation at 72 h was larger than that at 24 h (i.e., the rate-decreasing effect obtained at the 8-Gy dose in RP-16), the effects on response rate during the 24-h session were in general larger than or consistent with those that occurred 72 h after exposure. This was in particular evident in RP-16 and RP-9 at the 4.5-Gy dose, where the rate-decreasing effects obtained 24 h after exposure were notably larger than those obtained 72 h after exposure.

As can be seen in the lower panel of Fig. 1, the differences in control ranges for percent errors across subjects were not as large as those for overall response rate (i.e., accuracy was comparable for all four subjects). In general, exposure to radiation produced dose-dependent increases in percent errors in each subject. These effects were most evident at the 8-Gy dose for both the 24- and 72-h sessions. In this regard, the effects on accuracy were unlike those on overall response rate, where an intermediate dose (4.5 Gy) of radiation produced an effect in three of four subjects. Note that exposure to 4.5 Gy only increased percent errors in RP-16 and RP-9 at 72 h. In other words, decreases in response rate tended to occur at lower doses than those required to increase percent errors and increases in percent error occurred only at doses that substantially decreased overall response rate.

Interestingly, the effects of the 8-Gy dose of radiation on percent errors were different from the effects on response rate in that percent errors were affected more at 72 h than at 24 h in three of four rats. In these three rats, the increase in percent errors at 72 h occurred at a time when the overall response rates were comparable to those at 24 h. Moreover, in RP-9 this noticeably larger effect at 72 h occurred at the 4.5-Gy dose of radiation when the decrease in overall response rate was less than that which occurred at 24 h (i.e., at a time when response rate appeared to be returning to control levels).

Figure 2 illustrates some of the within-session effects of an 8-Gy dose of radiation in subject RP-9. Each cumulative record represents a complete session from a different day. As can be seen in the control record, errors decreased in frequency while the number of correct completions of the chain increased in frequency as the session progressed. This within-session error reduction, which occurred shortly after the start of the session, reflects acquisition of the response chain. Following acquisition, the pattern and rate of correct responding remained relatively constant throughout the session. Although some pausing did occur toward the end the session, the rat did obtain the total number of available reinforcers. At 24 h after an 8-Gy dose of radiation (middle record), there was a substantial decrease in the overall rate of responding, a decrease in the number of correct sequence completions, and an increase in pausing. Note that periods of no responding occurred earlier in the session and were longer in duration than under control conditions. In addition, there was little evidence of any within-session error reduction, as indicated by the relatively constant error rate that occurred on the event pen when the subject was responding. At 72 h after the 8-Gy exposure (bottom record), similar within-session effects on overall response rate occurred. As can be seen, long pauses occurred throughout the session and the total number of reinforcers obtained during the session was substantially reduced. In this session, however, the total number of errors was greater than that in the 24-h session even though the overall response rate was comparable. This difference in accuracy is evident in the pattern and frequency of errors indicated by the event pen in both records. In general, the within-session effects of this dose of radiation were replicated in two of the remaining three rats. Although RP-16 did show an increase in percent errors and a decrease in overall response rate at this dose, there was little or no difference in the within-session effects at 24 and 72 h.

Three of four rats (RP-9, RP-13, and RP-16) received a total γ-ray dose of 16.5 Gy. The other rat, RP-14, received a total dose of 13.5 Gy. This total dose was lethal in RP-9, RP-13, and RP-14. RP-9 and RP-13 died within 2 weeks of their final 8-Gy exposure, whereas RP-14 (the subject that received the smallest total dose) died more than 2 months later after completely recovering baseline levels of responding. The

