

THE UNIVERSITY OF MANITOBA
PRE- AND NEO-NATAL EXPOSURE TO 10^{19} HZ and 0.5 HZ ELECTROMAGNETIC
FIELDS AND DELAYED CONDITIONED APPROACH BEHAVIOR

by

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Dedicated to
Ernest Furchtgott
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ABSTRACT

Female rats that had been exposed to one of the following twelve Co^{60} gamma-irradiation, 0.5 Hz, Rotating Magnetic Field (RMF) or control conditions: 100 rad, 200 rad or control conditions on prenatal day 16; 0.5-3 gauss, 3-30 gauss or control conditions during prenatal days 13-16; 100 rad, 200 rad, or control conditions on post-natal day 4; and 0.5-3 gauss, 3-30 gauss or control conditions during post-natal days 1-4, were used as subjects. When the twelve groups were tested on a Delayed Conditioned Approach paradigm, the prenately Co^{60} irradiated rats, with reduced forebrain sizes, emitted significantly more inter-trial non-reinforced responses, relative to controls, in a second order DRL-discrimination situation and displayed behaviors that have been reported in other experiments. The prenately RMF-exposed and neonatally RMF-exposed and Co^{60} irradiated rats did not display such behaviors. Mid-way through one session ("step-day"), a delay was introduced in a step-like manner between the onset of a tone to which the immediate availability of reinforcement had been associated. The two neonatally RMF-exposed and 200 rad neonatally irradiated groups showed significantly greater transient increases in total responses, relative to controls, after the delay of reinforcement was instituted on "step-day" only. This increase was shown to be due, in large part, to the greater number of responses emitted during the delay. Total response differences between these three groups and their controls were not statistically significant on subsequent (post-step) days. Neither the prenately RMF-

exposed nor the prenatally irradiated groups differed from their controls in total responding after the delay had been instituted on the step day or on subsequent days. Total responses after the step on step day were significantly correlated with cerebellar sizes for only the neonatally RMF-exposed and neonatally irradiated groups, while measures indicative of greater intertrial non-reinforcement responding were correlated with only cerebral sizes in both prenatal and neonatal groups. Histological analysis indicated that cytoarchitectural and morphological pathology of the vermis of the cerebellum occurred in the neonatally 200 rad irradiated groups but not in the neonatally RMF-exposed groups. The similarity of the latter three groups' behavior, but differences in cytoarchitecture were discussed in terms of comparable biochemical changes that may have followed both radiation and RMF exposure. The data were then integrated into Marr's theory of cerebellar cortical function.

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CHAPTER I

INTRODUCTION

Certain very high energy electromagnetic radiations and rapidly moving particles can penetrate matter deeply, and by interacting with atoms with which they collide or pass near, cause them to become ions. Gamma rays (10^{19} Hz), X-rays (10^{17} Hz), electrons, neutrons, protons, along with high velocity atomic nuclei represent ionizing radiations. Prenatal and neonatal exposure to ionizing radiation is associated with a variety of later changes that have been reviewed by Kimeldorf and Hunt (1965) and Furchtgott (1963). The following review is restricted to the behavioral, physiological and chemical changes in rodents due to pre- or neonatal exposure to, unless otherwise specified, 100-200 R (roentgens) of X-irradiation.

Werboff, Havlena and Sikov (1962) have reported that rats exposed prenatally on either the 5th or 10th day of gestation to X-irradiation exhibit less activity than control rats in an open field situation, while those irradiated during the 15th or 20th day of gestation showed more activity. Similarly, Furchtgott and Echols (1961) noted that rats exposed to 100-300 R between days 14 and 17 of gestation showed more activity in the open field and tilting cage. Neonatal exposure to ionizing irradiation is associated with a significant general decrease in activity in the open field (Furchtgott & Echols, 1958a), tilting cage (Furchtgott & Echols, 1958a), and running wheel (Wallace & Altman, 1969; Nash, Napoleon, & Sprackling, 1970), although in one instance neonatally irradi-

iated mice have shown greater activity than controls in the open field (Manosevitz & Rostkowski, 1966).

Deficits in the ability to climb an inclined plane are most severe with animals irradiated in the latter part of gestation on days 15 or 20 (Werboff, Havlena & Sikov, 1962), or on days 16-18 (Wechin, Elder & Furchtgott, 1961). Rats irradiated on prenatal days 14-15 (Furchtgott & Echols, 1958b) or day 16 (Lipton, 1966) with 200 R were less able than controls to traverse parallel bars, where the distance between the bars was increased. Rats irradiated later in gestation or at birth could negotiate the bars similar to controls, although deficits could be induced in these groups by increasing the dose to 300 R (Furchtgott & Echols, 1958b). Rats irradiated on post-natal day 6 behaved similar to controls on this task (Lipton, 1966).

Fetally irradiated rats also show motoric disturbances in other situations. Werboff, Goodman, Havlena and Sikov (1961) exposed rats to 100 R of whole-body radiation on either day 5, 10, 15, or 20 of gestation. Again, rats exposed on day 15, when compared to the other irradiates and controls, showed the greatest retardation of upright and righting responses and a marked decrease in motor strength. According to these experimenters, day 15 animals never developed appropriate locomotor responses with their hind legs. This was exemplified by the fact that these animals "hopped" rather than exhibited the normal reciprocal movement of alternate hind legs.

Neonate head only exposure to repeated doses of 1-2 x 200 R to greater than 5 x 200 R during the first 5 days of birth can produce later

increases in tremors, clonic twitching, paralysis of extremities, and paresis (Wallace & Altman, 1969; Yamazaki, Bennett, & Clemente, 1962). Differences in standing on hindlegs, such as increased tendency to fall backwards (Yamazaki, et al., 1962) and falling or dragging of hind feet during locomotion (Altman, Anderson & Strop, 1971) have also been observed. The latter experimenters report that the neonatally irradiated rats were comparable to controls in weight pulling capacity. Hicks, D'Amato, Klein, Austin, and French (1969) used slow-motion movies to record the locomotor behavior of normal and irradiated rats. An animal whose whole body had been exposed to 200 R at birth had a moderately wide based gait, and less than normal smooth locomotor movements. Irradiation of the head only, in order to reduce possible muscle, joint or spinal effects on gait, produced similar patterns. Rats whose cerebellums were irradiated with 300 R on day 1 or day 5 after birth tended to lift their hind feet too high, in an almost slapping gait. The cycle of the movements of the limbs became out of phase frequently so that the hind feet stepped on the forefeet. When only regions of the cerebellum were irradiated, motoric disturbances depended on the area and extent of radiation damage, the greatest disturbances associated with irradiation of one lateral half of the cerebellum with encroachment on the other side or involvement longitudinally through the center. Irradiation of the forebrain (cerebrum) only did not produce the behavioral disturbances.

Associated with the motoric disturbances following pre- and neonatal exposure to radiation, were changes in susceptibility to various types of seizures. Werboff, Den Broeder, Havlena and Sikov (1961) found

that irradiation of rats on prenatal days 5 or 10 reduced the offsprings' susceptibility to electroshock seizure, while irradiation on days 15 or 20, increased this susceptibility. X-irradiation on prenatal day 14 produced full tonic-clonic seizure patterns earlier and with greater activity than control treatments (Vernadakis, Curry, Maletta, Irvine & Timiras, 1966). Accompanying this increased susceptibility were increased conduction velocity and amplitude but decreased thresholds of evoked responses from the cortices of young rats that had been irradiated in the latter days of fetal development, (Berry & Eayrs, 1970; Rosenthal & Timiras, 1963). Electroshock thresholds were lowered in rats exposed to 500 R whole-body irradiation 2 days postnatally (Vernadakis & Timiras, 1963). although whole body gamma-irradiation with 10 R at 6, 11, or 16 days after birth did not produce differences in the latency or severity of audiogenic seizures in mice (Tacker & Furchtgott, 1962).

Prenatal and neonatal irradiation is associated with changes in learning behavior in maze, classical, and operant situations. Kaplan (1962a) irradiated rats on days 2.5, 6.5, 7.5, 8.5, 11.5, and 12.5 of gestation with 50 R, and found that the 6.5 and 7.5 days group exhibited greater errors when tested in a Lashley III maze at 90 and 400 days of age. On the other hand, Werboff, Havlena and Sikov (1962) found that female rats that had been irradiated on day 5 or 10 of fetal life made less errors in the Lashley III maze than controls while those irradiated on prenatal days 15 or 20 made significantly more errors. No consistent differences were found between irradiated males and control males.

Levinson (1952) and Furchtgott, Echols and Oppenshaw (1958), also found that of the rats exposed between prenatal days 11-19, to 200-300 R, the 14-15 day group showed the greatest errors in the Lashley III maze when tested at 50 days of age. Fowler, Hicks, D'Amato and Beach (1962) reported similar decrements in behavior when rats that had been exposed to 150 R on prenatal days 13-14 were tested in a Hebb-Williams maze. In this case the irradiates emitted more and more errors, with respect to controls, as the "difficulty" of the problems increased. These experimenters noted that the irradiates also showed greater perseveration of left or right turn responses in a T-maze, than controls. Neonatally irradiated rats continued to show more errors in a Lashley III and Hebb-Williams open field test, the greatest deficits occurring with those animals irradiated during the first four days of birth (Levinson & Zeigler, 1958). Deficits due to neonatal and juvenile irradiation with up to 350 R rapidly decreased as the irradiation takes place later and later after birth, until those rats irradiated after 18-22 days of age, displayed errors similar to controls (Levinson & Zeigler, 1958; Furchtgott, 1951).

Using a classical conditioning procedure developed by Kotyarevsky, in which the conditioned response (CR) was pushing open a door for food during a tone, Furchtgott and Walker (1969) found that rats irradiated fetally with 200 R on day 16 showed fewer responses than controls during initial acquisition stages and a smaller portion of short response latencies to the tone than control rats. This tendency for greater response latencies following the onset of a stimulus associated with food

reinforcement has also been reported by Sharp (1968). On the other hand, the irradiates made more responses when a tone, not associated with food, was presented (Furchtgott & Walker, 1969). A greater number of illicited CRs was also noticed in an auditory discrimination situation where two tones were presented, one being associated with reinforcement, the other with no reinforcement. Both irradiated and control groups established the auditory discrimination to the same level of accuracy (Walker & Furchtgott, 1970). Piontkovsky (1961, 1959) also noted that acquisition and extinction of classically conditioned motor responses were prolonged in fetally irradiated rats.

With respect to operant conditioning procedures, earlier experimenters, using small numbers of animals, found that rats irradiated with 150-200 R doses between the 13th and 19th day of gestation performed as well as control rats in the operant discrimination of visual patterns (Falk, 1966). Walker and Furchtgott (1970) reported that Kaplan (1962) found no differences between prenatally irradiated and control rats in several operant discrimination procedures. Using larger groups of rats, Furchtgott and Walker (1969) noted that, similar to the results found with the Kolyarevsky procedure, day 16 fetally irradiated (200 R) animals had lower rates of bar pressing during acquisition but higher rates of responding during extinction, the latter difference being significant only testing on the first day. Also, rats irradiated with 150R on the 14th day of fetal life have been shown to emit more responses during the negative (non-reinforced) stimulus in a visual discrimination task (Fowler, Hicks, D'Amato & Beach, 1962). The overall response rate of day 16 animals was

less than controls if the reinforcement was given with every response during the appropriate stimulus in a light dark discrimination, but equal to controls if reinforcement was given on a Fixed Interval (FI) schedule (Furchtgott & Walker, 1969). When placed on a DRL (Differential Reinforcement of Low Rate of Responding)-30 second schedule, the irradiates pressed at a higher rate than controls, and received fewer reinforcements during the first four sessions only. Both groups eventually obtained rewards at the same rate. Radiates maintained on an FI schedule exhibited a lower rate of responding just after reinforcement, and a higher rate just before reinforcement. From these data Furchtgott and Walker suggested that fetally irradiated rats showed better time discrimination than controls.

Although fetally irradiated rats can learn visual discriminations as well as controls, their behavior is more severely effected by lower intensities of illumination than controls (Van Der Elst, Porter & Sharp, 1963; Graham, Marks, & Ershoff, 1959). Apparently, this may be due to changes in sensory thresholds. Sharp (1968) has noted that day 16 fetally irradiated rats have higher critical-flicker-fusion (CFF) thresholds than controls, while Furchtgott, Lore and Morgan (1964) have noted that these rats have greater difficulties with depth perception. Similarly, Furchtgott and Kimbrell (1967), while testing the olfactory thresholds of day 16 irradiates, reported that they could discriminate a 100 % solution of oil of cloves from propylene glycol solvent, but could not discriminate a 50% solution and the solvent, the latter discrimination being achieved by all control rats.

Shock avoidance tasks have been shown to successfully discriminate between fetally irradiated and control rodents. Rats irradiated on days 17, 19, and 21 with 196 R exhibited significantly more bar press escape/avoidance responses as a function of increasing shock intensity than did sham-irradiated controls (Martin, 1970). The irradiates made a greater number of responses during time-out as compared to time-in periods and received fewer shocks than controls, the latter decrease being most pronounced in the day 17 animals. Day 16 irradiates have also been shown to receive less shocks in a shuttle avoidance situation by obtaining criterion avoidances significantly sooner than controls (Furchtgott & Weckin, 1962). That these differences are due to a greater baseline activity of fetally irradiated rats in these situations seems unlikely since these animals showed greater conditioned suppression (Sharp, 1965) and more passive avoidance responses (Deagle & Furchtgott, 1968) than controls. It is also unlikely that these behavioral differences are due solely to increased sensitivity to shocks since Furchtgott and Weckin (1962) found the correlation between shock threshold and number of trials to criterion in the shuttle box to be barely at the .05 level. In addition, Tacker (1964), found that escape conditioning, where presumably response to shock is the major variable, did not differentiate irradiated and control rats.

Furchtgott and co-workers have repeatedly suggested that differences between control and irradiated rats in shock avoidance situations are due to the latter's increased "fearfulness". That these animals are more autonomically reactive to aversive or novel stimuli may be sur-

mized from the ambulatory behavior of irradiates upon exposure to novel open field situations reported earlier. In addition, both prenatal and neonatally irradiated rodents showed significant differences in defecation when exposed to open field situations (Nash, Napoleon & Sprackling, 1970; Werboff, Havlena & Sikov, 1962; Furchtgott & Echols, 1958a). The duration of sniffing at novel objects was lowered in rats irradiated during the 16th day of fetal life on the first test day only, and reached the level of control animals by the second test day (Furchtgott, Tacker & Draper, 1968). These experimenters also found that the initial higher heart rate of irradiates when exposed to a novel situation, gradually reached control values by the end of a 60 minute period. Furchtgott, Murphee, Pace and Dees (1959) and Hupp, Pace, Furchtgott and Murphee (1960), found that male rats that had been fetally irradiated between day 18-20 showed diminished copulatory behavior. Again, the behavior has been interpreted as greater "fearfulness" (autonomic reactivity) in fetally irradiated rats.

The juvenile and adult behavioral changes associated with pre- and neonatal irradiation are assumed to be a consequence of the changes in susceptibility of different tissues, during different periods of gestation, to the altering effects of ionizing radiation (Hicks, D'Amato & Falk, 1962). It is known that the migrating and multiplying cells from the various proliferative zones in the embryo and fetus are especially radiosensitive. In the Central Nervous System (CNS), however, irradiation as early as day 5 or 10 of gestation did not result in morphological pathology owing to the absence of radiosensitive neuroblasts (Hicks,

1952), while irradiation in late gestation (day 15 or 20) resulted in long lasting pathology. Although the developing organism is a progressively changing mosaic of cell populations whose precisely organized proliferating and differentiating cells are never long in a steady state, definite pathological changes of morphology in the CNS as a function of time or irradiation can be predicted.

