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Effects of Sublethal Doses of Ionizing Radiation on Schedule-Controlled Performance in Rats[1]

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MELE, P. C., C. G. FRANZ AND J. R. HARRISON. *Effects of sublethal doses of ionizing radiation on schedule-controlled performance in rats*. PHARMACOL BIOCHEM BEHAV 30(4) 1007–1014, 1988.—Male rats responded under a fixed-ratio (FR) 50 or a fixed-interval (FI) 120 sec schedule of milk delivery. Separate groups were acutely exposed to 0.5, 1.5, 4.5 or 0 (FI only) Gray (Gy) of cobalt-60 gamma radiation 3 times at 43-day intervals. All rats received an acute dose of 6.5 Gy 64 days after the last of these exposures. One-half and 1.5 Gy did not alter FR or FI performance significantly. After 4.5 Gy, no observable changes in performance occurred within 1 hr of exposure. Maximal reductions in FR response rates occurred 24 hr after exposure and recovery followed over the subsequent 72 hr. Postreinforcement pause was increased and running response rate was decreased by 4.5 Gy. Similar effects were found after each 4.5 Gy exposure. In contrast, FI performance (overall response rate, postreinforcement pause, running response rate, index of curvature) was not altered reliably by 4.5 Gy. Both FR and FI response rates were reduced by 6.5 Gy beginning 24 hr after exposure; FR rates tended to be reduced more than FI rates 24–72 hr after exposure. Response rates under both schedules recovered gradually over 7 weeks. The behavioral effects of 6.5 Gy did not vary as a function of irradiation history. In contrast, irradiation history affected survival in that 4/9 rats previously exposed to 4.5 Gy died during weeks 4–5 after 6.5 Gy, whereas there were no deaths in the rats previously exposed to lower doses. Radiogenic disruption of operant performance was dose-related, reversible, noncumulative and dependent on the schedule of reinforcement.

Ionizing radiation Sublethal doses Repeated exposures FR, FI performance

IONIZING radiation became of interest nearly a century ago after Roentgen's discovery of X-rays in 1895 [35]. Since that time, both the beneficial and detrimental effects of ionizing radiation have received much attention. Human exposure to ionizing radiation above background levels has occurred through clinical treatment, the work place environment, industrial accidents, and immediate and delayed effects of nuclear weapon detonations [19]. Recent accidents at the Three Mile Island [1] and Chernobyl [2,21] nuclear power plants point to the current possibility of large-scale population exposure to radiation. The problems posed for manned space travel by ionizing radiation are receiving a growing amount of attention [4, 28, 36].

Exposure to ionizing radiation produces a dose-dependent sequella of signs and symptoms that progresses over time [19,33]. In humans, early effects of relatively low doses of radiation may include weakness, fatigue, nausea, vomiting, anorexia, and headache. These effects have a latency to onset of several hours and may last for hours, days or weeks [40]. As the dose of radiation is increased up to the 30 day LD_{50}, hemopoietic damage (loss of functional blood cells) occurs in most mammals and increases in severity for up to 4–6 weeks after expousre [33]. Further increases in dose produce lethal gastrointestinal damage within 1–2 weeks of exposure, while yet higher, supralethal doses produce cardiovascular shock, neuronal damage and death within hours or days.

Dose- and time-related changes in the behavior of animals following expousre to ionizing radiation have been studied for some time (see [18,25] for reviews). Included among the behaviors studied are locomotor activity [23,29,32], motor performance [5,13], food and water intake [29,31], conditioned taste aversion [34], maze performance [14,16], conditioned avoidance responding [12,20], and responding maintained by schedules of positive or negative reinforcement [7–11, 22, 39]. Typically, ionizing radiation depresses

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behavioral output with the magnitude and duration of effect being directly related to the dose administered. Behavioral recovery generally occurs after sublethal exposure.

The present study was conducted to more thoroughly evaluate the dose- and time-related effects of acute, sublethal exposure to ionizing radiation on schedule-controlled performance in rats. Fixed-ratio (FR) and fixed-interval (FI) schedules of reinforcement [15] were used here because it is well documented that they provide sensitive behavioral endpoints for detecting and measuring exposure to a wide variety of drugs and toxic agents [24,37]. Several studies have examined the short-term effects of one type of ionizing radiation (X-rays) on FR performance [7–9, 39]; there are no published reports to our knowledge on the effects of ionizing radiation on FI performance. Radiation-induced changes in rates and patterns of responding were evaluated for up to seven weeks after acute exposure in order to more thoroughly describe time-course effects. It was of particular interest to look for temporal relationships between the behavioral and the well documented physiological effects of ionizing radiation mentioned above. Individual animals received multiple exposures to ionizing radiation to determine whether cumulative effects might occur under the conditions used here.