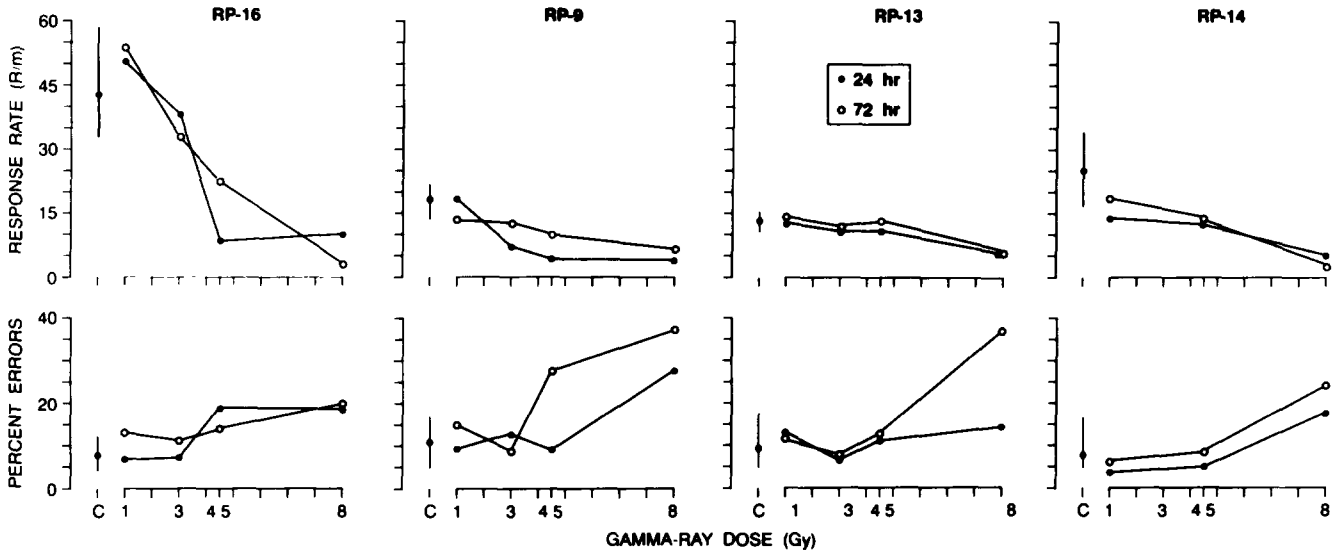

FIG. 1. Effects of varying doses of ^{60}Co γ-rays on the overall response rate (upper panel) and percent errors (lower panel) for each subject. The unconnected filled point and vertical line at C indicate the mean and range of the control data (i.e., data from the 10 baseline sessions immediately preceding the first exposure and 2–5 sessions between irradiations where sham exposures were conducted). The filled points indicate the data obtained 24 h after each exposure; the open points indicate the data obtained 72 h after each exposure.