The cerebrum of the rat is essentially built from the proliferative cell zone that lines the ependymal layer of the ventricles. Oster-tag (1969) reported that localized malformation of the dorsolateral angle of the ventricle, the transition of the precentral region to the sensory cortex or area striata, followed irradiation with 180 R on the 12th day of fetal life. Irradiation with 150-200 R on prenatal day 13-14 resulted in a very thin neo-cortex (Hicks, D'Amato & Lowe, 1959; Brizzee, Jacobs & Kharectchko, 1961), especially over the crown of the pallium with an associated ectopic mass of cortical tissue lying between the thin cortex and the lateral ventricle below. The hippocampal commissure was essentially normal, but some aberrant fornical fibers ran forward in small bundles in front of the anterior commissure, through the septa, and then back in the ventral hypothalamus to the mammillary nuclei. The lateral neocortex, pyriform, olfactory, and other basal corticles were reduced in size, but not distorted architecturally. An increased proliferation of glial cells has also been reported (Valcana, Vernakakis & Timiras, 1966). Animals irradiated on the 16th or 17th day of fetal life with 200 R showed markedly reduced forebrains (Hicks, and D'Amato, 1966), the hemispheres and cortex being chiefly affected. The neocortex was cyto-

architecturally scrambled (Lipton, 1966), with layers of abnormally large neurons, while the diencephalon and striatum were somewhat reduced in size but not necessarily in deficit (Hicks & D'Amato, 1966). Abberant bundles of thalamocortical fibers ran irregularly into the cortex. Exposure to 200 R on prenatal day 18 also produced a smaller forebrain in the rat, but the patterns were different from those just described. The cerebral mantle, which includes the cortex and sub-adjacent white structures, was reduced in amount. The cortex, about half the normal thickness, was laminated, but with abnormal neurons. From day 19-23 the outer layers of the cortex were most severely affected, layers II, III, and IV failing to develop (Berry & Eayrs, 1966) along with the corpus collosum (Berry & Eayrs, 1970). As the cerebrum became more and more radioresistant after birth, less damage was detectable. However, doses of up to 1000 R on the first day of birth produced pathological changes in the basal ganglia, medulla, and hypothalamus (Clemente, Yamazaki, Bennett & McFall, 1969).

The cerebellum, which first becomes recognizable between the 16th and 17th day of fetal life, showed only slight disturbances of basic shape and little change in cytoarchitecture when irradiated during this time with 200 R (Hicks, 1959). By the 18th day of fetal life, the cerebellum became more and more sensitive until at day 22, there was a jumbling of granule cell and Purkinje cell layers. Rats irradiated with 200 R on the first day of birth showed small cerebelli and irregular configurations in virtually all lobes, but most marked in the hemispheres (Lipton, 1966). The Purkinje cells were out of place and penetrated into the

granule cells layer and folial white matter. Myelinated fibers (mostly Purkinje cell axons), followed tangled courses and were diminished in numbers, though many went appropriately to the basal cerebellar nuclei (Hicks, et al., 1969). Apparently as little as 20 R in the 1-day old rat permanently, if subtly, altered the morphology of the Purkinje cells (D'Amato & Hicks, 1965).

Irradiation on postnatal day 3 was associated with irregularities in the folia of the vermis and a reduction in volume of fibers running from side to side in the anterior part of the base of the cerebellum (Lipton, 1966). The cytoarchitecture of the Purkinje cells were similar to day 1 rats. Postnatal day 5 and 6 animals featured an ectopic granule cells layer arrested in the molecular zone among the Purkinje cells dendrites, which formed arrays with their own mossy fiber endings. The ectopia was most noticeable in the anterior half of the vermis. Focal irradiation of the irradiation on day 5 was also associated with reduction of pontine and restiform fibers, although the basal cerebellar nuclei were unaffected as to individual nerve-cell bodies and glial cell populations (Hicks, et al., 1969).

The external granular layer covers the surface of the developing cerebellum and is essential for the production of cell populations in the cerebellar cortex (Mares, Lodin & Srajer, 1970). Altman, Anderson and Wright (1969) have found that this proliferative cell matrix can recover from a single head only dose of 200 R on postnatal day 3. With repeated daily doses of 200 R, however, this zone showed less regeneration (Altman & Anderson, 1971). (These authors contend that even after

head only doses of 10 x 200 R, the number of Purkinje cells are not affected, although after only two doses of 200 R there was disoriented growth in these structures.) During neurogenesis in the cerebellum, the migration of granule cells from the external granular layer is in a precise phase relationship with the developing Purkinje cells (Altman & Das, 1970; Altman, Anderson & Wright, 1968). Apparently, the important consequence of exposure to low (1-2 x 200 R) doses of ionizing irradiation is not only that the time left for possible recovery of the external granular layer before neurogenesis ends (about 21 days after birth in the rat) is reduced, but that the Purkinje cells are forced seriously out of phase with the production of granule cells. The latter desynchronization, could lead to permanent, if subtle changes in the cortical morphology of the cerebellum. Dobblings, Hopewell, Lynch and Sands (1970) showed that recovery following 600 R head only irradiation on postnatal day 7 was far from complete, even in adult animals. Juvenile animals irradiated after 21 days of age with doses that cause disturbances of neurogenesis in the first two weeks of postnatal life, showed such little cytoarchitectural deficits, that they were often used as controls (Hicks, et al., 1969).

Altman, Anderson & Wright (1968) have reported that the anterior-posterior growth of the cerebellum, the main axis of growth of the arborizing dendrites of Purkinje cells was considerably retarded following irradiation during the first few days of life. The arrest of caudal-rostral growth was obvious even in 90 day old animals and was a function of the number of daily doses (Wallace & Altman, 1969). There was no

discernable influence upon the lateral growth of the cerebellum. The total weight of the cerebelli of rats irradiated with more than 200 R during the first seven days of postnatal life was much smaller than controls, being reduced as much as 35-61% to that of controls at 60 days of age (Dobbing, et al., 1970; Maletta & Timira, 1966).

The developing nervous system is not alone in its radiosensitivity. Malformation of the skeletal system occurred as early as the first day of embryonic life (prenatal day 1), with doses as low as 15 R (Ohzu, 1965). Other systems became increasingly radiosensitive after the period of major organogenesis (between 7 to 13 days after conception), when the ability of radiation to give rise to structural malformations was much reduced. The fetal hematopoietic system, as reflected by the peripheral blood cells, was radiosensitive at 15 days of gestation (Hazzard & Budd, 1969). Irradiation between the 15th and 18th day of gestation with 160-220 R resulted in reduced spleen, thymus, kidney and sometimes liver weights in juvenile and adult rats (Martin, 1969; Martin & Murphee, 1969; Sikov, Resta & Lofstrom, 1969). Martin (1969) reported that these reductions were due to decrements in total cell numbers in these organs. Alimentary and urogenital problems were also noticed in these rats. The testes of rats become especially radiosensitive from the 18th day of fetal life to a few days after birth, the major effect of irradiation being associated reduction in total weight. Hupp, Pace and Furchtgott (1960) have shown that rats exposed to 150 R on prenatal days 19-22 had the lowest testicle weights when compared to rats irradiated before this time and to controls. The thyroid gland, which has

recently been shown to have an important role in neurogenesis (Hamburgh, 1970) rapidly became radiosensitive on the 17th day after conception (Spert, Quimby & Werner, 1951; Sikov, 1969; Walinder & Sjoden, 1969). The main effect was impairment of thyroid growth and activity. Irradiation of the neonate was less effective than prenatal exposure, although a head only dose of 100-250 R depressed the uptake of tri-iodothyronine by the CNS, relative to controls (Cohan, Ford, Rhines & Thompson, 1969). By the time of weaning (21 days of age), the radiosensitivity of the thyroid had reached adult levels (Doniach, 1957).

Irradiation effects are not isolated to pathological changes measureable only after necropsy or upon histological analysis. Gross changes in either appearance, mortality, and/or body weight were noticed in rats exposed prenatally or neonatally to irradiation. Hicks (1953), Hicks and D'Amato (1961) and Rugh and Wolf from (1965) have published time-tables concerning LD-50³⁰s, deformities, and other gross observations of rodents that have been fetally irradiated. (In this situation, the LD-50, lethal dose-50, is the dose of prenatally administered radiation required to produce 50% mortality in the offspring within the first 30 postnatal days) These changes vary with the LD-50³⁰ dose for the offspring, which ranges from 155-200 R between the 7th and 9th day of fetal life to over 400 R by late gestation and birth. Exposure to 100-400 R on prenatal days 6-9 resulted in gross malformations or absences of parts of the head, e.g., exencephaly, microcephaly, and deformed eyes, ears, shortened tails, and overlapping jaws and teeth. By prenatal days 10-13, these gross anomalies in the offspring were more rare, although there was a persis-

tence of dactylic abnormalities (Kriegel & Reinhardt, 1969). While days 13-14 animals showed a greater incidence of hydrocephaly, irradiation after day 15 is associated with a marked reduction of gross changes in appearance. Other changes following prenatal irradiation have been reviewed by Brent (1971). The high mortality that is characteristic of fetally irradiated animals occurred mainly during the first few days of birth (Murphree & Pace, 1960), and was typified by more frequent cases of still birth (Sikov, Resta & Lofstrom, 1969), persistent amnions, and cyanosis (Rugh & Wohlfrom, 1965). Fetally irradiated animals, when compared to controls, showed a reduction of birth weights, ranging from 16-22% less than controls (Martin & Murphree, 1969). By 30 days of age this difference may be as great as 50% less than controls (Martin, 1969), but decline to as little as 15-20% after 60 days of age (Martin & Murphree, 1969; Sharp, 1965). Apparently, these weight decrements could be amplified by such environmental factors as food deprivation (Tacker & Furchtgott, 1963). Gross physical anomalies, with the possible exception of eye problems, were uncommon in neonatally irradiated rodents, although their adult weights remained as much as 13% less than that of controls (Nash, Napoleon & Sprackling, 1970). However, hydrocephaly and microcephaly can be demonstrated with higher (1000 R) doses (Clemente, Yamazaki, Bennett & McFall, 1969).

It has been assumed that the morphological and cytological changes that follow pre- and neonatal exposure to ionizing radiation are a consequence of the associated physio-chemical changes of the exposed matter (e.g., Schjeide & de Vellis, 1969). Investigations of such

chemical changes have been isolated mostly to neonate exposures, although significant increases in cerebrosides in the diencephalon has been reported in juvenile rats that had been exposed on the 14th day of gestation to 100 R (Vernadakis, Casper & Timiras, 1968). Head only irradiation of up to 900 R of X-irradiation on the first four days of post-natal life resulted in a decrease of brain 5-Hydroxytryptamine and noradrenaline levels (Palaic & Supek, 1969), but a long lasting increase of aerobic acetate in the medulla (De Vellis, 1968). Maletta and Timiras (1966) measured the various levels of total esterase in the blood and acetylcholinesterase (AChE) in various parts of the brains of rats that had been head only exposed to 450 R at three days of age. AChE was selected since it is a hydrolyzing enzyme of acetylcholine (ACh), a candidate transmitter in the CNS. At 10 days of age, the irradiated rats showed significant decreases in AChE in the sensorimotor cortex and cerebellum, but not in the hypothalamus or brain stem, while after 24 days of age, the decrease was noted only in the hypothalamus. An initial transient decrease of total blood level of esterase was noted in only the 10 day old rats. On the other hand, acetyltransferase (ChAc), the synthesizing enzyme of ACh was increased in the cerebelli of irradiated rats even at 61 days of age, but was not altered in the cerebral cortex, hypothalamus or spinal cord (Valcana, Vernadakis & Timiras, 1969). These authors suggested that the observed increase in ChAc activity in the cerebellum of the X-irradiated rat reflected preferential destruction of granular cells.

As a consequence of the volumes of data that have been collected

on the behavioral, morphological, and biochemical changes following pre- and neonatal exposure to ionizing radiation, possible relationships between these levels of investigation have emerged. Fetal irradiation before the 13th day of gestation seems to have little effect upon learning behavior. However, after prenatal days 14-15, when the waves of sensitive neuroblasts begin building the cortex, irradiation is associated with marked decrements in learning behavior. Most of these decrements were associated with perseveration of incorrect responses in several learning procedures. Also, an increase in activity in ambulatory situations was noted for these irradiates. These differences have been argued to be due to the lack of inhibitory control over subcortical centers by the cerebral cortex, whose size and cytoarchitecture have been grossly disturbed. The concomitant greater increase of cerebrosides an important component of myelin sheaths, in the diencephalic-midbrain regions, further allows relatively greater subcortical activity, thus possibly allowing greater sensitivity to electrical stimulation, seizures, and reactivity to novel, e.g., open field, stimuli. It is known that cortical excitability is modified not only by changes in intrinsic dendritic excitability, but by input from the brain stem reticular formation and diencephalon as well (Berry & Eayrs, 1970). Accompanying the "fearfulness" which had been described in rats irradiated between prenatal days 14 and 17 are the malformations of the fibers and structures of the limbic system, long associated with "emotional" behavior. Motoric disturbances during this time were related to the development of essential reflex systems that were being completed at

the time of irradiation. However, as the fetus develops and the radiosensitivity of the cerebrum was decreased and that of the cerebellum was increased, different behavioral abnormalities were observed. Following neonatal irradiation motoric disturbances were restricted mostly to those associated with coordinated activity, a finding that fits well with one current supposition that the cerebellum is a regulator rather than an initiator of CNS activity. (Everett, 1971). The relative increase of the chemical precursor of ACh concomitantly with a decrease in the latter's hydrolyzing enzyme was suggested to reflect the known destruction of granule cells, perhaps allowing greater reactivity to electroshock. Finally, the juvenile rat's relative radioresistance to ionizing radiation was reflected about the same time (circa 16-22 days of age) in both its behavioral and physiology. These are but a few of the plausible relationships that could exist between the behavioral, physiological, and biochemical changes in the irradiated organism.

Recently, Halasz, Hughes, Humpherys and Persinger (1970) have argued that rats with radiogenically malformed cerebelli in a DCA (delayed conditioned approach) paradigm (Halasz, 1969), would not be expected to show gross differences in learned motor behavior during maintained (steady-state) contingencies, when deficits would be masked by compensation, but rather in the transient behavior associated with changes in reinforcement schedule. As shown in Figure 1, the DCA procedure is a discrete trial, discriminated interval response associated with a "second-order" DRL component ("trial abort") between signals. The animal must delay its response to the signal (CS) associated with availability of rein-

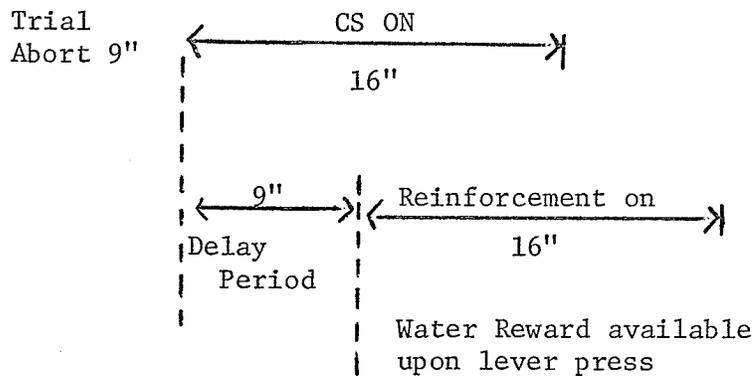


Figure 1. DCA procedure

reinforcement for lever pressing since "premature" responses are not reinforced with that reinforcement. This is called the "delay" component of the schedule. Since the DCA paradigm is a discrete trial procedure, intertrial responses (S^{Δ} responses) are attenuated by the use of a second-order DRL ("trial abort") component. Responses emitted within some programmed time before the onset of the CS of the next trial, will result in the "loss" of that trial ("trial abort"). In the Halasz, et al. (1970) study, a nine second trial abort was instituted into the procedure so that a lever press nine seconds or less before the onset of the next trial prevented the occurrence of that trial.

Since the DCA paradigm is designed so that both "premature" responses emitted during a non-reinforced delay period and responses emitted between trials can be measured, a "breakdown" in what has been termed an animal's "inhibitory behavior" in this situation might be reflected by increased "premature" responding during the delay component, increased trial aborts (indicative of greater intertrial respond-

ing), or by both measures. If neonatal irradiation interferes with elimination of responses during periods of non-reinforcement, such decrements would be manifested by an increase in one or both of the above measures, i.e., increased number of "delay" responses and increased "trial aborts."