METHOD

Animals

Thirty-five experimentally naive male rats [Crl: (CD(SD)BR] (VAF Plus) were used. The rats were 90–120 days old at the start of the experiment and were maintained at approximately 80% of their free-feeding body weights. Rats were quarantined on arrival and screened for evidence of disease. They were individually housed in plastic Microisolator cages containing sterilized woodchip bedding; commercial rodent chow and acidified tap water were provided. Animal holding rooms were maintained at 21±1 C with 50±10% relative humidity using at least 10 air changes per hour of 100% conditioned fresh air. A 12-hr lighting cycle was in effect with full-spectrum lights on from 0600–1800.

Apparatus

Six operant conditioning chambers were used (Coulbourn Instruments, Inc.). The front wall of each chamber contained a response lever mounted on a microswitch, a set of three cue lights located above the lever, a house light, a Sonalert speaker and an opening that allowed access to a dipper that presented 0.06 ml of sweetened condensed milk (a 1:1 mixture of Bordens Eagle Brand and tap water). Each chamber was enclosed in a sound- and light-attenuating compartment which also contained an exhaust fan for ventilation and a speaker for the presentation of white masking noise. Control of experimental stations and recording of data were accomplished with a PDP8 computer and cumulative recorders located in an adjoining room.

Behavioral Procedure

Animals were trained to press the lever using an automated procedure that consisted of two schedules of milk delivery being in effect simultaneously. A variable-time (VT) schedule presented the dipper automatically on the average of every 60 sec, while an FR 1 schedule presented the dipper after each leverpress. Presentation of the dipper lasted for 5 sec and was signalled by a light over the dipper and the Sonalert tone; the house light and cue lights were extinguished during dipper presentation. The VT schedule was discontinued after 10 responses had been made within a single daily session. Sessions lasted for 60 min or until 100 responses had been made, whichever occurred first. After an additional one or two sessions under FR 1, 15 rats were exposed to a series of incremental FR schedules over several weeks until the final FR 50 schedule was in effect. The remaining 20 rats were exposed to an incremental series of FI schedules until the final FI 120 sec schedule was in effect. Under FI schedules, reinforcers are delivered for the first response occurring after the interval has elasped; responses occurring prior to the end of the interval have no programmed consequences. Session duration was 30 min for FR and 60 min for FI. Training was conducted until the performance of each rat was stable (no consistent trends in rates and patterns of responding from day to day over three to five consecutive weeks). After responding had stabilized the first radiation phase was begun.

Radiation Procedure

Rats were assigned to radiation dose groups (n=4–5 per group) such that group mean baseline response rates were similar within each reinforcement schedule. Animals from different dose groups were balanced across test chambers and time of day for testing to the extent possible.

Bilateral, whole-body, midline tissue doses of 4.5, 1.5, 0.5 or 0 (FI only) Gy of gamma photon radiation were delivered at a fixed rate of 2.5 Gy/min from a cobalt-60 source. Each rat received its designated dose of radiation three times at 43-day intervals. A final irradiation with 6.5 Gy was given to all rats 64 days after the third exposure. The time intervals between exposures were chosen to allow for (1) testing over at least 30 days after exposure, the conventional time period for expressing radiobiological LD_{50} data (the $LD_{50/30}$ for gamma radiation in the rat is 9.5 Gy [6]), and (2) the collection of sufficient control data prior to the next exposure.

Rats were placed in well ventilated, clear plastic restraining tubes for irradiation. Test sessions began 5 min after exposure ceased. Sham exposures, consisting of placing the animals in the tubes and transporting them to the exposure room, were conducted on at least eight occassions prior to the first irradiation. Forty-six days after the last exposure, all surviving rats were euthanized with an overdose (80 mg/kg) of IP pentobarbital. Tissue and blood samples were taken for general pathological evaluation. Rats not surviving until this time underwent pathological evaluation whenever possible.

Data Collection and Analysis

Animals were tested five days per week, Monday through Friday, throughout the first three exposure phases. Following the fourth (6.5 Gy) exposure animals were tested for 12 consecutive days and then five days per week thereafter. All exposures occurred on a Monday and rats were always tested on the immediately preceeding Sunday. Prior to each exposure control data were taken from 6–7 sessions.