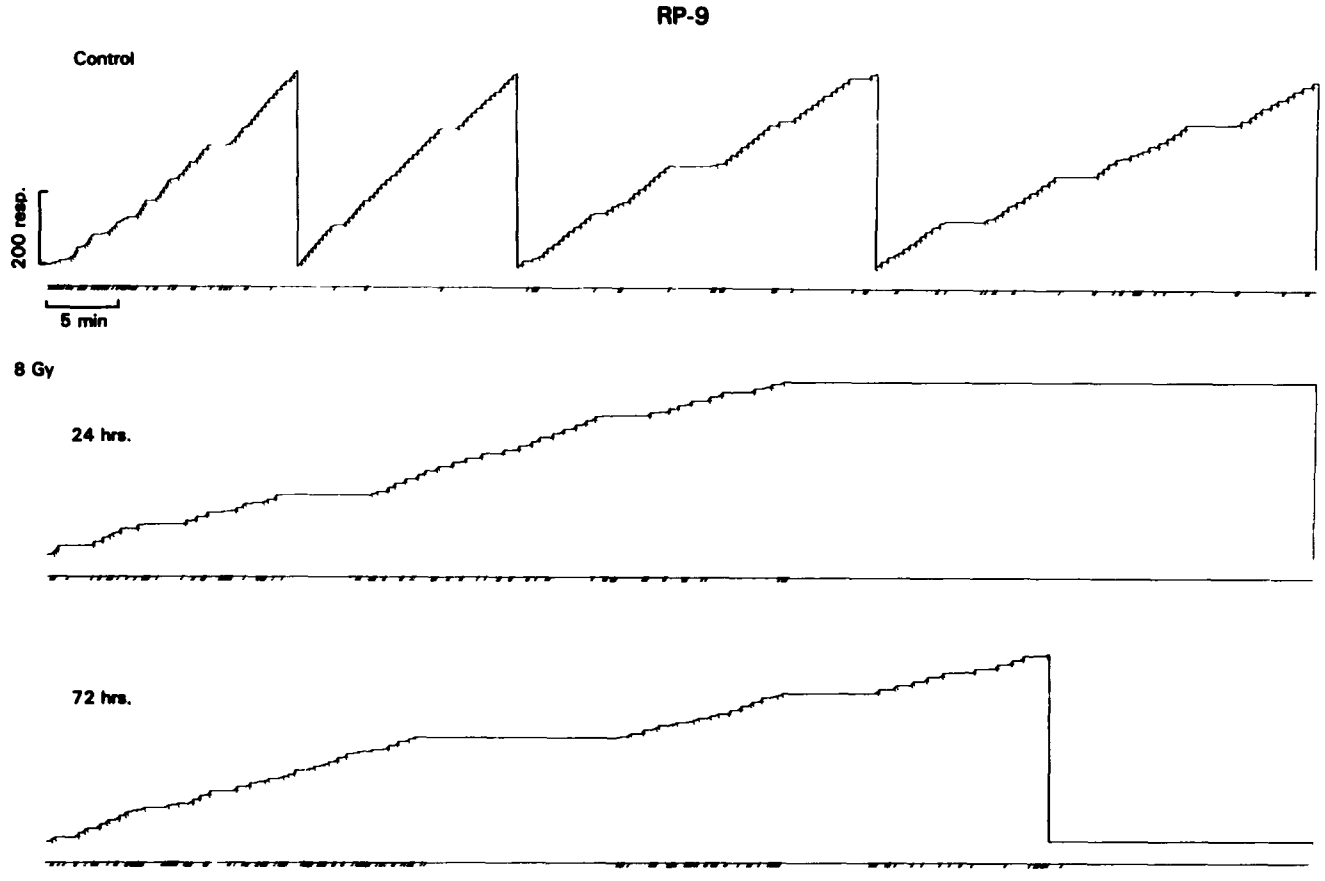

FIG. 2. Within-session effects of ^{60}Co γ-rays during a control session (top record) and two sessions following exposure to an 8-Gy dose (middle and bottom records) in subject RP-9. Each of the three cumulative records is from a different day and shows a complete 90-min session. In each record, the response pen stepped upward with each correct response and was deflected downward each time the three-response chain was completed. Errors are indicated by the event pen (below each record), which was held down for 5 s during each timeout.

surviving subject, RP-16, received the 8-Gy dose and a 4.5-Gy dose 13 weeks afterward. Except for small decreases in food intake for several days following exposure, this subject remained in good health with baseline recovery after each exposure.

DISCUSSION

Unlike many of the previous studies examining the effects of ionizing radiation on acquisition behavior in rats, the present experiment found substantial effects on both rate and accuracy of responding after administration of 1-8 Gy of γ-rays. The large dose-dependent effects on overall response rate were similar to effects found in other studies using either X-rays or γ-rays and schedule-controlled operant behavior (4,5,12, 13,25). In these studies, whole-body irradiation with comparable doses produced dose-dependent decreases in responding regardless of the schedule (fixed ratio or variable interval) or positive reinforcer (food or water) used. Wicker and Brown (25), for example, found that repeated exposures with 1.9, 3.9, and 7.7 Gy of gamma radiation decreased responding under an FR 1 schedule of water presentation. More recently, Mele et al. (13) reported that 4.5 and 6.5 Gy of whole-body γ-ray exposure produced marked decreases in overall responding under an FR 50 schedule of milk presentation. As in the present study, the effects on response rate in that study tended to peak 24 h after exposure and remained evident for extended periods of time (e.g., 5 days) depending upon the dose administered. Also of note was the fact that repeated exposures at 6- to 9-week intervals showed no evidence of cumulative behavioral effects. More specifically, repeated exposures in the same subjects with the same doses produced reliable redeterminations whereas a subsequent exposure after these redeterminations with a different dose produced dose-dependent effects.

The effects of gamma radiation on accuracy in the present study were in general different from those found in previous studies involving other complex acquisition tasks (i.e., maze acquisition tasks). Only a few studies have reported error-increasing effects (6,8,24), and only two found effects of whole-body irradiation at comparably low sublethal doses and post-exposure days. Fields (8), for example, reported that maze errors in an elevated T-maze were greatest 72 h after exposure to 3.5 or 5.8 Gy of X-rays. Other maze studies, however, have found acquisition behavior relatively unaffected (2,9) or enhanced (3) after radiation exposure. Although the disruption of acquisition behavior under the repeated-acquisition task in this study occurred only at doses that substantially decreased overall response rate, the effects on percent errors were clearly evident in all four subjects. In one of the few other rodent studies using a repeated-acquisition procedure and a within-subject design, error-increasing effects were reported with microwave radiation. Schrot et al. (18) found that microwave exposure at varying power densities dose dependently increased errors four to six times over control levels while decreasing sequence-completion rates. In addition, higher power densities of microwave radiation completely disrupted the pattern of acquisition in each of the subjects tested.

The effects on accuracy in the present study may have been more extensive than those found in other studies involving ionizing radiation for a variety of reasons. First, use of a within-subject design may have helped eliminate some of the variability that can often obscure effects on learning in group studies [cf. (21)]. Another possibility is that the repeated-acquisition task used in the present study may be more sensitive than other tasks for examining the effects of radiation on acquisition behavior. Studies investigating the effects of both ionizing radiation (8,24) and microwave radiation (10,18) on accuracy have noted that complex behavioral tasks are more sensitive to radiation than simple behavioral tasks. This view has already been demonstrated to be true for a variety of drug effects (22,26). In regard to radiation effects, for example, Urmer and Brown (24) reported that the effects of 4 Gy of gamma radiation on learning were most notable when the subject was rechallenged or asked to "reorganize" a preirradiation response pattern into a new response pattern. If procedural manipulations of this type are critical to showing radiation-induced deficits in learning, as the authors suggest, a repeated-acquisition task may be particularly sensitive because subjects are rechallenged (i.e., required to learn a different sequence) daily.