In addition, the parameters of both the "delay" and "trial abort" components can be incremented in such a way that step, impulse or ramp inputs are simulated (Halasz, 1968, 1967). Such manipulation of the delay and trial abort components potentially adds another dimension of analysis to the DCA procedure: Increased "premature" responding and trial aborts during steady-state (maintained) contingencies but not during changes of schedules (transient responses) or vice-versa, could suggest what neural structure(s) are associated with these particular behaviors. For example, forebrain damage might be indicated by increase in "premature" responses during delay and intertrial intervals when the animal is on a maintained reinforcement contingency, i.e., "defect of inhibition" while damage to the cerebellum whose neural role can be seen as analogous to a "regulator" of on-going motor behavior, might be reflected by transient increases in one or both of the above measures only following schedule changes.

Halasz, Hughes, Humpherys and Persinger (1970) found that adult rats which had been gamma-irradiated at three days of age with 250 rad, (the roentgen, R, is the unit for energy released in the air following exposure to ionizing radiation, while the rad is the unit for energy absorbed in the exposed matter. In this manuscript, the effects of

the same R or rad doses are considered comparable), exhibited behaviors similar to controls in a simple S^D-S^A situation, where water reinforcement was available during a tone (S^D , CS). However, when a nine second "trial abort" was instituted into the paradigm, the irradiated rats emitted more total and intertrial responses, than controls. These differences attenuated after two to three sessions. Finally, when a "delay" of 0-9 seconds was instituted in a step-like manner between the onset of the CS and the availability of the reinforcement, irradiated rats emitted significantly more "premature" responses which occurred in a series of rapid "bursts" during the "delay" period. Control animals responded at a rate similar to rates emitted before the step-input or waited until the delay was completed before responding was resumed. Malformation of the cerebelli of the irradiated rats was histologically confirmed.

The present study undertook to replicate and extend these procedures in the following ways: 1. by testing not only neonatally but also prenatally Co^{60} irradiated animals in the DCA problem, 2. by testing the effects of not only ionizing (Co^{60}) radiation, but also those of an extremely low frequency (ELF) electromagnetic field on steady-state and transient behavior in the paradigm, 3. by correlational analysis between numerical indices of forebrain and cerebellar malformation and those of observed behavioral abnormalities, and 4. by including control experiments for possible "drive" differences between normal and irradiated subjects.

The first of these was dictated by the consideration that not only high frequencies of "trial aborts" but also "premature" response

bursting could be explained in terms of a "perseverative" forebrain syndrome, (Green, Saporta & Walter, 1970; Thompson, 1964) based on the definite, if slight, reduction of cerebral hemispheres in the neonatally exposed rats (Altman, Anderson, and Wright, 1969; Humpherys, 1971). Rather than continuing to press the role of the cerebellum by argument from the differences between transient and steady-state behaviors, it seemed best to compare the effects of neonatal treatment, which combines great cerebellar and slight cerebral size reduction, with that of prenatal treatment, which results in great cerebral, but slight cerebellar size reduction.

Secondly, unpublished experiments with rats that have been exposed during their entire prenatal development to an ELF (Extremely low frequency) Rotating Magnetic Field (RM F), have shown behaviors similar to Co^{60} irradiates in the DCA procedure. If the cerebellum is indeed the major neural structure associated with these behaviors, neonatal exposure, e.g., days 1-4 postpartum, to the ELF-RMF should increase the observed effects while exposure only on prenatal days 13-16 should reduce the effect. Although further statements cannot be made until the histological and behavioral data have been collected, there is the suggestion that the developing cerebellum can indeed be affected by the ELF field. Rats exposed during their prenatal development to a 0.5 Hz, 0.5 to 30 gauss, RMF show significantly less ambulatory behavior in the open field, (Ossenkopp, 1971; Persinger, 1969), greater variance in ambulatory behavior (Persinger, 1971) fewer lever presses in a Sidman avoidance situation (Persinger & Foster, 1970), greater

conditioned suppression (Persinger & Pear, 1971), heavier but more variable thyroids (Ossenkopp, Koltek & Persinger, 1971), and a delay in eye opening and teeth eruption (Ossenkopp, 1971). Collectively, these behavioral and physiological changes characterize hypothyroid rats. Hypothyroidism, induced by thyroidectomy during the first three days of birth, delays the later migration of cells from the external granular zone and results in hypoplasia of the dendritic spread of Purkinje cells (Hamburgh, 1970; Legrand, 1969). Evidence for such an effect due to ELF neonatal exposure would have immediate social relevance since similar fields occur daily in the geophysical-meteorological environment. Extremely low frequency (ELF) electromagnetic fields (0.1 to 40 Hz, Ludwig and Ranscht-Froemsdorff, 1966) and very low frequency (VLF) carrier waves modulated with ELF pulses are associated with tropospheric lability ranging from lightning discharges as distant as the Amazon Valley and central Africa (Holzer & Deal, 1965) to atmospheric changes as close as a few km from the measurement point (König, 1962). Different frequencies within the ELF range are associated with different types of weather. Electromagnetic (EM) waves of 2-5 Hz are "top-waved" and appear before thunderstorms (König & Ankermüller, 1960) and during rain or heavy deep lying clouds (König, 1962). Signals of 9-10 Hz (Schumann resonance), which show sine-like oscillations are apparently produced by strong lightning and show diurnal changes in intensity. Sine-like ELF signals between 0.5-2 Hz have also been measured, but their origin is unclear.

During stable weather conditions, ELF pulse frequencies of 1-3 Hz superimposed upon a 10 kHz carrier wave have been measured, while during unstable weather conditions (e.g., close passage of a cold and warm front), a marked increase in the incidence of pulse frequencies of 30-100 Hz, superimposed upon a 10-100 kHz carrier have been measured (Lotmar, Ranscht-Froemsdorff & Weise, 1969). ELF-EM waves also show a significant increase 29 days following 200 MHz bursts associated with solar eruptions (Aarons & Henissart, 1953). Even the geomagnetic field has an ELF component (Graf, Cole, Weathers, Simms & Johnson, 1967; Campbell, 1967). Local geophysical-geographical variables such as underground water level, mineral content of water, and altitude, effect ELF-EM wave and VLF carrier distributions (Ranscht-Froemsdorff, Weise & Klein, 1969; Ludwig, Mecke & Seelewind, 1968). The intensities of geomagnetic pulsations average less than one gamma [the intensity of the main "static" dipole field of the earth is about 5×10^4 gamma (0.5 gauss)] with some cavity resonances typically measuring 0.2mV/m (Campbell, 1967). The intensities of the electrical component of the ELF wave ranges from >100mV/m to <1mV/m, while the magnetic component is about 10^{-5} A/m (<1 gamma). The energy available, for instance, to a synaptic cleft from these fields has been calculated to be 1.5×10^{-14} ergs (Ludwig & Ranscht-Froemsdorff, 1966). This is well within the range of the 0.5×10^{-14} erg energy change that occurs in a synaptic cleft during miniature excitatory post synaptic potentials (EPSPs) (Eccles, 1964).

In addition, there are definite physiological changes that follow

ELF exposure which may be associated with the observed behavioral modifications. Using ELF-pulse frequencies which simulated natural wave forms in both frequency and intensity, Lotmar, Ranscht-Froemsdorff & Weise, 1969) found a 42% decrease in the respiration rate of exposed mouse liver tissue. Similar decreases in oxygen uptake during exposure to a 1.75 Hz (no carrier wave) electromagnetic field have been observed in several species by Altman (1969). Piccardi (1962) found that VLF (10 kHz) EM fields (he does not mention possible ELF pulses) specifically affected the clotting-precipitation time of colloids, e.g., blood, in water solution. Although the mechanism by which these physiological effects occur is not known, Persinger, Glavin and Ossenkopp (1971) have suggested that ELF-EM fields effect the macromolecules of specific size and shape that exist in a liquid crystalline state in the living organism. Ludwig (1971) has mathematically localized these effects to changes in the ionic milieu of the synaptic cleft in the CNS.

Another modification of the main replication experiments was the use of more than one exposure dose. Despite the precautions, previous results with both RMF and gamma-irradiation exposures might be attributed to artifacts of procedure. One way of minimizing this problem was by measuring the behavior of rats that had been given different doses of gamma and ELF-RMF fields. Hence it was decided to use two irradiation doses of 100 and 200 rad (plus controls) and two RMF intensities of 0.5-3 and 3-30 gauss (plus controls).

A final modification of the main replication experiments was the use of female rats as subjects. Females were used because: 1) accord-

ing to the results of preliminary experiments, they showed greater total responses over baseline after the institution of a 0-9 second delay; 2) the body weight difference between irradiated and RMF-exposed rats, relative to controls, was less exaggerated in the females (this was considered to be an important factor in a lever pressing situation); and 3) there was a large amount of pilot data collected on this sex in our laboratory which showed that once the S^D-S^Δ and trial abort components are added to the schedule, there is little variability of total lever presses from day to day. The contribution of the oestrus cycle to this situation was minimal.

In summary, this study was conducted in order to compare the behavior of rats exposed to electromagnetic fields of two different energies (gamma-irradiation, 10^{19} Hz; and Extreme low frequency (ELF) fields, 10^0 Hz), at two different times of development (prenatal day 16 and neonatal day 4). The latter comparison was used to indicate the possible association of predominantly forebrain damage (exposure on prenatal day 16) or cerebellar damage (neonatal day 4) with behavior in the DCA procedure.

The remaining contents of this manuscript are placed in five chapters (Chapters II, III, IV, V & VI). Chapter II is concerned with preliminary experiments that deal with possible artifactual factors that may have contributed to the observed "abnormal" transient behaviors in the experimental subjects tested in the DCA procedure. Thus differences are examined between irradiates and controls as a function of different water deprivation levels. Differences between pre- and neo-

natally exposed irradiated and RMF rats are examined in acquisition and extinction of a bar press response and the frequency of running wheel activity. The results of preliminary DCA testing of neonatally irradiated and control subjects along with those that had been exposed during their entire prenatal development to an ELF-RMF, are then presented. Chapter III deals with the Method for the main experiments. Chapters IV and V report the results of the behavioral and physiological-histological data, respectively. Chapter VI relates these in a discussion section.

CHAPTER II

PRELIMINARY EXPERIMENTS: METHOD AND RESULTS

METHOD

Subjects

Experiment I. Five 70 day old naive Holtzman strain female rats that had been exposed to 200 rad on post-natal day 4, day 1 being the day of birth, and five female control rats of comparable age, were used as subjects.

Experiment II. Twenty-four, 60 day old naive Holtzman female rats were used as subjects. Four different females had been exposed to each of six conditions: 1. to 200 rad of gamma-irradiation on prenatal day 16, day 1 being the day that spermatozoa was found in their mother's vaginal smears; 2. to a 3-30 gauss, 0.5 Hz, RMF between prenatal days 13-16; 3. to prenatal control conditions; 4. to 200 rad of gamma-irradiation on post-natal day 4 (again, three days of age); 5. to a 3-30 gauss, 0.5 Hz, RMF on post-natal days 1-4, and 6. to neonatal control conditions.

Experiment III. The twenty-four female rats, 66 days of age, that had been selected in Experiment II, were used as subjects.

Experiment IV. Twenty-eight 60 day old naive female Holtzman rats were used as subjects. They had been exposed to the following six conditions, the number in each condition being noted parenthetically; 200 rad on prenatal day 16 (6); control conditions on prenatal day 16

(4); 200 rad on neonatal day 4 (5); control conditions on that day (5); a 3-30 gauss 0.5 Hz, RMF on neonatal days 1-4 (4); and neonatal control conditions (4).

Experiment V. Three naive 60 day old Holtzman female rats that had been exposed at three days of age to 200 rads of gamma-irradiation and three control females, 60 days of age, were used as subjects.

Experiment VI. Five, 100 day old Holtzman female rats that had received 200 rad gamma-irradiation at three days of age and five control females of comparable age, were used as subjects. All subjects had been subjected to extinction of lever pressing for water reinforcement 20 days before the experiment.

Experiment VII. Sixteen, 60 day old Holtzman naive female rats were used as subjects. Four had been exposed to a 0.5 Hz, 0.5-3 gauss RMF, while another four had been exposed to a 3-30 gauss RMF during prenatal days 1-21. Four other females had been exposed to sham-RMF control conditions, while the remaining four females had been exposed to non-sham RMF control conditions, during the same period of prenatal development. All animals had been removed from their respective conditions at birth.

Apparatus

Rotating Magnetic Field Apparatus. The Rotating Magnetic Field (RMF) was created by two horseshoe magnets rotating in opposite directions about their major axes at 30 RPMs by an electric motor. The intensity, as measured by a Rawson-Lush Gauss-meter) ranged from 3-30 gauss in the central exposure compartment and from 0.5-3 gauss in the

two peripheral exposure compartments. More precise details and a diagram of the apparatus have been reported elsewhere (Persinger & Pear, 1971; Persinger, 1969).

Gamma-Irradiation Apparatus. The gamma-irradiation source was a Co^{60} isotope that delivered 5.6 rad/minute and was located at the Cancer Research Division of the University of Manitoba Medical College.

Operant Chambers and Running Wheels. Two sound-attenuated Lehigh Valley Operant Chambers, with the right lever adjusted so that a force of 24 gm produced water reinforcement, were used. The CS, a 1 kHz, 74 db pure tone, was generated by a EICO Model 377 sine-square wave audio generator. Experimental contingencies were programmed by BRS logic units (Halasz, 1968). Precision probability units ensured the "randomization" of trial presentations. Six commercial running wheels were also used.

Procedure

Exposure. Once pregnancy had been determined by the presence of spermatozoa in the vaginal smears, the mothers of the females that were used as subjects in the seven experiments were placed in their respective conditions. Prenatal exposure to the RMF entailed placing the pregnant mothers in either the central (3-30 gauss) compartment on days 13-16 of gestation (Experiments II & III) or on days 1-21 of gestation (Experiment VII), or, in the peripheral compartments (0.5-3 gauss) during the latter period (Experiment VII). Prenatal exposure to gamma-irradiation involved exposing the pregnant mothers on day 16 of gestation, day 1 being the day spermatozoa was found in the vaginal smears, to 200 rad

(Experiments II, III & IV). Other pregnant mothers were placed in prenatal control conditions. In Experiment VII, the RMF control mother had been placed in the usual control conditions 200 cm from the RMF while the sham-RMF control mothers had been placed in the running RMF-apparatus, with the magnets removed. Neonatal exposure to either irradiation or RMF conditions was completed by exposing the neonates to 200 rad on post-natal day 4 (Experiments I-VI) or on the 3-30 gauss RMF on post-natal days 1-4 (Experiments II-IV).

On day 22 postpartum (21 days of age), the (female) subjects were weaned and sexually segregated from their male litter mates. At 30 days of age, the subjects were separated into pairs of the same condition and placed in standard steel housing cages.

Testing. Experiment I. At 70 days of age, under 48 hours of water deprivation, the subjects were trained to press a lever for water reinforcement in the operant chambers. For the next six 30 minute daily sessions, the irradiated and control subjects were maintained on 23 hours of water deprivation, the total reinforcements received each session for each subject being recorded. Each group was then placed for three days on each of the following water deprivation schedules: 16 hours, "0" hours, 8 hours, 48 hours, and again, 23 hours. The total number of reinforcements received (lever presses made) during each of the 30 minute daily sessions for each subject was recorded.

Experiment II. At 60 days of age, subjects from the six conditions were exposed to the operant chambers in which a lever press produced water reinforcement. On the first day, the subjects were under

48 hours deprivation, but from then on they were maintained on 23 hours of water deprivation. The total number of lever presses displayed (reinforcements received) during each of the five 30 minute daily acquisition sessions for each subject was recorded.

Experiment III. At 66 days of age, after five days of continuous reinforcement in the operant chambers, the subjects, still under 23 hours of water deprivation, were placed on extinction. In this situation, a lever press was no longer associated with water reinforcement. The total number of lever presses made during the five consecutive 30 minute daily extinction sessions was recorded for each subject.