Individual performance measures calculated for each session for FR and FI responding included mean overall response rate, postreinforcement pause duration and running response rate. Overall response rate was calculated by dividing the total number of responses emitted by the total session time (excluding the time the dipper was raised). The postreinforcement pause was defined as the time elapsed from the end of a dipper presentation until the first response

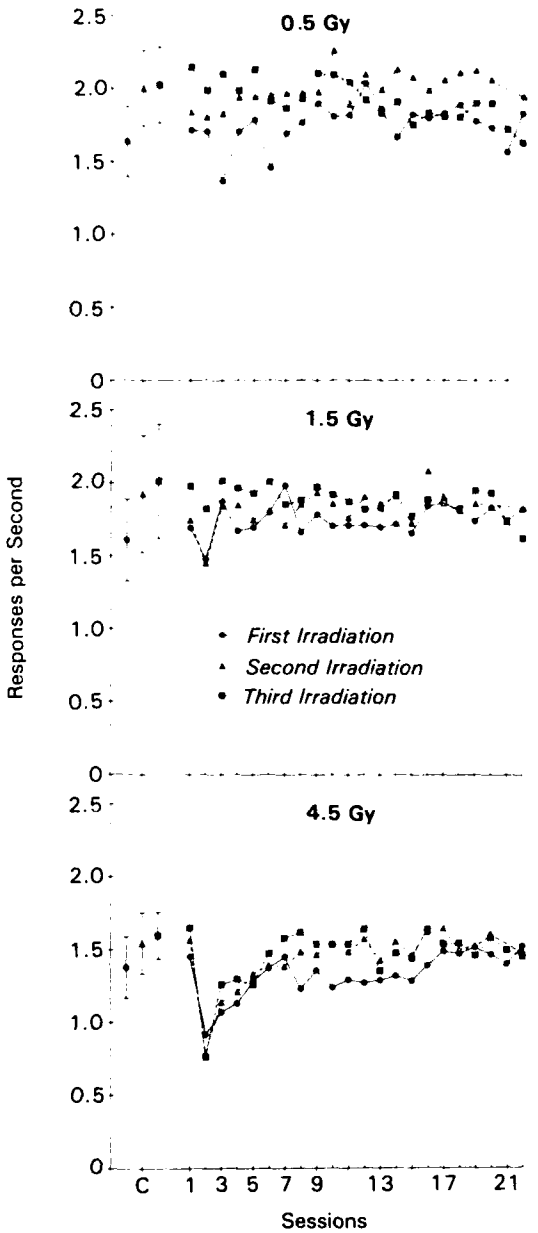

FIG. 1. Effects of gamma radiation on FR 50 response rates. Each panel represents a separate group of five rats. Each group was exposed to the indicated dose of radiation on three separate occasions at 43-day intervals. Session 1 began 5 min after exposure ceased. Subsequent sessions occurred at 24-hr intervals, Monday through Friday, over 30 days following irradiation. Points at C represent group mean control data for each of the three irradiations; vertical lines indicate ±1 SEM. Group means are based on the mean response rate of each rat across 6–7 sessions prior to irradiation.

of the next ratio or within the next interval. Running response rate was the response rate calculated with the postreinforcement pause omitted. Since responding under FI schedules typically occurs at an increasing rate as the interval times-out, the index of curvature was calculated to provide a measure of this temporal distribution of responses [17].

Performance measures were analyzed statistically using analysis of variance with the Greenhouse-Geisser correction for repeated measures [27]. Subsequent comparisons between pairs of means were performed with *t*-tests. Since virtually all of the studies examining radiation-induced changes in schedule-controlled responding have reported that response rates or frequencies were reduced following exposure, one-tailed tests were used when possible as reductions in response rates were expected. The alpha level for significance was set at 0.05.

RESULTS

Changes in FR response rates as a function of radiation dose and repeated irradiations are presented in Fig. 1. Neither 0.5 (top) nor 1.5 (middle) Gy of gamma radiation altered group mean response rates over 22 test sessions (30 days) after each of the three exposures. The only apparent effect was that the response rate of one rat was reduced below its control range 24 hr after each of the three 1.5 Gy exposures. At 4.5 Gy (bottom), changes in FR response rates were observed after each exposure. Response rates were not altered during the session which began 5 min after exposure (session 1), were reduced 24 hr later to the lowest levels observed (rates were reduced by 30–50% over the three exposures), and gradually returned to control levels by the fifth or sixth session after exposure. Following recovery, response rates remained stable throughout the remainder of each exposure phase. Changes in response rates did not vary as a function of repeated exposures. Analysis of variance performed on the response rates of each group separately (mean preirradiation control response rates and response rates from postirradiation sessions 1–10) revealed a significant effect of sessions only at 4.5 Gy; all main effects of radiation phase and radiation phase × session interactions were nonsignificant. One-tail *t*-tests revealed that sessions 2–5 differed significantly from control after the 4.5 Gy exposure.