A simple explanation could be that many prior studies (2,3,6,9) failed to examine the effects of radiation at the critical times postexposure. In the present study, the effects on percent errors were greater at 72 h than at 24 h in three of four subjects. These effects on accuracy were unusual in that peak effects on percent errors were obtained long after the onset of effects on overall response rate. Different time courses for radiation-induced decreases in response rate (and for recovery from such decreases) have already been shown to be partially dependent upon the schedule of reinforcement, type of reinforcer (positive or negative), and even the particular behavior being tested (12–15). However, these factors have not yet been shown to influence radiation-induced effects on accuracy. One factor that has been shown to play a role in the effects on response rate, but been restrictive to establishing effects on accuracy, is radiation sickness (i.e., a syndrome generally characterized in a variety of species by weakness, fatigue, lethargy, and a decrease in food intake). The influence of radiation sickness has previously been so problematic in many maze studies (3,6,9) that investigators have tested for effects on learning after long postirradiation intervals (e.g., 20–60 days). Unfortunately, all of these studies failed to find any significant disruptions of learning following radiation exposure.

The present study does seem to indicate that decreased motivation resulting from radiation sickness cannot solely account for the disruptive effects on accuracy and that motivational deficits associated with radiation sickness may have a time course independent of that for radiation-induced decreases in accuracy. At the doses tested (1–8 Gy), onset of radiation sickness in rats would in general be expected within the first 24 h after radiation exposure. Jarrard (12), for example, has shown that decreases in food consumption were clearly evident 24 h after exposure and beginning to return to baseline 72 h after exposure depending upon the dose. In their study on the effects of radiation on schedule-controlled performance, Mele et al. (13) also stress that there are severe limitations on attempts to relate radiation-induced changes in performance to specific food intake changes that occur during radiation sickness. They found little correlation between the magnitude and time course of disruption in performance and whether or not postsession chow was consumed. Moreover, repeated-acquisition studies with both monkeys (23) and pigeons (21) have specifically shown that prefeeding manipulations (which decrease deprivation level and, thereby, the effectiveness of food reinforcement) generally produce rate-decreasing effects but little or no effects on accuracy.

As was the case with another ^{60}Co gamma radiation study involving operant schedules of reinforcement and food pre-

sentation (13), lethality in this study did not appear to be strictly the result of the total cumulative dose received. Rather, lethality seemed to depend upon the order of doses administered and the interirradiation interval. Given the small number of animals used, it is impossible to say with any certainty to what degree lethality was influenced by radiation history. However, it should be noted that the lethal effects of radiation on individual subjects in this study were in accordance with previously established effects of γ-rays or X-rays on groups of rodents. Specifically, dose fractionation increased the total cumulative dose that could be tolerated without producing lethality (13,16), and recovery from behavioral disruptions did not necessarily reflect recovery from the long-term physiological effects that produce lethality (13,15). This last point was reflected in the present study, and in the Mele et al. study (13), by the fact that there was often a temporal separation between the more acute behavioral disruptions and the lethal effects. In the present study, for example, two of the three rats that died did so many days after showing more immediate behavioral disruptions. The third rat, RP-13, died over 2 months after completely recovering baseline levels of responding. Moreover, the data from the surviving subject (RP-16) seems to indicate that future studies that incorporate longer interirradiation intervals after high doses could potentially provide the same information about the acute effects of γ-rays on learning without obtaining a lethal effect.

In summary, the present research found that acute sublethal exposure to ionizing radiation readily disrupts learning in individual rats responding under a repeated-acquisition procedure. Although overall response rate was more sensitive to disruption than percent errors (i.e., decreases in response rate tended to occur at doses lower than those required to increase percent errors), presentation of three or four graded doses of ^{60}Co γ-rays did produce dose-dependent disruptive effects on both overall response rate and accuracy in all subjects tested. Of further importance was the finding that percent errors at a given dose were differentially affected during a 72-h period postexposure. Unlike the effects on response rate, which were relatively consistent (or in some cases lessened) over the 24- and 72-h periods after exposure, the effects on percent errors were notably larger at 72 h than at 24 h. Together, these findings emphasize the need for extending the evaluation of the effects of ionizing radiation in both rats and other species using complex operant procedures such as repeated acquisition.

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