Experiment IV. After being maintained for five days on a 23 hour water deprivation schedule, the subjects from the prenatally and neonatally 200 rad exposed groups and their controls were run for eight consecutive daily 30 minute sessions in running wheels. The total number of wheel rotations for each rat in a session was recorded. The rats that had been exposed neonatally to the RMF, along with their controls, were run for only five consecutive daily 30 minute sessions in the running wheels. Again, the total number of wheel rotations for each rat in a session was recorded.

Experiments V, VI and VII. At 60 days of age, the subjects from the various conditions of the three experiments were trained to press a lever for water reinforcement. On the first day, the subjects were under 48 hours water deprivation, but from then on they were maintained on 23 hours water deprivation. After four days of CRF (continuous reinforcement), 30 minutes per day, a S^D-S^{Δ} schedule was initiated.

In this phase of the experiment, water only became available during the CS (tone). Lever presses during the absence of the CS produced no reinforcement. The CS and reinforcement availability onset and offset at the same time and lasted 25 seconds per trial. From the beginning of S^D-S^Δ training until the end of the experiments, a total of 30 trials were presented per session. When five testing days had elapsed a 9 second trial abort was instituted in order to reduce intertrial responding. A response by the subject 9 seconds or less before the onset of a subsequent trial resulted in the loss (elimination) of that trial. A response by the subject 9 seconds or more before the onset of a possible trial did not interfere with the presentation of that trial.

Six running days after the institution of the trial abort, a 9 second delay was inserted between the onset of the CS and the reinforcement in a step-like fashion on trial 16 of the session. For the next five sessions, and until the end of the experiments, reinforcement was delayed from the onset of the CS by 9 seconds. Lever presses during the delay period would not produce water reinforcement. For each subject the total responses emitted per session during the five sessions, before the delay was instituted, were used as baseline. Again, the dependent measure for these experiments was total responses emitted per session.

RESULTS

Experiment I. The average number of reinforcements received (responses emitted) for neonatally irradiated (NR2) and control (NRC)

groups as a function of different hours of water deprivation is presented in Figure 2. Each rat's average total reinforcements over the three days in each condition were the value used to compute the group averages for a given deprivation level. As a function of the 23, 16, 0, 8, 48, and 23 hours of deprivation, the irradiates averaged 1000, 426, 26, 398, 679, and 650 reinforcements, while the controls averaged 620, 222, 33, 230, 1090, and 639 reinforcements, respectively. The differences between the two groups were found by repeated measures analysis of variance not to be statistically significant ($F = 1.09$; $p > .05$).

Experiment II. The average total number of reinforcements received (responses emitted) by the prenatally 200 rad irradiated (PR2), 3-30 gauss RMF-exposed (PMH), control (PC) neonatally 200 rad irradiated (NR2), 3-30 gauss RMF-exposed (NMH) and control (NC) groups, over the five days of acquisition training is presented in Figure 3. A repeated measures analysis of variance found no significant differences between the groups ($F = 1.21$).

Experiment III. The average responses emitted during the five days of extinction for the above groups are presented in Figure 4. Again there were no significant differences between the groups for total lever presses displayed (responses emitted).

Experiment IV. The average number of running wheel rotations over sessions for the prenatally irradiated (PR2), control (PC), neonatally irradiated (NR2), control (NRC), and neonatally RMF-exposed (NMH) and control (NMC) groups is presented in Figure 5. A repeated

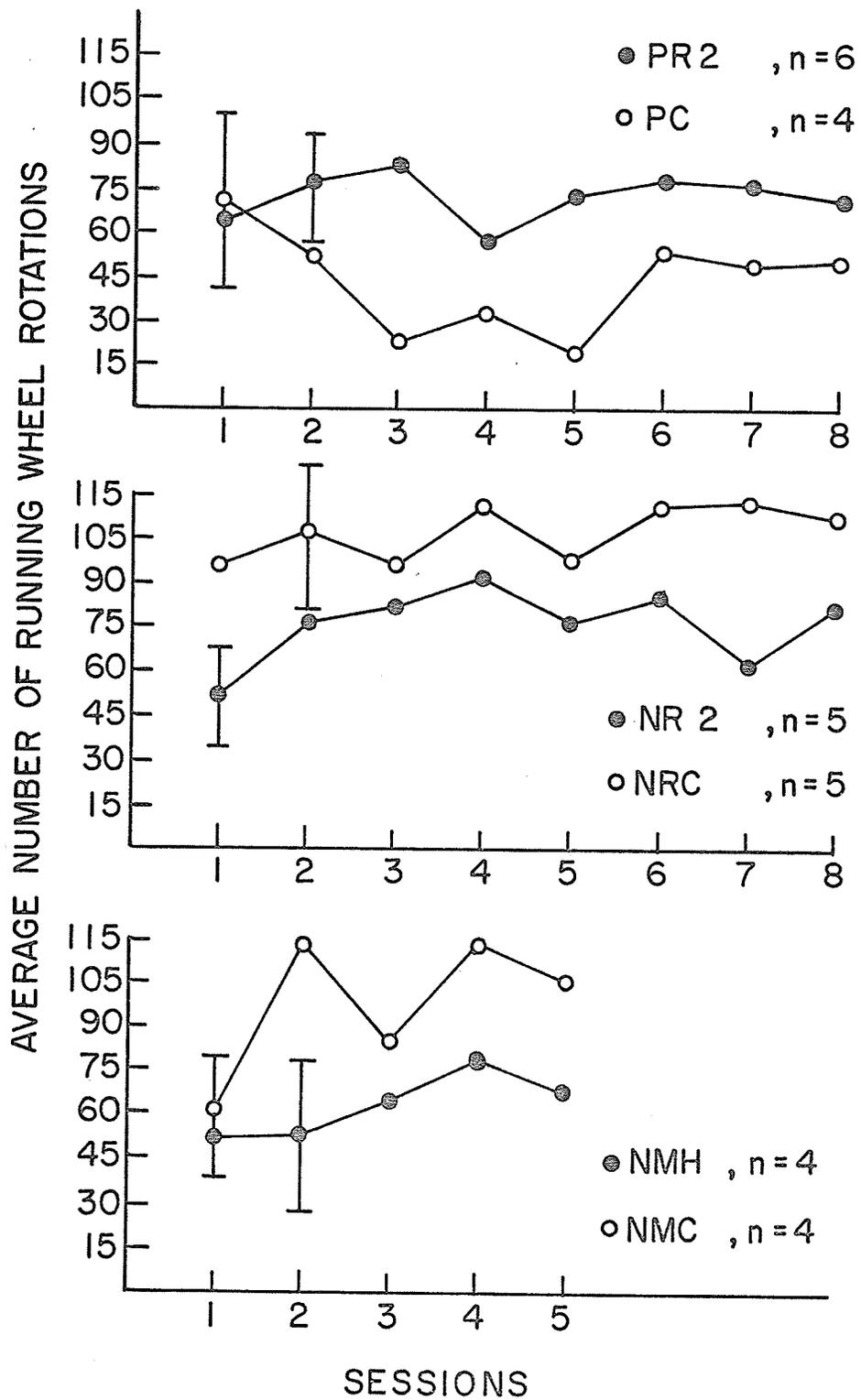


Figure 5. Average Number of Running Wheel Rotations Over Sessions for the Six Pre- and Neonatally Irradiated (PR2, NR2), RMF-exposed (NMH) and Control (PC, NRC, NMC) Groups. A typical standard deviation is given for each group.

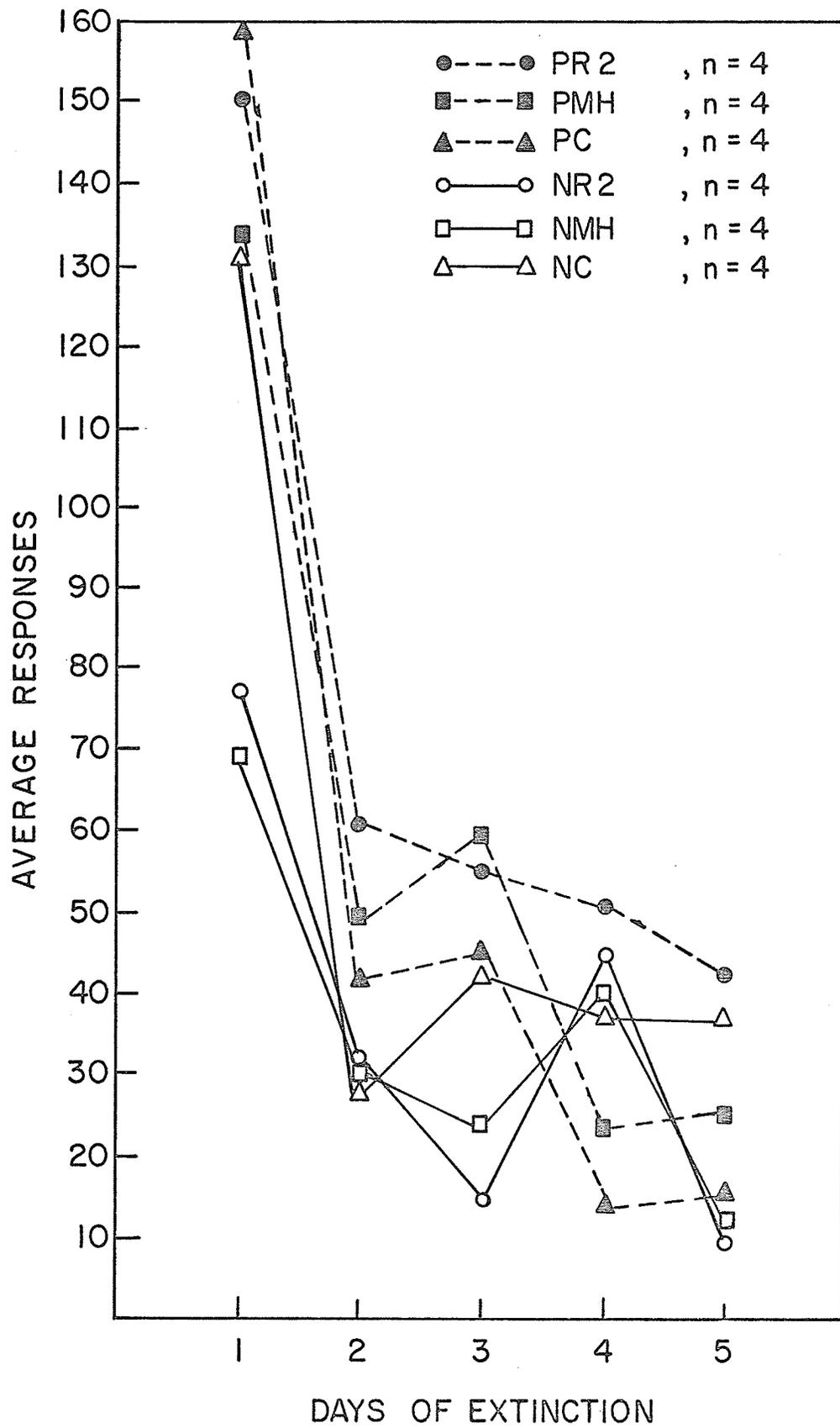


Figure 4. Average Total Responses Emitted as a Function of Days of Extinction, for the Six Pre- and Neonatally Irradiated (PR2, NR2), RMF-exposed (PMH, NMH) and Control (PC, NC) Groups.

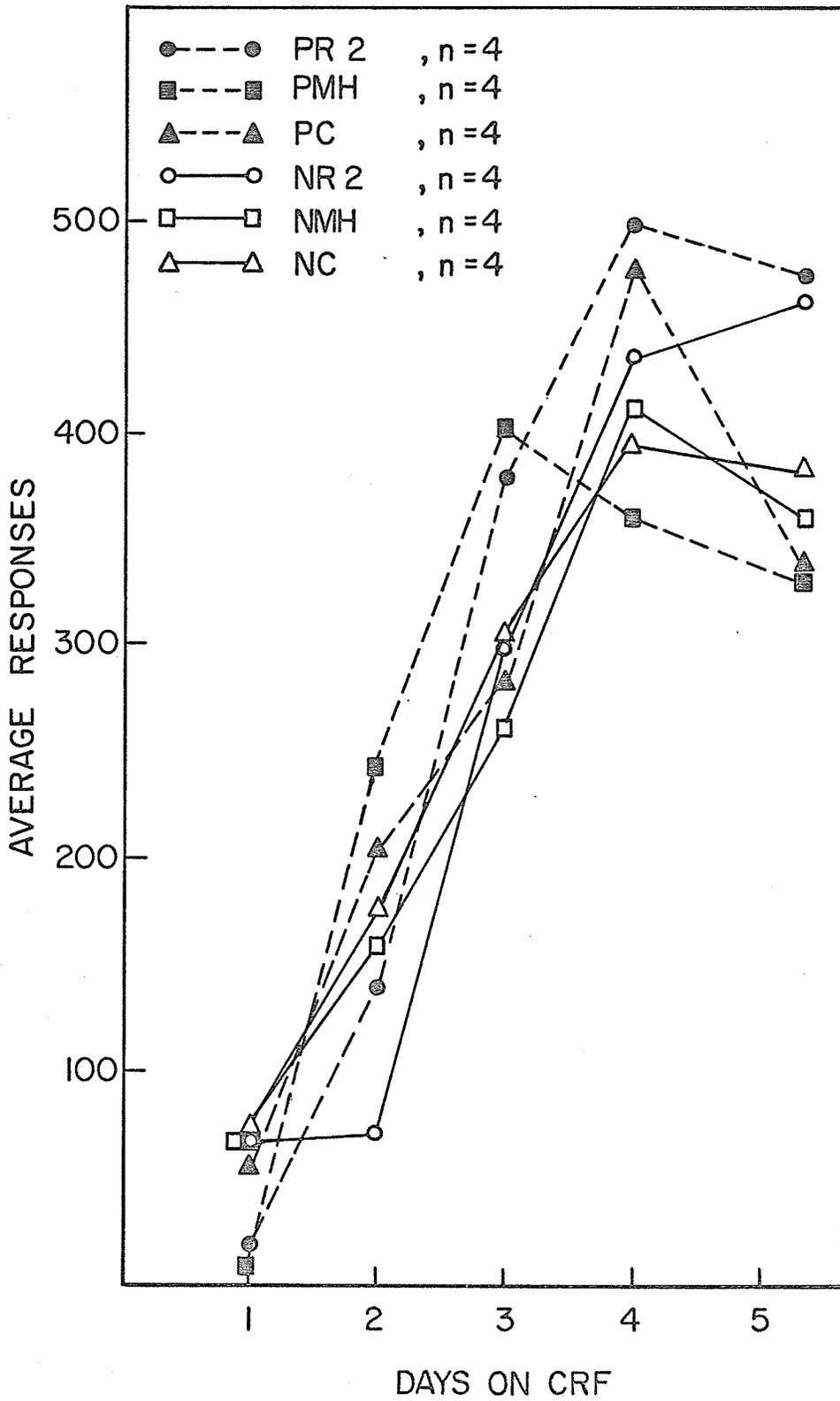


Figure 3. Average Total Reinforcements Received (Average Responses Emitted) as a Function of Days of Acquisition, for the Six Pre- and Neonatally Irradiated (PR2, NR2), RMF-exposed (PMH, NMH) and Control (PC, NC) Groups.