Changes in FR postreinforcement pause after each 4.5 Gy exposure are presented in Fig. 2. Mean postreinforcement pause was not altered immediately following irradiation (session 1), but was increased two- to three-fold 24 hr later. During the third session after each exposure there was a substantial degree of recovery although the pause remained elevated above control values. Postreinforcement pause was elevated throughout the remainder of the first week of testing after exposure and returned to control levels during the second week. Changes in postreinforcement pause did not vary with repeated 4.5 Gy exposures. These effects were confirmed with an analysis of variance performed on the mean control pause and the pause from sessions 1–10 after the three 4.5 Gy exposures; the main effect of sessions was significant while the main effect of exposure phase and the interaction were nonsignificant. With the data collapsed across the three exposures, two-tail *t*-tests revealed that sessions 2–6 and 8 differed significantly from control. There were no consistent changes in postreinforcement pause after exposure to 0.5 or 1.5 Gy (not shown).

Running response rates under the FR schedule were not altered after exposure to 0.5 or 1.5 Gy of radiation. At 4.5 Gy, running rates were not altered on the day of exposure and were decreased to the lowest levels observed (by 20–40% of control over the three exposures) 24 hr later (Fig. 3). Running rates returned to control levels over the next 2–4 sessions and were stable throughout the remaining portion of each exposure phase. Analysis of variance on the running

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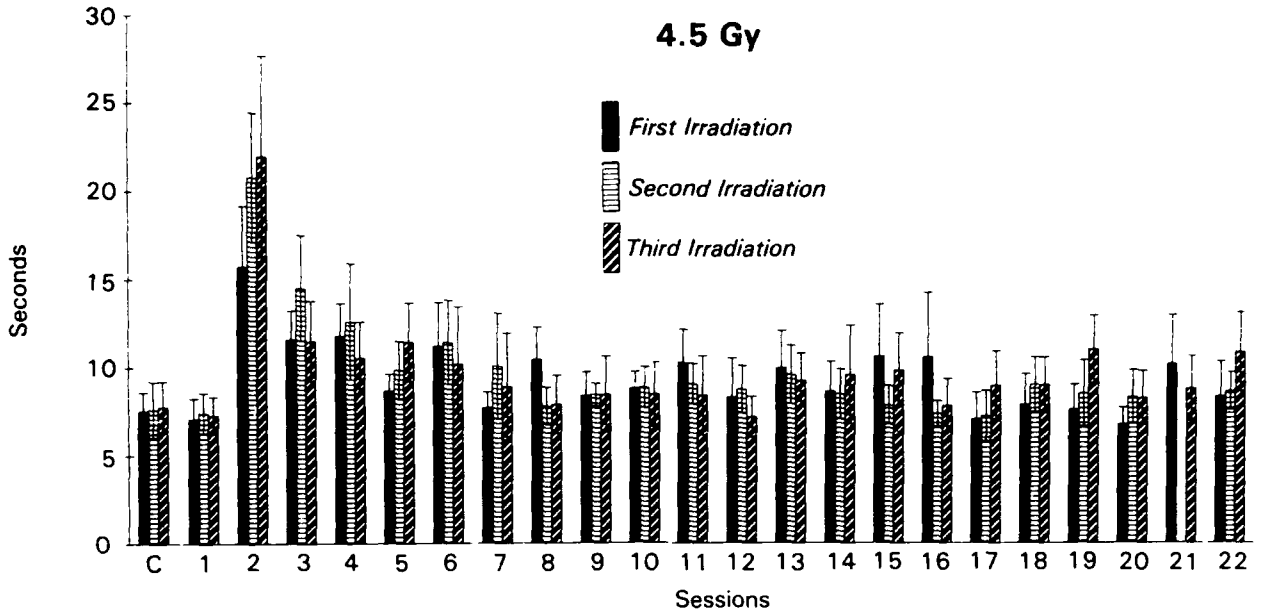

FIG. 2. Effects of 4.5 Gy of gamma radiation on FR 50 postreinforcement pause (see Fig. 1 for details).

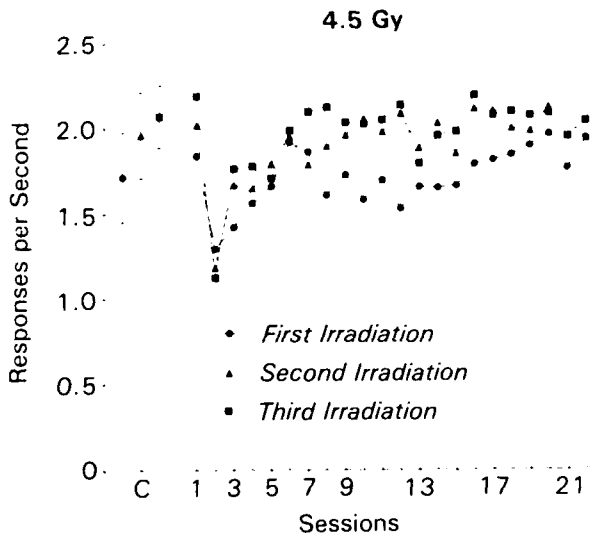

FIG. 3. Effects of 4.5 Gy of gamma radiation of FR 50 running response rates (response rates calculated with the postreinforcement pause omitted; see Fig. 1 for details).

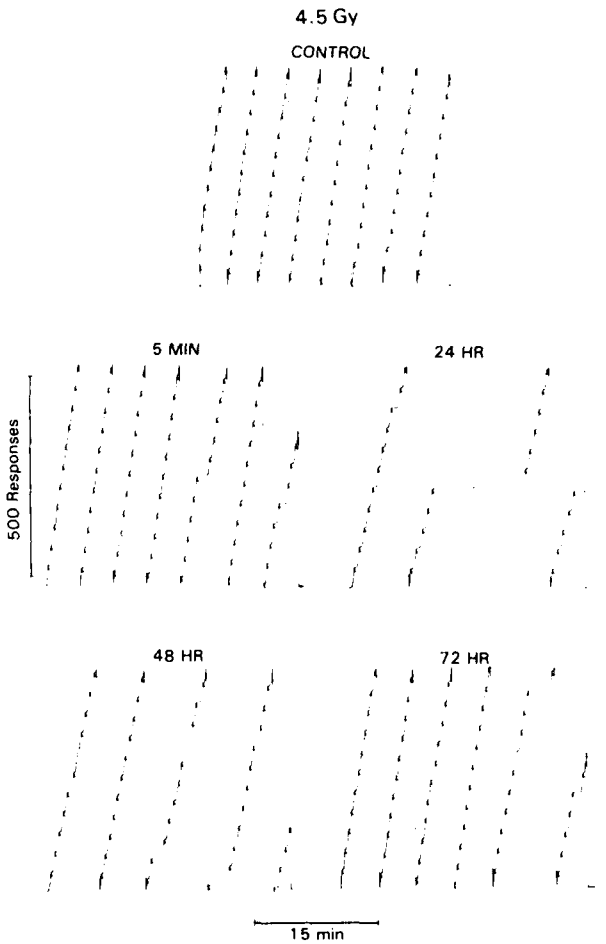

FIG. 4. Cumulative records showing the performance of one rat under the FR 50 schedule of milk presentation. Control performance prior to irradiation and performance over four successive sessions after exposure to 4.5 Gy of gamma radiation are shown. Each response stepped the pen in an incremental fashion across the page. Delivery of the milk reinforcer with the completion of the ratio is indicated by the diagonal deflections.

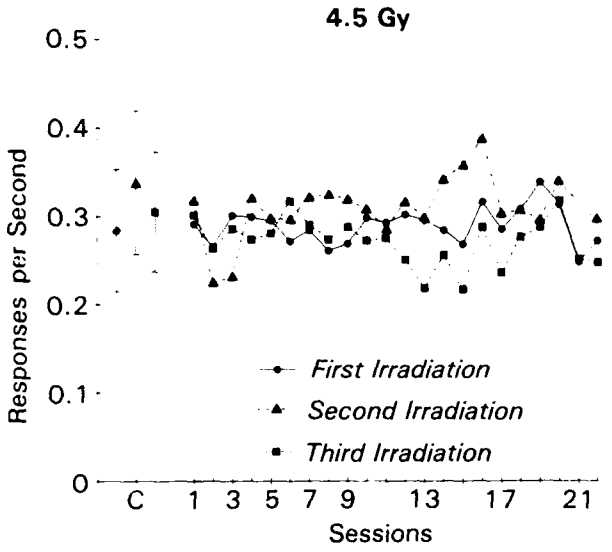

FIG. 5. Effects of 4.5 Gy of gamma radiation on FI 120 sec response rates (see Fig. 1 for details).

rates of the 4.5 Gy exposure group revealed only a significant effect of sessions, indicating that rate changes did not vary significantly as a function of repeated irradiations. One-tail *t*-tests revealed that sessions 2–4 differed significantly from control.

Sample cumulative records depicting control FR performance and performance over sessions 1–4 after exposure to 4.5 Gy are presented in Fig. 4. The overall response rate during the session that began 5 min after irradiation was within the range of control rates for this rat. At 24 hr postirradiation there was noticeable disruption in performance which included a slowing in the overall rate of responding, a lengthing of the postreinforcement pause, and an extended pause in responding. Progressive recovery of control-like performance was evident during the sessions which occurred 48 and 72 hr after exposure.