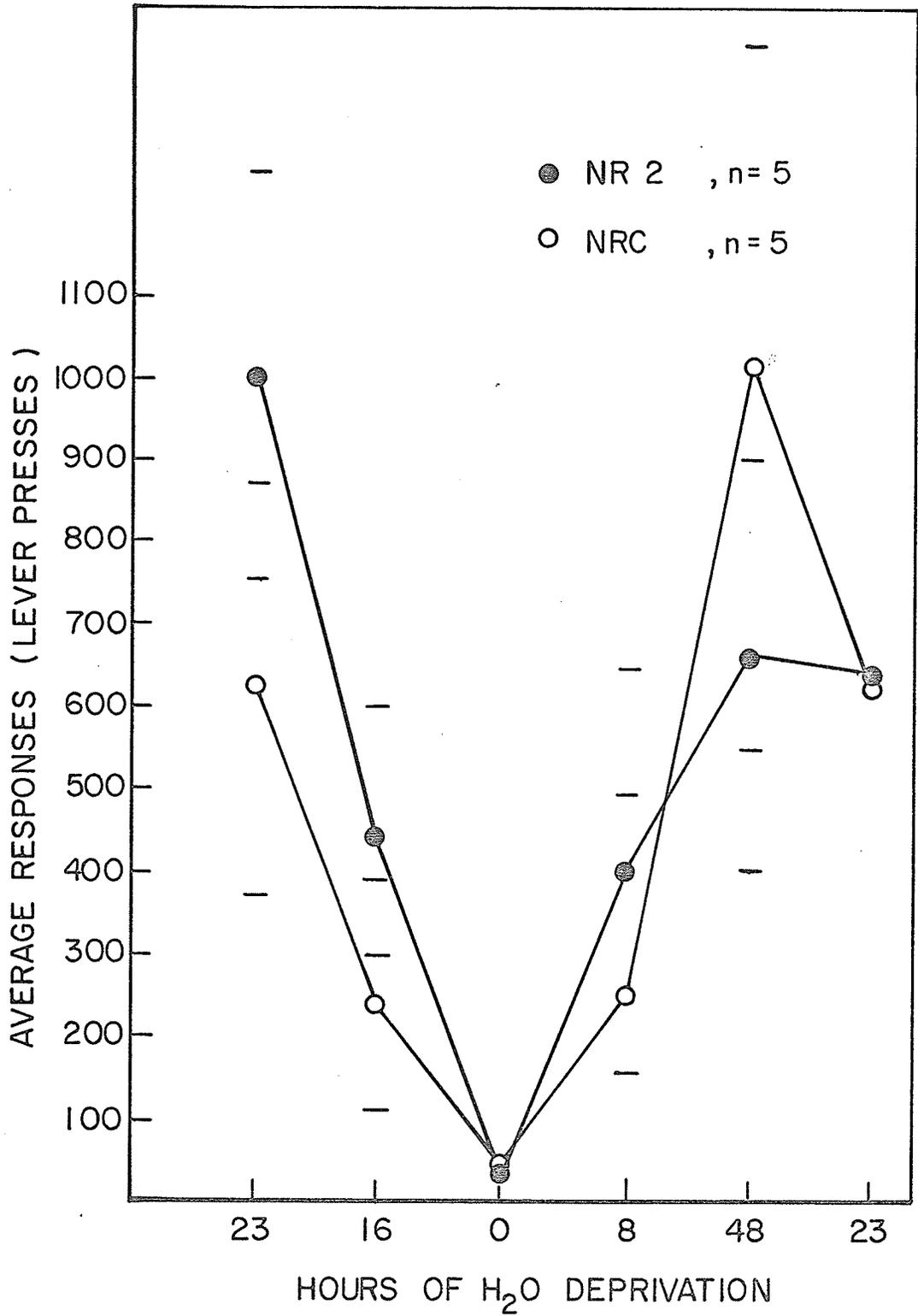


Figure 2. Average Responses (Reinforcements Received) as a Function of Hours of H₂O Deprivation for Groups Exposed Neonatally to 200 rad of Gamma-Irradiation (NR2) and Control (NRC) Conditions. The Horizontal Lines Indicate the Upper and Lower Limits for the Standard Deviation of a Given Data Point.

measures analysis of variance did not find any significant differences between the three experimental and their respective control groups ($F = 2.59, 4.50, \text{ and } 2.74$, respectively).

Experiment V. The average ratios of total responses to mean baseline total responses for the neonatally irradiated (NR2) and control (NRC) groups before and after the institution in a step-like fashion of a 0-9 second delay (Γ), are presented in Figure 6. The baseline was obtained by averaging the total responses emitted daily during the five 30 trial sessions before the institution of the step. As can be seen there was no difference between the average ratios of irradiated and control groups during baseline and the 15 trials before the step on step day. However, for the 15 trials after the institution of the delay (Γ), the irradiates had significantly higher ratios, indicative of more "premature" responding during the delay period, than controls ($p < .05, t = 2.85$). A repeated measures analysis of variance on post-step days showed no significant differences between groups ($F = 1.68$).

Experiment VI. The average ratios of total responses to mean baseline total responses for neonatally irradiated (NR2) and control (NRC) groups before and after the institution of the 0-9 second delay are presented in Figure 7. No significant differences were found between the two groups after the step (Γ) on step day or on post-step days ($t = 1.88; F = 1.98$, respectively).

Experiment VI. The average ratios of total responses to mean baseline total responses for groups exposed during their entire

Figure 6. Average Ratios of Total Responses/Mean Baseline
Total Responses During Baseline Step-Delay (Γ) and Post-Step
Sessions for Groups Exposed Neonatally to 200 rad (Gamma-Irradiation
and Control Conditions.

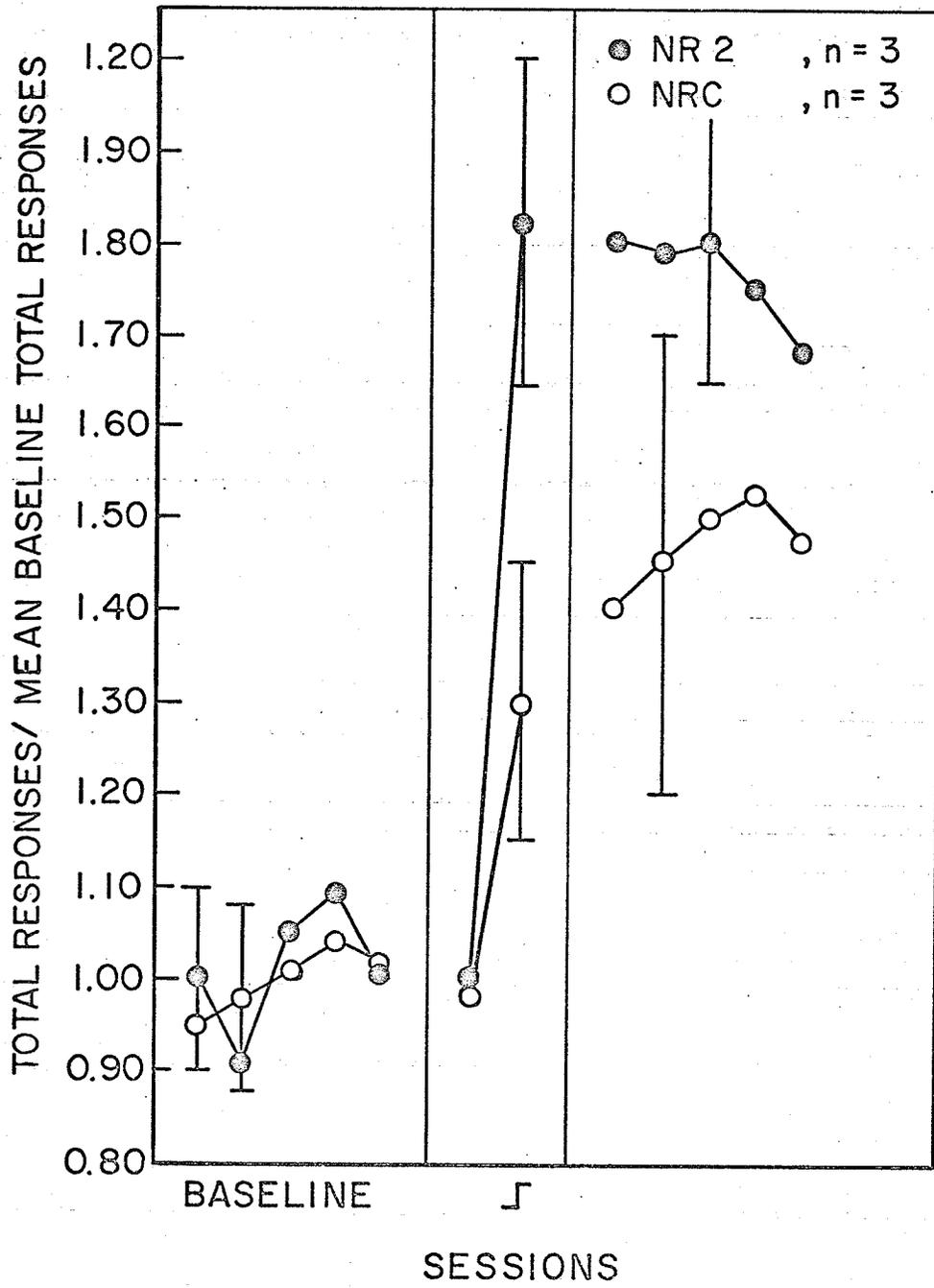
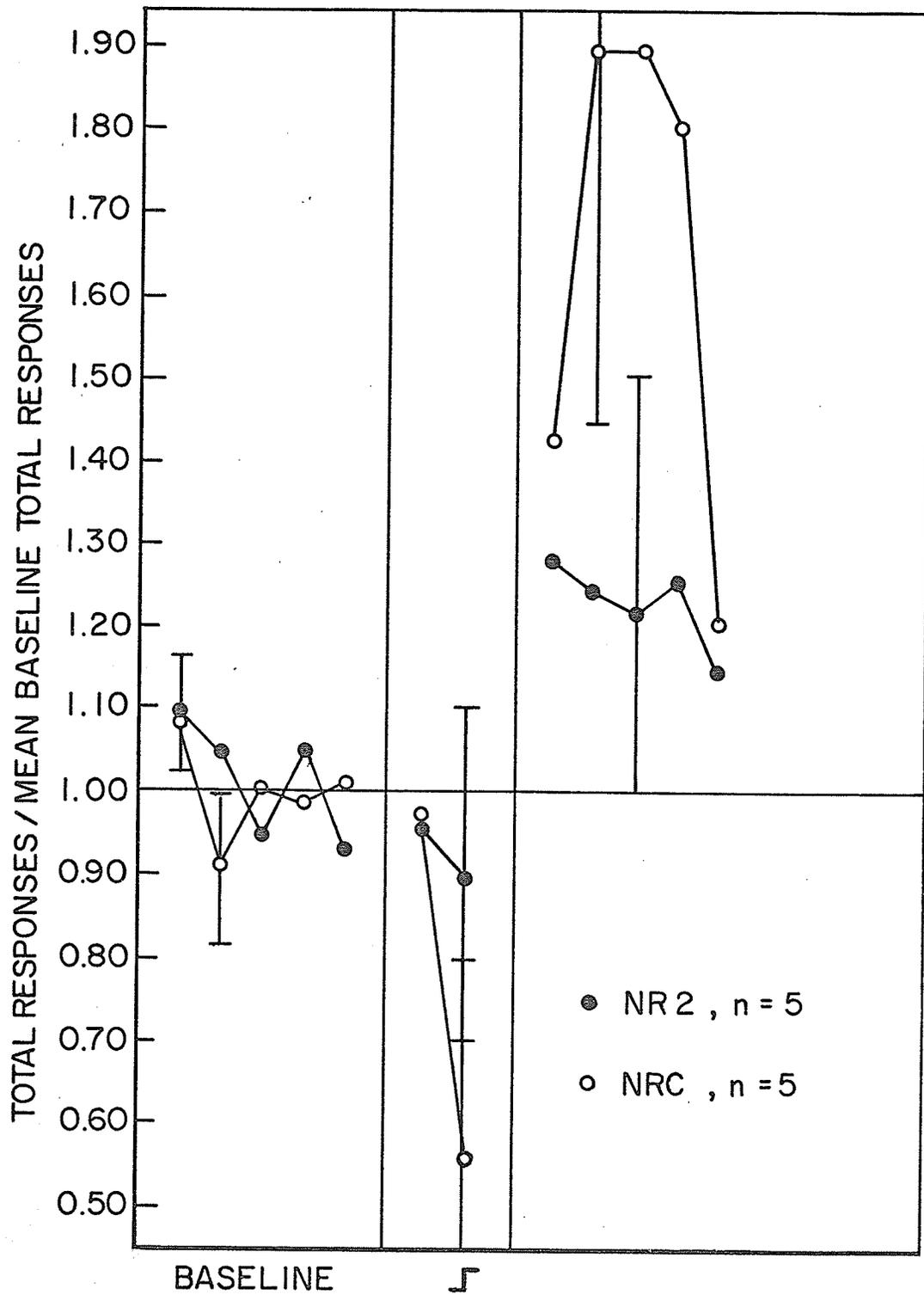


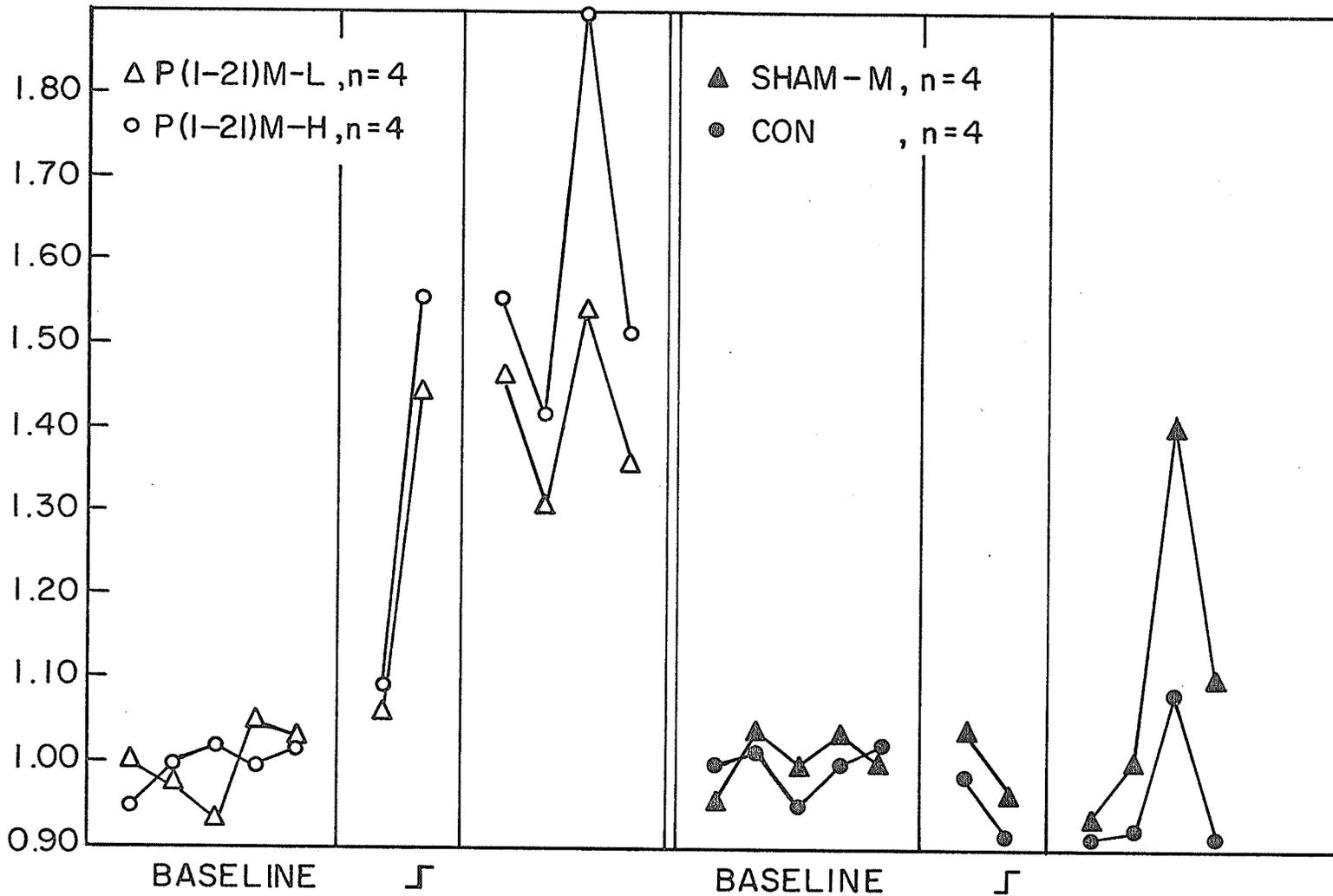
Figure 7. Average Ratios of Total Responses/Mean Baseline Total Responses During Baseline Step-Delay, and Post-Step Sessions for Groups Exposed Neonatally to 200 rad Gamma-Irradiation and Control Conditions.



prenatal development (days 1-21) to a 0.5-3 gauss (P (1-21) ML) or 3-30 gauss (P (1-21) MH) RMF and to either sham-RMF control or usual control conditions are presented in Figure 8. As can be seen in the figure, there were no significant differences between groups or baselines before the institution of the delay (\square). However, the ratios of the two RMF-exposed groups after the institution of the delay (\square) were significantly higher, indicative of greater responding during the delay period, than control groups ($t = 2.61, p < .05$). It should be pointed out that the sham-field group responded in a similar manner to the other control group when the delay was instituted. Post-step ratio differences were not statistically significant ($F = 1.39$).