Under the FI schedule, average response rate, running response rate, postreinforcement pause and index of curvature were not altered consistently by 0.5–4.5 Gy of radiation over the three exposures (all main effects and interactions of analyses of variance were nonsignificant); response rates after 4.5 Gy are shown in Fig. 5. Individual mean control postreinforcement pauses ranged from 50 to 85 sec, while individual mean control indices of curvature ranged from 0.50 to 0.65. Fixed-interval responding did not appear to be completely unaffected by radiation, however, since the response rate of each rat in the 4.5 Gy exposure group was reduced below its control range for 24–48 hr after the second exposure.

Figure 6 presents the effects of 6.5 Gy of gamma radiation on FR response rates in rats with a history of exposure to 0.5–4.5 Gy. Response rates are presented as a percentage of mean control rates to facilitate comparison among groups. In

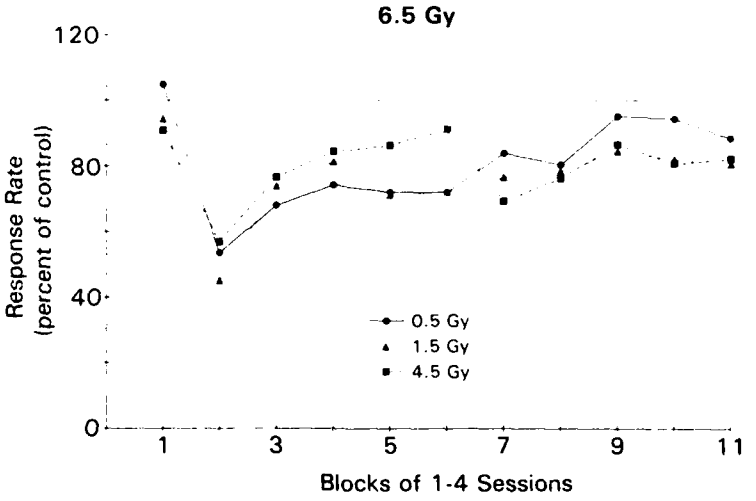

FIG. 6. Effects of 6.5 Gy of gamma radiation on FR 50 response rates. The key indicates the dose of radiation received on three separate occasions prior to exposure to 6.5 Gy. For each rat, the average response rate for a block of sessions was expressed as a percentage of the average control rate derived from 7 sessions prior to the 6.5 Gy exposure. Individual percentages were then averaged to provide group data. The first block represents the test session which began 5 min after exposure. Subsequent blocks are the mean of three sessions except for block 7 which is the mean of four sessions. For the 0.5 and 1.5 Gy exposure groups n=5. For the 4.5 Gy exposure group n=4 for blocks 1–6, n=3 for block 7, and n=1 for blocks 8–11.

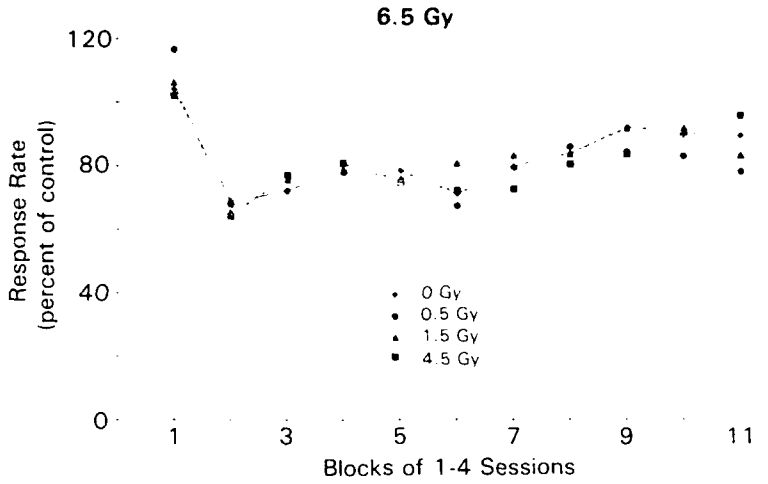

FIG. 7. Effects of 6.5 Gy of gamma radiation on FI 120 sec response rates. The key indicates the dose of radiation received on three separate occassions prior to exposure to 6.5 Gy. Each point is the mean of five rats for the 0 and 1.5 Gy exposure groups and four rats for the 0.5 Gy exposure group. For the 4.5 Gy exposure group $n=5$ for blocks 1–8 and $n=4$ for blocks 9–11 (see Fig. 6 for details).

none of the three groups of rats did 6.5 Gy alter response rates during the session that began 5 min after exposure (session block 1). Response rates were reduced in each group over the following three sessions (block 2). Response rates recovered somewhat and stabilized over the subsequent 5–6 blocks of sessions before showing additional recovery toward mean control values over the remaining blocks of sessions. Most importantly, differential radiation history did not alter the effect of 6.5 Gy on FR response rates. This was confirmed by analysis of variance on the absolute response rates which revealed that only the main effect of session block was significant. Control response rates and response rates through block 6 only were included in this overall analysis due to deaths that occurred in the 4.5 Gy exposure group during blocks 7 (one death) and 8 (two deaths). Two-tail t-tests on response rates collapsed across the three groups ($n=14$) revealed that blocks 2–6 differed from control.

Under the FI schedule, the 6.5 Gy exposure did not alter response rates on the day of irradiation in any group, while relatively stable reductions in response rates occurred over session blocks 2–7 in each group (Fig. 7). Response rates generally showed recovery over the remaining blocks of sessions. Similar to what was observed for FR responding, changes in FI response rates after exposure to 6.5 Gy of gamma radiation did not vary as a function of exposure history. The absence of any observable effect of exposure history on FI response rates is shown most dramatically by comparing the 0 Gy exposure group with the three groups that had previously been irradiated. Analysis of variance on the absolute response rates of the four FI groups ($n=19$) revealed only a significant effect of blocks. Because one rat in the 4.5 Gy exposure group died during session block 9, this overall comparison was restricted to the first eight blocks of sessions. Two-tail t-tests revealed that response rates during blocks 2–8 differed significantly from control rates.

Comparison between Figs. 6 and 7 suggests that 6.5 Gy reduced FR response rates to a greater degree than FI rates during the early postexposure period (session block 2). Response rates across the three FR groups were reduced to 51.5±4.0% (mean±SEM) of control values during block 2, while FI rates of rats with similar exposure histories (rats with a history of 0 rad exposures were excluded) were reduced to 65.7±6.1% of control. A two-tail t-test of these reductions in response rates revealed $p<0.07$. The 6.5 Gy dose increased FR postreinforcement pause and decreased FR and FI running rate; FI postreinforcement pause and index of curvature were not altered.

Lethality following the 6.5 Gy exposure was preceeded by a general deterioration in the condition of the animals for several days. Reduced food intake, weight loss, lowered body temperature, and paleness of the eyes which suggested failure of the hemopoietic system were observed. Prior to this each rat showed at least partial recovery from the disruption in performance seen shortly after irradiation. Pathological examination confirmed hemopoietic failure as the probable cause of death. Hemopoietic effects in surviving animals were restricted to a moderate anemia.

DISCUSSION

The effects of gamma radiation on schedule-controlled responding varied as a function of the dose and the schedule of reinforcement. At the lower doses (0.5 and 1.5 Gy) significant changes in performance were not observed. At the intermediate dose of 4.5 Gy, FR response rates were decreased after each of the three exposures, while FI response rates were not altered reliably. At the highest dose of radiation tested (6.5 Gy), both FR and FI response rates were decreased though FR rates tended to be decreased more than FI rates for several days after exposure. These findings indicate that over the range of doses used here, FR responding was more sensitive to radiogenic disruption than FI responding.

The differential effects of gamma radiation on FR and FI

performance may be due to differences in baseline response rates [24]; the higher rates under FR were disrupted at doses that did not alter or disrupted less the lower rates under FI. Effects of radiation did not appear to be solely a matter of baseline rate, however, since responding within the FI was not affected in a way that was related to the baseline rate. Under baseline conditions, responding within the FI showed the typical pattern of lower-rates early and higher-rates later in the interval. The quantitative measure of this pattern of responding, the index of curvature, was not altered by any dose of radiation even though overall response rate was reduced. This indicates that responding was decreased in a relatively uniform fashion throughout the FI. Thus, both baseline response rate and schedule of reinforcement may be important determinants of radiation-induced disruption of performance. Changes in other meausres of performance also varied in a schedule-dependent manner. The short postreinforcement pauses under FR were increased after exposure, while the longer pauses under FI were not altered. Extended pauses in responding after irradiation were generally restricted to FR. These differences contributed to the schedule-dependent changes in response rates.

At the doses of gamma radiation that produced consistent decreases in FR response rates (4.5 and 6.5 Gy), duration rather than magnitude of effect appeared to be a better indicator of dose. Averaged over the three exposures, 4.5 Gy produced maximal decreases in FR response rates to 59.0±10.3% of control values 24 hr after exposure; recovery occurred over the next several days. Similar maximal reductions were observed 24 hr after exposure to 6.5 Gy, when FR response rates were reduced to 50.4±6.3% of control values. At this higher dose, however, FR response rates remained depressed for two additional days (response rates were reduced to 57 and 47% of control values, respectively, 48 and 72 hr after the 6.5 Gy exposore) before showing signs of recovery.