Figure 8. Average Ratios of Total Responses/Mean Baseline Total Responses During Baseline, Delay (□), and Post-Step Sessions for Groups that had been Exposed Prenatally to the Two RMF and Control Conditions. Note that after the Institution of the Delay both RMF Exposed Groups, as Indicated by their Ratios, Showed a Marked Increase in Responding During the Delay Period, when Compared to the Control Groups on that Day. Note also that the Sham-RMF Group Ratio did not Differ Significantly from that of Usual Control Group after the Delay was Instituted on the Step Day.

TOTAL RESPONSES / MEAN BASELINE TOTAL RESPONSES



CHAPTER III

MAIN EXPERIMENT: METHOD

METHOD

Subjects

Experiment I: Neonate Exposure. Eighteen litters from 18, 3 to 6 month old primiparous Holtzman females were subjected to six conditions. Nine litters, 3 litters per condition, were exposed on post-natal days 1-4, the day of parturition being day 1, to 0.5-3 gauss, 3-30 gauss, and control Rotating Magnetic Field (RMF) conditions. Nine other litters, 3 litters per condition were exposed on post-natal day 4 to 100 rad, 200 rad, or control gamma-irradiation conditions.

Twenty-four females, four females drawn from the three litters of each condition, were used as subjects.

Experiment II: Prenatal Exposure. Eighteen 3 to 6 month old primiparous females were exposed to the six conditions mentioned above during pregnancy. Nine of the pregnant females, pregnancy being determined by noting the presence of spermatozoa in vaginal smears (day 1), were exposed to the two RMF and control conditions on prenatal days 13-16. Nine other pregnant females, 3 females per condition, were exposed to the two gamma-irradiation and control conditions on day 16 of gestation.

Twenty-four females, four females drawn from the three litters of each condition, were used as subjects.

Experiment III: Neonate Exposure Replication. The number of

litters and subjects used were the same as in Experiment I.

Experiment IV: Prenatal Exposure Replication. The number of litters and subjects used were the same as in Experiment II.

Apparatus

Rotating Magnetic Field Apparatus. The Rotating Magnetic Field (RMF) was created by two horseshoe magnets rotating in opposite directions about their major axes at 30 RPMs by an electric motor. The intensity (as measured by a Rawson Lush Gauss-meter) ranged from 3-30 gauss in the central exposure compartment and from 0.5-3 gauss in the two peripheral exposure compartments. More precise details of the apparatus can be found elsewhere (Persinger & Pear, 1971; Persinger, 1969).

Gamma-Irradiation Apparatus. The gamma-irradiation source was a Co⁶⁰ isotope located at the Cancer Research Division of the University of Manitoba Medical School. Irradiation was delivered at 5.6 rad/min.

Operant Chambers. All sessions were conducted in two sound-attenuated Lehigh Valley Operant Chambers, with the right lever adjusted so that a force of 24 gm produced water reinforcement. The CS, a 1 kHz, 74 db pure tone was generated by a EICO Model 377 sine-square wave Audio Generator, Experimental Contingencies were programmed by BRS logic units. Precision probability units ensured the "randomization" of trial presentation. A commercial print-out counter, which recorded response latencies, was connected to the circuit of one chamber.

PROCEDURE

Breeding and Housing of Females: Neonate Exposure. From 1800

to 0900 on various nights, the breeder females were placed with breeder males. Vaginal smears were taken at 0900, and the presence of spermatozoa detected by microscope. Each female that showed spermatozoa in the smear was randomly placed into one of three 70 cm x 23 cm x 26 cm rubber tile cages in the experimental room. The cages were divided into three compartments and covered on the top with 2.5 cm wire mesh. One or two females were placed in each compartment, but the number in a given compartment was controlled for each condition.

In the experimental room illumination was constant and furnished by 20w fluorescent lamps 45 cm above the cages. Temperature averaged 23 ± 1 degree C. Apparatus for measurements of other meteorological variables were not available. Cedar shavings were used as absorbent material and removed once every three-four days.

On day 20, as parturition approached, shredded paper was introduced into the compartments. The presence of the paper for temporary nest material presumably reduced convective loss of the pups' body temperature.

Housing of Young Animals: Neonate Exposure. At the completion of birth, when the female had gathered the newly born pups into a nest (about 1-3 hours after the birth of the first neonate), half the litters born as the result of a single breeding period were removed from the tile cages and placed in a 18 cm x 24 cm x 0.8 mesh wire bottom cage filled with 25 gm of shredded paper. To minimize handling effects and temperature drops, each neonate was transferred into the new nest within five seconds. This was important since pups exposed to these

factors alone for longer durations on postnatal days 2-11, have shown definite increases of cell proliferation in the external granular layer of the cerebellum (Altman, Das, & Anderson, 1968). Litters larger than 12 were reduced to that number. The cages were then taken to the department's colony room which was maintained at 23 ± 1 degree C and on a light-dark, 12 hour:12 hour cycle.

The remaining litters were administered the same procedure described above, only they were replaced into a new nest of 25 gm of shredded paper in the same compartment of the tile cage. One cage was then placed in the RMF from day 1, the day of birth, until day 4. Since the motor secured to a plywood base produced some vibration, the cage was placed on a platform 1.3 cm above and independent of the base. The control cage was placed 300 cm from the nearest magnet. Neither a Rawson Lush Gauss-meter or hand compass showed any deviation at this distance. The noise level measured 59 db in the RMF exposure area and 57 db in the control exposure area. After 72 hours of exposure to the RMF and control conditions, the litters were removed, reduced to 9-10 in number, placed into cages filled with 25 gm of paper (described previously), and taken to the colony room.

On day 4 (3 days of age), 10 pups from each of the other litters that had been transferred to the colony room on day 1 were immediately placed into 10 cm x 10 cm x 10 cm cardboard exposure boxes. Two pups from each litter remained with the mothers in order to prevent possible eating of other pups when returned. The exposure boxes were placed into two cardboard insulated boxes containing two hot water bottles, and

transferred to the irradiation source. The hot water bottles surrounding the exposure cages were used to prevent the ambient temperature, which was monitored, from falling below 35 degrees C (normal body temperature for neonates) while in transport.

At the irradiation source, the pups in the exposure boxes were removed from the transport boxes and placed the appropriate distance from the source. Shredded paper was placed over the boxes in order to attenuate excessive body heat loss during the exposure. The control litters received similar treatment, but were placed in a part of the room furthest from the source. Once 100 rad had been delivered, the boxes of 100 rad litters were removed and placed by the boxes of control litters. The remaining boxes of litters received another 100 rad (200 rad total). Boxes containing pups were then repacked into the transport boxes, the hot water bottles refilled, and the animals returned to their mothers. The entire operation required about three hours. The pups which remained with the mothers were removed and terminated.

During the first ten days, special attention was focused upon the condition of the litter paper, since damp or wet paper can contribute to loss of body temperature by the neonates. As noted previously, such temperature drops can produce changes in later behavior (Schaefer, 1966) as well as cerebellar changes (Altman, et al., 1968). The addition of dry paper to a single nest was accompanied by the addition of similar amounts of paper to all other nests. During the last six days before weaning, i.e., days 15-22, dirty litter paper, which was usually

pushed out of the nest by the mother, was removed every day. Mothers (and pups) were given teramycin (1 gm/1500 ml H₂O) on days 14-15. Except for the brief periods on days 1 and 4, at no other time before weaning were the pups handled.

On day 22 postpartum (21 days of age), the litters were weaned, weighed, earpunched, and sexually segregated into standard steel cages. Food was available on the floor of the cage and in the feeder. Teramycin was given on days 22-23 and 29-30. At 30 days of age, pups were separated into pairs of the same condition and sex per cage.

Breeding and Housing of Females: Prenatal Exposure. Breeder females received a similar breeding procedure as the females in the neonate experiments. Since ovulation, in the rat, occurs about six hours after copulation, the age of the fetuses at irradiation and initial RMF exposure was known within less than 12 hours. One cage of impregnated females was placed in the RMF apparatus with the magnets removed (sham-field) while the other two cages were placed in the control area. On days 13-16, the magnets were replaced and the females exposed to the RMF, after which time the magnets were removed again.

Females from the other cages, were removed from the experimental room on day 16, day 1 being the day spermatozoa was found in the smears, placed in insulated cardboard boxes which was maintained at 23 ± 2 degrees C, and transported to the irradiation source. Females were exposed to either 100 or 200 rad. Control females were placed in a part of the room furthest from the source. After exposure the females returned to the experimental room and their respective chambers. On

day 20, paper was delivered to the chambers.

Housing of Young Animals: Prenatal Exposure. Following the previous housing procedure as closely as possible, litters were reduced to 10 pups, placed into a prepared colony room cage, and taken (with mothers) to the colony room. Maintenance procedure was similar to the neonate experiments. Except for five seconds after birth, at no time were the pups touched or disturbed from the nest. On day 22 (21 days of age), the litters were weaned, weighed, and earpunched following the procedure used in previous experiments.

DCA (Delayed Conditioned Approach) Procedure. At 60 to 70 days of age, females from the 12 conditions were weighed, housed singly, and trained to press a lever for water reinforcement in the chamber in which a given subject was tested for the duration of the experiment. On the first day, the subjects were under 48 hours deprivation, but from then on they were maintained on 23 hours water deprivation. After four days of CRF (continuous reinforcement), 30 minutes per day, a S^D-S^{Δ} schedule was initiated. (Fig. 9a). In this phase of the experiment, water only became available during the CS. Lever presses during the absence of the CS produced no reinforcement. The CS and reinforcement availability onset and offset at the same time and lasted 25 seconds per trial. From the beginning of S^D-S^{Δ} training until the end of the experiment: 1. a total of 30 trials were presented per session, and 2. total running time for the 24 subjects in each experiment in the two chambers required about eight to nine hours per day (average about 40 minutes per animal) between 1300 and 2100-2200 CST.

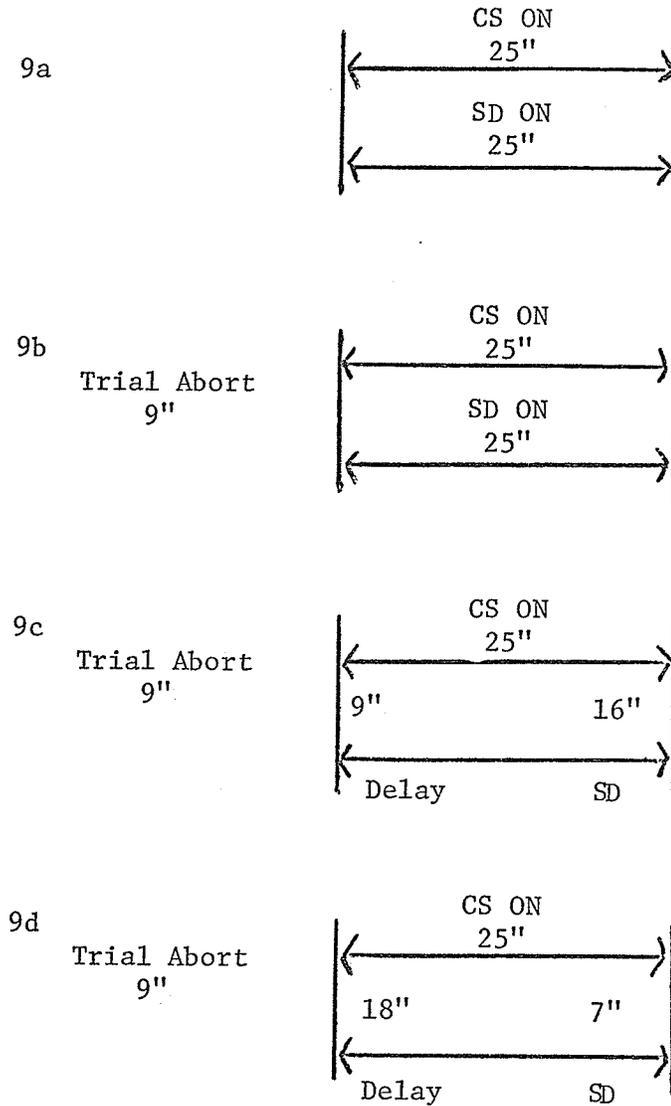


Figure 9. Various stages of paradigm; SD indicates water reinforcement available.

- 9a S^D-S^Δ only;
 9b S^D-S^Δ and trial abort
 9c 9 sec delay
 9d 18 sec delay

When five testing days had elapsed, a 9 second trial abort (Fig. 9b) was instituted in order to reduce intertrial responding. A response by a subject 9 seconds or less before a subsequent trial resulted in the "abortion" of that trial. A response by a subject 9 seconds or more before the onset of a possible trial did not interfere with the presentation of that trial. The number of trial aborts (possible trials), total responses, and total reinforcements were recorded until to the end of the experiment (actual trials per session still equal to 30).

Six running days after the institution of the trial abort, a 9 second delay (Fig. 9c) was inserted between the onset of the CS and the reinforcement in a step-like fashion on trial 16 of that session. For the next five sessions, reinforcement was delayed from the onset of the CS by 9 seconds. Lever presses during the delay period did not produce water reinforcement for each subject, the total responses emitted per session during the five sessions before the delay was instituted were used as baseline.

In the Halasz, et al. (1970) study, reinforcement, because of the 9 second delay, continued to occur (was "displaced") for nine seconds after the termination of the CS. However, pilot studies suggested that the offset of the CS could act as a discriminative stimulus ("cue") for lever pressing. In order to avoid this problem, reinforcement duration in the present study was reduced by the length of delay duration so that CS and reinforcement offset simultaneously (Fig. 9c & 9d).

After five sessions of 9 second delay, another 9-18 second delay (Figure 9d) was inserted in an impulse-like fashion between the onset of the CS and reinforcement. That is, for the entire 30 trials of that session, reinforcement was delayed for 18 seconds per trial. In the subsequent two sessions of the experiment, all delays were removed and the schedule was returned to the pre-step S^D-S^Δ and trial abort situation (no delays), in order to redetermine baseline. Daily water consumption (for 20 minutes) in the home cage and weekly body weights were also recorded. In addition, response latencies to the onset of the CS were recorded for four subjects in each of the twelve conditions which used the operant chamber connected to the print-out counter. Latencies were taken from five sessions before the institution of the step (for baseline) until the completion of the experiments.

In summary, the following dependent behavioral measures were taken: 1) total trials/session, 2) total reinforcements/session, 3) total trial aborts/session, 4) water consumption in the home cage/day 5) body weight changes/week, and 6) response latencies (for half the subjects in each condition/session).

Physiology and histology. Once the behavioral data had been collected, the subjects were killed by ether and perfused through the innominate-carotid artery with a 10% formalin solution. Brains were removed and measured with a vernier caliber. Sample brains from the twelve conditions were photographed. Sample brains were also frozen and sliced into either 25 or 40 μ sections with a commercial microtome.

Some sections were photographed while others were stained first with cresyl violet and then photographed. Further histological analysis on other brains was completed by a technician at the University of Manitoba Medical School.

CHAPTER IV

RESULTS: BEHAVIORAL DATA

For the purposes of clarity, data from each of the twelve groups will henceforth be presented in this standard order: Prenatal Irradiated 100 rad (PR1), 200 rad (PR2), control (PRC), Prenatally RMF-exposed 0.5-3 gauss (PML), 3-30 gauss (PMH), control (PMC), neonatally irradiated 200 rad (NR1), 200 rad (NR2), control (NRC), and Neonatally RMF-exposed 0.5-3 gauss (NML), 3-30 gauss (NMH) and control (NMC). Also to minimize confusion, the combination of three letters and/or numbers presented in the above parentheses will be used when data from the groups are reported.

Since data from preliminary and main experiments suggested that differences between groups could occur on the first day of exposure to other new schedule changes, in addition to the institution of the delay, average total responses for the twelve groups on the first day of CRF and S^D-S^A training were analyzed. In Table 1, the average responses and standard deviations (SDs) on the first day of CRF training for each group are presented. In standard order, the groups averaged 17.0 (PR1), 12.8 (PR2), 45.0 (PRC), 10.0 (PML), 9.5 (PMH), 28.8 (PMC), 32.5 (NR1), 55.0 (NR2), 63.0 (NRC), 108.1 (NML), 56.9 (NMH), and 111.8 (NMC) responses. These differences were found by analysis of variance to be significant beyond the .01 level ($F = 3.81$). T-test values for selected comparisons between groups are presented in Table 2. Both prenatally irradiated groups (PR1 & PR2) emitted significantly ($p < .001$)

Table 1

Means (M) and Standard Deviations (SD) of Total Responses Emitted
on the First Day of Lever Press Training for the Twelve
Pre- and Neonatally Irradiated, RMF-exposed
and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal (P)					
N	8	8	8	8	8	8
M	17.0	12.8	45.0	10.0	9.5	28.8
SD	16.3	9.7	9.5	6.9	6.2	30.3
	Neonatal (N)					
N	8	8	8	8	8	8
M	32.5	55.0	63.0	108.1	56.9	111.8
SD	31.2	59.2	58.9	114.9	65.7	67.4

Table 2

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Responses Emitted on the First Day of Lever Press Training for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed and Control Groups

Groups	df	t	Groups	df	t
PR1:PRC	14	4.21***	NML:NMC	14	.08
PR2:PRC	14	6.74***	NMH:NMC	14	1.65
PR1:PR2	14	0.63	NML:NMH	14	1.09
PML:PMC	14	1.71	NR:NM	30	1.24
PMH:PMC	14	1.76	NRC:NMC	14	1.54
PML:PMH	14	0.15	PR1:NR1	14	1.24
PR:PM	30	.62	PR2:NR2	14	1.99
PRC:PMC	14	1.44	PML:NML	14	2.41*
NR1:NRC	14	1.29	PMN:NMH	14	2.03
NR2:NRC	14	0.27	PR:NR	30	1.74
NR1:NR2	14	0.95	PM:NM	30	2.31*
			PC:NC	30	2.01

*p<.05

***p<.001

fewer responses than their control groups. The prenatally RMF (0.5-3 gauss) exposed groups emitted fewer responses than its neonatal (NML) counterpart ($p < .05$). Both prenatal RMF-exposed groups (PM) also made significantly fewer responses than both neonatally exposed groups (NM) ($p < .05$). The t -test values from the other comparisons were not statistically significant.

The average total responses emitted on the first day of S^D-S^A training for the twelve groups (Table 3) was 453 (PR1), 601 (R2), 337 (PRC), 351 (PML), 331 (PMH), 370 (PMC), 235 (NR1), 387 (NR2), 323 (NRC), 222 (NML), 368 (NMH) and 257 (NMC). These differences were found by analysis of variance to be significant beyond the .01 level ($F = 3.21$). T-test values for selected comparisons between groups are presented in Table 4. The 200 R prenatally irradiated group (PR2) displayed significantly ($p < .01$) more responses than their control (PRC) group while the group irradiated prenatally with 100 R (PR1) emitted significantly more responses than their neonatally irradiated (NR1) counterparts ($p < .01$). Together, both prenatally irradiated groups (PR1 & PR2) emitted more responses than the two neonatally irradiated (NR1 & NR2) groups ($p < .01$).

In order to determine the degree of responding during periods (S^A , no CS) of no reinforcement, before the institution of the trial abort, the ratio of total responses per total responses during reinforcement (S^D , CS) periods was taken for each subject over the four days before trial abort was instituted. The average ratio of the four days for each subject was the value used to compute the group

Table 3

Mean (M) and Standard Deviations (SD) of Total Responses Emitted on the First Day of S^D - S^Δ Training for the Twelve Pre- and Neonatally Irradiated, RMF-exposed, and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	453	601	338	351	331	370
SD	167	247	100	232	101	80
	Neonatal					
N	8	8	8	8	8	8
M	235	387	323	222	368	257
SD	116	199	125	129	193	148

Table 4

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Responses Emitted on the First Day of S^D-S^A Training for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed Control Groups

Groups	df	t	Groups	df	t
PR1:PRC	14	1.70	NML:NMC	14	0.50
PR2:PRC	14	2.82**	NMH:NMC	14	1.29
PR1:PR2	14	1.41	NML:NMH	14	1.77
PML:PMC	14	0.23	NR:NM	30	0.32
PMH:PMC	14	0.86	NRC:NMC	14	1.49
PML:PMH	14	0.21	PR1:NR1	14	3.03**
PR:PM	30	1.99	PR2:NR2	14	1.91
PRC:PMC	14	0.74	PML:NML	14	1.37
NR1:NRC	14	1.47	PMN:NMH	14	0.47
NR2:NRC	14	0.77	PR:NR	30	2.81**
NR1:NR2	14	1.86	PM:NM	30	0.68
			PC:NC	30	0.60

* $p < .05$

** $p < .01$

averages presented in Table 5. In standard order, the groups averaged ratios of 2.03 (PR1), 2.50 (PR2), 1.87 (PRC), 1.54 (PML), 1.92 (PMH), 1.72 (PMC), 1.61 (NR1), 1.48 (NR2), 2.10 (NRC), 1.94 (NML), 1.52 (NMH), and 1.85 (NMC). These differences were found by analysis of variance to be significant beyond the .01 level ($F = 3.77$). The values of selected t-test comparisons between groups are presented in Table 6. The prenatally irradiated groups (PR1 & PR2), as indicated from their ratios, had significantly more non-reinforcement (S^{Δ} , no CS) responses than the prenatal RMF-exposed ($p < .05$), or neonatally irradiated (NR1 & NR2) groups ($p < .001$). In addition both neonatally irradiated groups (NR1 & NR2) had significantly ($p < .001$) fewer non-reinforcement responses, as indicated by their low ratios, than their control group (NRC). The 3-30 gauss neonatally RMF-exposed (NMH) group had significantly ($p < .05$) lower ratios than the 0.5-3 gauss group (NML) and the prenatal 3-30 gauss group (PMH). No other comparisons were statistically significant. The total responses/total S^D responses ratio averages for the twelve groups on the day of the institution of trial abort (T.A.) and on days after the institution of the T.A., are presented in Figure 10. There were no significant differences between groups on the day of the trial abort (T.A. ($F = 1.20$), or on days after the institution of the trial abort ($F = 1.08$).

The average number of trial aborts on the first day that this modification was introduced into the paradigm for the twelve groups is presented in Table 7. The groups averaged 25.0 (PR1), 31.3 (PR2), 20.8 (PRC), 16.8 (PML), 20.0 (PMH), 24.5 (PMC), 14.8 (NR1), 24.8 (NR2),

Table 5

Means (M) and Standard Deviations (SD) of Total Responses/Total S^D
 Responses Ratios, Before Institution of Trial Abort, for
 the Twelve Pre- and Neonatally Irradiated RMF-Exposed,
 and Control Groups.

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	2.03	2.50	1.87	1.54	1.92	1.72
SD	0.37	0.91	0.43	0.36	0.36	0.44
	Neonatal					
N	8	8	8	8	8	8
M	1.61	1.48	2.10	1.94	1.52	1.85
SD	0.07	0.18	0.30	0.48	0.25	0.37

Table 6

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Total Responses/Total S^D Responses Ratios for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed and Control Groups

Groups	df	t	Groups	df	t
PR1:PRC	14	0.82	NML:NMC	14	0.44
PR2:PRC	14	1.77	NMH:NMC	14	2.05
PR1:PR2	14	1.34	NML:NMH	14	2.19*
PML:PMC	14	0.86	NR:NM	30	1.62
PMH:PMC	14	0.97	NRC:NMC	14	1.47
PML:PMH	14	2.03	PR1:NR1	14	3.22**
PR::PM	30	2.61*	PR2:NR2	14	3.09**
PRC:PMC	14	0.68	PML:NML	14	1.85
NR1:NRC	14	4.45***	PMH:NMH	14	2.52*
NR2:NRC	14	4.95***	PR:NR	30	3.96***
NR1:NR2	14	1.83	PM:NM	30	0.01
			PC.NC	30	1.29

*p<.05

**p<.01

***p<.001

Figure 10. Total Responses/Total S^D Responses Ratio Averages on the Day of Trial Abort (T.A.) Institution and on Days after the Institution of the T.A., for the Twelve Pre- and Neonatally Irradiated (PR1, PR2, NR1, NR2) RMF-exposed (PML, PMH, NML, NMH), and Control (PRC, PMC, NRC, NMC) Groups.

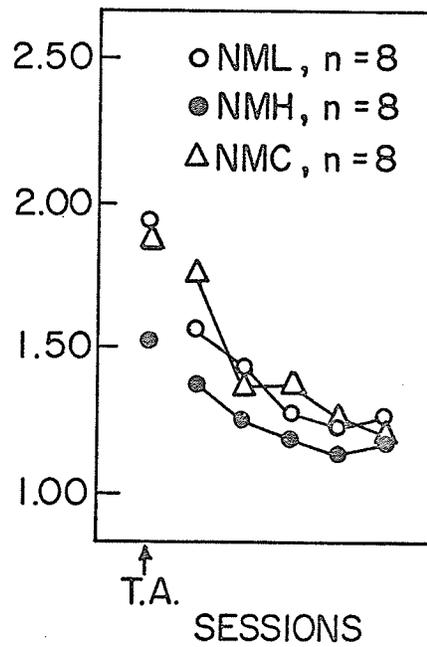
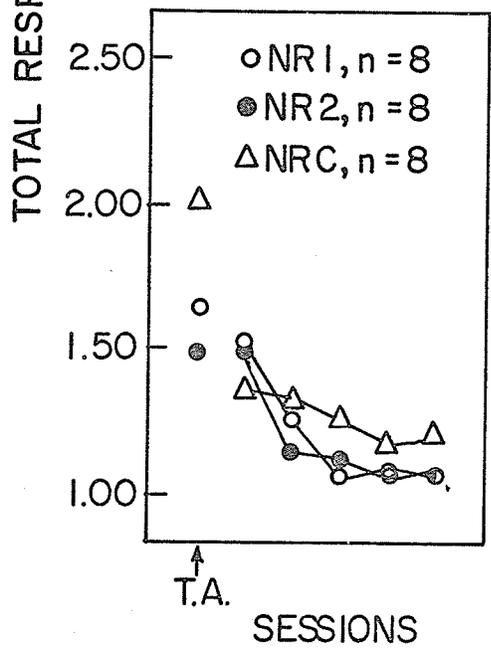
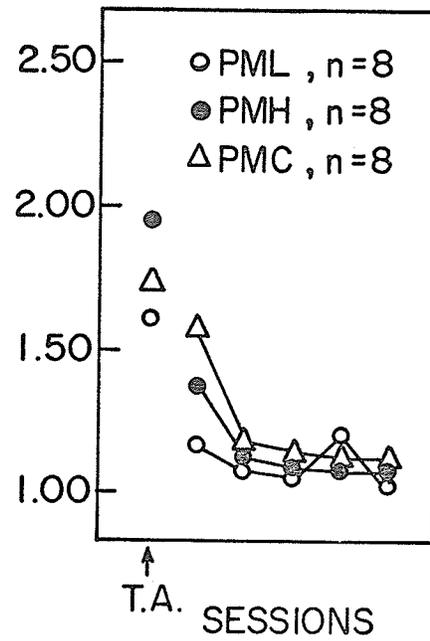
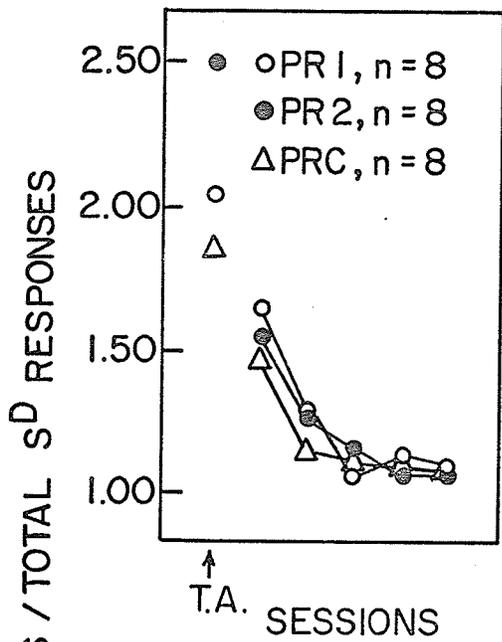


Table 7

Means (M) and Standard Deviations (SD) of the Total Number of Trial Aborts (T.A.) on the First Day of T.A. Institution for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	Rc	ML	MH	MC
	Prenatal (P)					
N	8	8	8	8	8	8
M	25.0	31.3	20.8	16.8	20.0	24.5
SD	11.1	7.3	2.3	4.5	2.0	6.0
	Neonatal (N)					
N	8	8	8	8	8	8
M	14.8	24.8	20.0	19.5	15.9	22.3
SD	4.2	7.8	6.7	2.7	8.2	9.5

20.0 (NRC), 19.5 (NML), 15.9 (NMH), and 22.3 (NMC). These differences were found by analysis of variance to be significant beyond the .01 level ($F = 4.04$). Values for selected t-test comparisons between groups are presented in Table 8. The prenatally 200 rad irradiated group (PR2) had significantly ($p < .001$) more trial abortions on the first day than control (PRC) group. Together, both prenatally irradiated groups (PR1 & PR2) had significantly more trial abortions than the prenatally RMF-exposed (PML & PMH) groups ($p < .001$) and neonatally irradiated (NR1 & NR2) groups ($p < .05$). On the other hand the 100 rad neonatally irradiated group (NR1) showed fewer trial abortions than its control (NRC) group ($p < .05$) or the 200 rad (NR2) group ($p < .01$). The neonatally 3-30 gauss RMF-exposed group (NMH) also made fewer ($p < .05$) trial abortions than its prenatal (PMH) counterpart. The average number of trial abortions for the twelve groups for the remainder of the experiment, including those made on step (Γ) and impulse (Λ) days is presented in Figures 11a and 11b. Analysis of variance on step days, impulse days, and intermediate days showed no statistical significance.

The average baseline total responses, derived from the average total responses made per day during the five days before the institution of the (step) delay, are presented in Table 9. The groups averaged 326 (PR1), 315 (PR2), 327 (PRC), 368 (PML) 327 (PMH), 381 (PMC), 320 (NR1), 483 (NR2), 368 (NRC), 363 (NML), 301 (NMH) and 315 (NMC), responses. These differences were found by analysis of variance not to be statistically significant ($F = 1.51$; $p < .05$).