There are few previous reports on the effects of acute exposure to ionizing radiation on schedule-controlled performance. In one study, 1.0–5.0 Gy of X-rays reduced variable-interval response rates for 1–4 days while rates under a shock avoidance schedule were unaltered [22]. In another, 8.0 Gy reduced responding under an FR 1 schedule averaged over four days after exposure, whereas 2.0 and 4.0 Gy were ineffective [39]. Although neither of these studies conducted behavioral testing on the day of irradiation, the present investigation showed that performance was not altered over the immediate postexposure period after doses of 0.5–6.5 Gy. In contrast, much higher, acute doses have been shown to produce more immediate behavioral effects. Disruptions in responding under FR [8] and shock avoidance [11] schedules in rats were reported within one hour after exposure to supralethal doses (40–100 Gy), while delayed match-to-sample performance of monkeys was disrupted within minutes of supralethal irradiation [10].

Even though ionizing radiation generally depresses behavioral output, the time-course of this effect is highly dependent on the behavior examined. Here, performance changes were greatest 1–3 days after irradiation and were followed by recovery over several days or weeks. In contrast, swimming capability of rats decreased steadily over 3–4 weeks after X-irradiation and then gradually recovered [26]. Moreover, running-wheel activity of rats decreased for several days after X-irradiation, then recovered before a second, more pronounced decrease began at about day 10 postexposure [23]. These markedly different temporal relationships suggest fundamental differences in the factors underlying radiation-induced depression of schedule-controlled responding, swimming and running-wheel locomotion.

Decreased food intake is one of the earliest effects seen in humans and animals after low to moderate radiation exposure [22, 29, 40] and this may account for the disruptions in FR and FI performance observed here. However, there appear to be limitations on attempts to relate radiation-induced changes in schedule-controlled performance to a general effect on food intake, at least in the present study. At 6.5 Gy, even though most rats failed to consume their entire ration of chow on one or more days after exposure, there was little correspondence between the magnitude and time course of disruption in performance and whether or not chow was consumed. After exposure to 4.5 Gy of radiation when it was generally uncommon for any portion of the daily ration of chow to remain uneaten, the days when chow was not entirely consumed always occurred after the days when the most pronounced reductions in FR responding were found. Ionizing radiation induces a variety of subjective effects in humans that would likely disrupt ongoing behavior: these include weakness, fatigue, nausea, lethargy, headache and dizziness [40]. The performance changes reported here may provide an index of effects in animals that reflect or are in some way analogous to the subjective effects reported by humans. The use of schedule-controlled behavior in providing such an index of exposure to toxic agents has been suggested [38]. Additional research is necessary, however, to more precisely define and attempt to measure these types of effects in animals [30].

Repeated irradiations of the same animals failed to provide evidence of cumulative behavioral effects. This suggests that the 6–9 week period separating successive irradiations allowed for adequate recovery of the physiological systems underlying the behavioral effects observed here shortly after exposure. Long-term, latent physiological effects would have been expected to result in enhanced behavioral disruptions over successive irradiations. In contrast, several previous studies showed that decreases in FR responding were enhanced when rats received multiple irradiations; doses ranged from 0.5–8.0 Gy delivered every 1–7 days [7, 9, 39]. These results suggest that the dose of radiation, the time between irradiations, and the number of irradiations are important determinants of the behavioral effects of multiple exposures to ionizing radiation.

In contrast to disruption of FR and FI performance, lethality appeared to be influenced by radiation history in that all deaths that occurred after the 6.5 Gy exposure were found in the groups previously exposed to 4.5 Gy. Since no deaths occurred until 3 weeks following the 6.5 Gy exposure, there was a clear temporal separation between early, acute behavioral and later, lethal effects of radiation resulting from hemopoietic failure. Lethality was not merely the result of the total cumulative dose received, however. The total cumulative dose of 11 Gy received by the 1.5 Gy exposure groups exceeded the $LD_{30/30}$ dose of 9.5 Gy for gamma radiation in rats [6], yet no deaths occurred in these animals. The 4.5 Gy exposure groups received a total cumulative dose of 20 Gy; a single dose of this size would have been lethal to 100% of exposed animals within several days [19]. Thus, in agreement with previous data [3], dose fractionation increases the total cumulative dose that can be tolerated without producing lethality.

In summary, under the conditions used here the effects of gamma radiation on schedule-controlled performance were

found to be dose-related, reversible, noncumulative, and dependent on the schedule of reinforcement. Due to the continuing, if not increasing possibility of human exposure to ionizing radiation under a broad range of circumstances, the systematic examination of the behavioral effects of ionizing radiation should be pursued.

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