Table 8

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Trial Aborts on the First Day for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed and Control Groups

Groups	df	t	Groups	df	t
PR1:PRC	14	1.25	NML:NMC	14	0.55
PR2:PRC	14	4.18***	NMH:NMC	14	0.79
PR1:PR2	14	1.33	NML:NMH	14	0.19
PML:PMC	14	1.67	NR:NM	30	1.40
PMH:PMC	14	1.66	NRC:NMC	14	1.42
PML:PMH	14	1.79	PR1:NR1	14	2.45*
PR:PM	30	3.75***	PR2:NR2	14	1.72
PRC:PMC	14	2.02	PML:NML	14	0.29
NR1:NRC	14	2.26*	PMH:NMH	14	2.86*
NR2:NRC	14	0.34	PR:NR	30	2.68*
NR1:NR2	14	3.20**	PM:NM	30	1.43
			PC:NC	30	1.22

*p<.05

**p<.01

***p<.001

Figure 11a. Average Number of Trial Aborts on Trial Abort (T.A.) Institution, Delay Step (\bar{J}), Delay Impulse (Λ), and Intermediate Days for Prenatally Irradiated (PR1, PR2), RMF-exposed (PML, PMH), and Control (PRC, PMC) Groups.

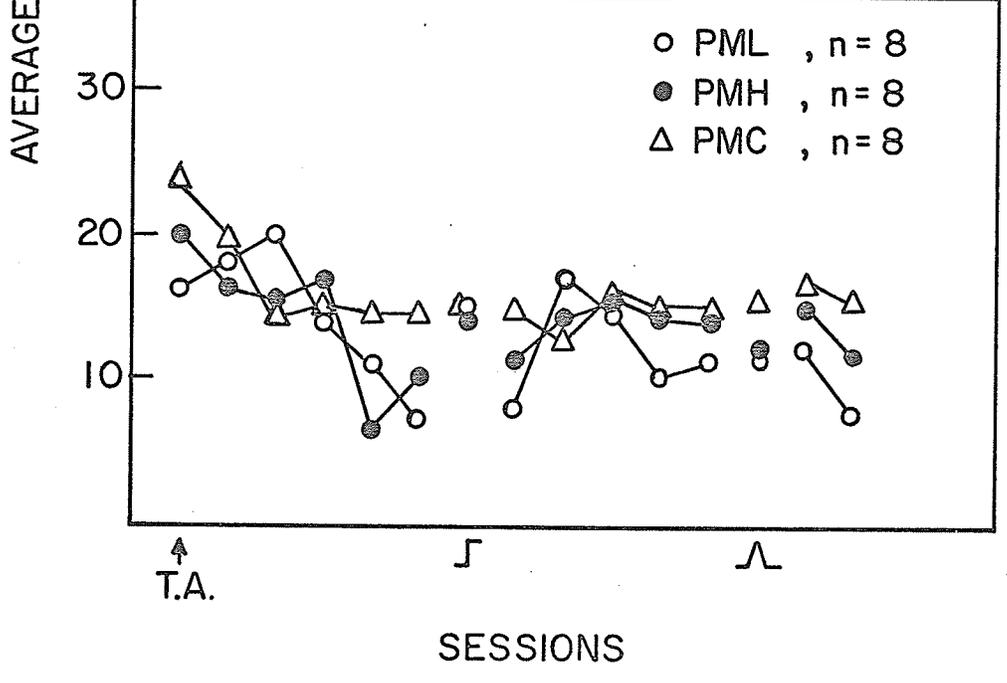
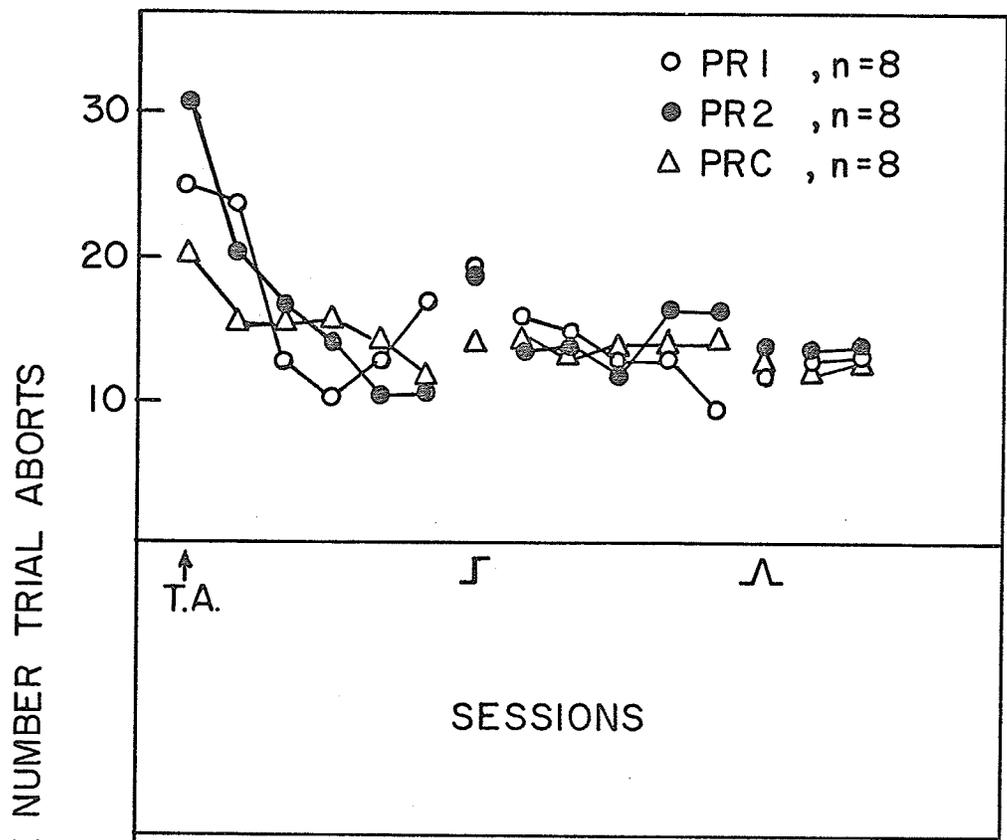


Figure 11b. Average Number of Trial Aborts on Trial Abort (T.A.) Institution, Delay Step (Γ), Delay Impulse (Λ), and Intermediate Days for Neonatally Irradiated (NR1, NR2, RMF-exposed (NML, NMH) and Control (NRC, NMC) Groups.

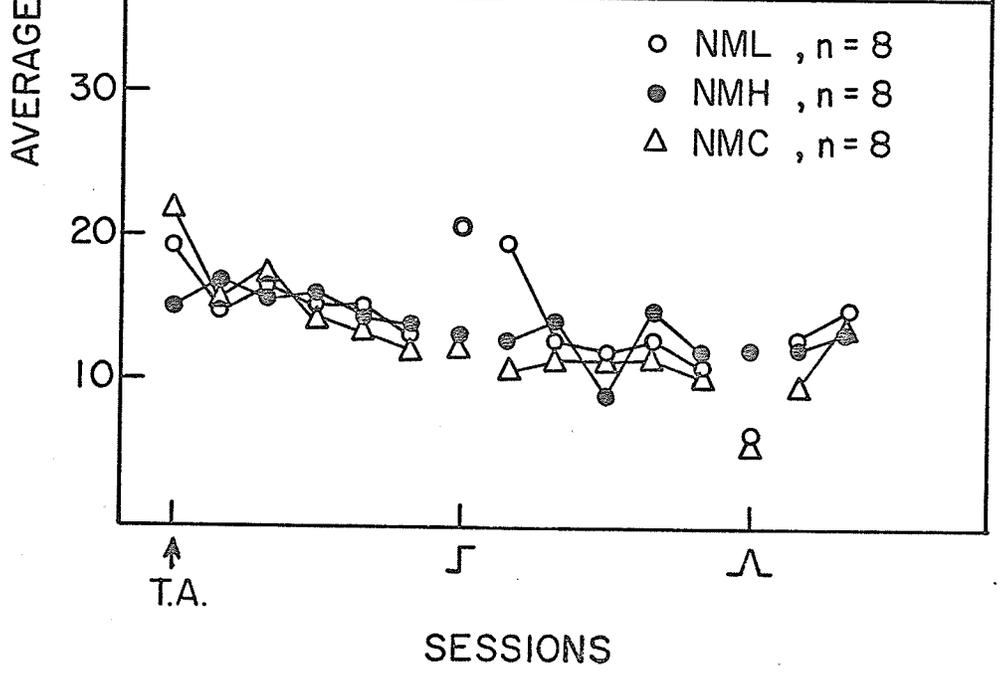
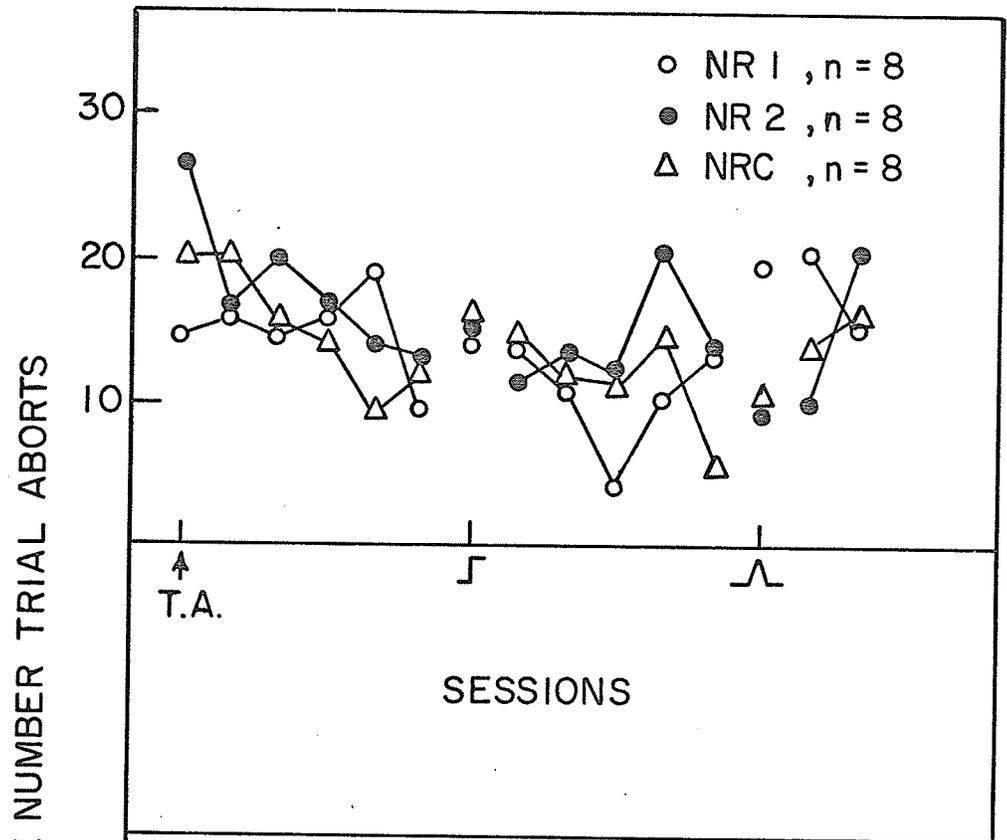


Table 9

Means (M) and Standard Deviations (SD) of Total Responses Emitted per Day During the Baseline Period Before Institution of Step Delay for Pre- and Neonatally Irradiated, RMF-Exposed, and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	326	315	327	368	327	381
SD	82	72	76	122	115	95
	Neonatal					
N	8	8	8	8	8	8
M	320	483	368	363	301	315
SD	82	128	106	108	55	96

The average total reinforcements received per day during the baseline period for the twelve groups (Table 10) were 265 (PR1), 241 (PR2), 280 (PRC), 316 (PML), 268 (PMH), 309 (PMC), 260 (NR1), 346 (NR2), 303 (NRC), 284 (NML), 260 (NMH), and 243 (NMC). Again these differences were not significant beyond the .05 level ($F = 1.01$).

The ratios of total responses to mean baseline total responses for each of the twelve groups during baseline, delay step (Γ), post-step, delay impulse (Δ), and return baseline (B) sessions are presented in Figures 12a and 12b. The average ratios of total response to mean baseline total responses during the 15 trials before the institution of the delay on step-day for the twelve groups did not differ significantly. However, the average ratios of total responses to mean baseline total responses during the 15 trials after the institution of the delay on that day for the twelve groups are presented in Table 11. The groups averaged ratios of 1.30 (PR1), 1.22 (PR2), 1.25 (PRC), 1.20 (PML), 1.28 (PMH), 1.29 (PMC), 1.01 (NR1), 1.59 (NR2), 1.00 (NRC), 1.63 (NML), 2.04 (NMH), and 0.84 (NMC). These differences were found by analysis of variance to be significant beyond the .01 level ($F = 3.06$). Values for t-test comparisons of selected groups are presented in Table 12. Only the neonatal groups showed significant t-values. The 200 R neonatally irradiated group showed a significantly ($p < .05$) higher ratio, indicative of more total responses emitted, than the control (NRC) group. Both neonatally RMF-exposed groups (NML & NMH) had significantly higher ratios (and total responses) than their control group ($p < .05$ and $p < .001$, respectively). The two neonatal RMF-

Table 10

Means (M) and Standard Deviations (SD) of Total Reinforcements
 Received per Day During the Baseline Period Before
 Institution of Step Delay for Pre- and
 Neonatally Irradiated, RMF-Exposed,
 and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R1	RC	M1	MH	MC
	Prenatal (P)					
N	8	8	8	8	8	8
M	265	241	280	316	268	309
SD	68	65	83	137	76	94
	Neonatal (N)					
N	8	8	8	8	8	8
M	260	346	303	284	260	245
SD	71	107	75	86	49	88

Figure 12a. The Ratios of Total Responses to Mean Baseline Total Responses during Baseline, Delay Step (Γ), Post-Step, Delay Impulse (Δ), and Return Baseline (B) Sessions for Prenatally Irradiated (PR1, PR2), RMF-exposed (PML, PMH), and Control (pRC, PMC) Groups.

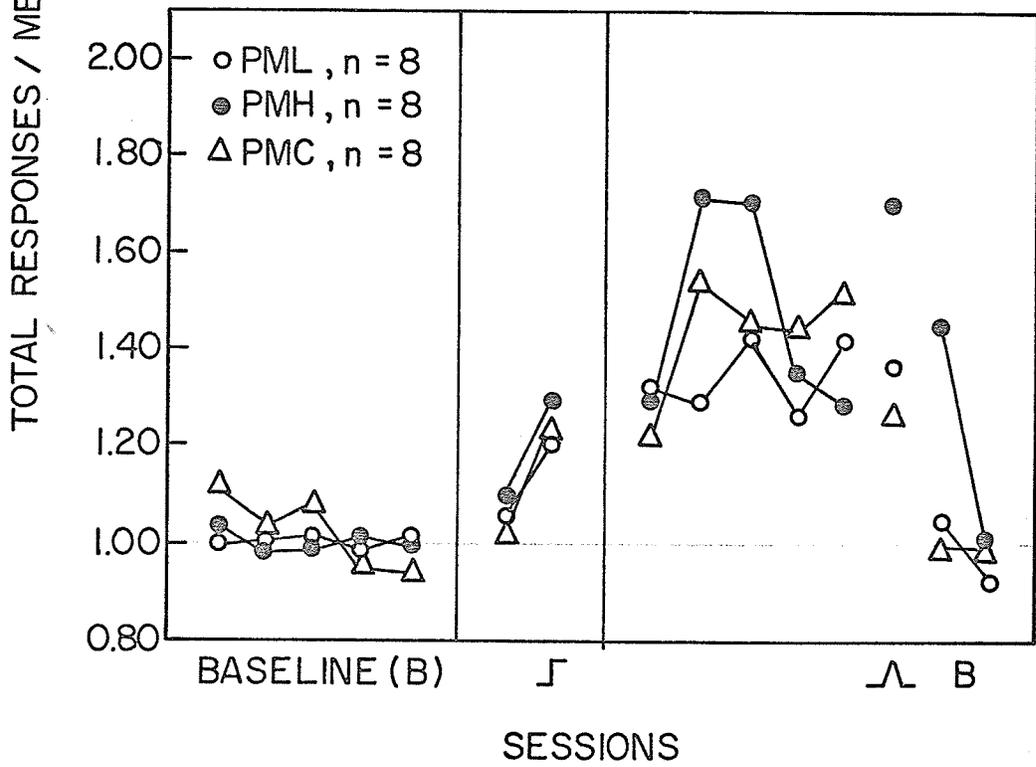
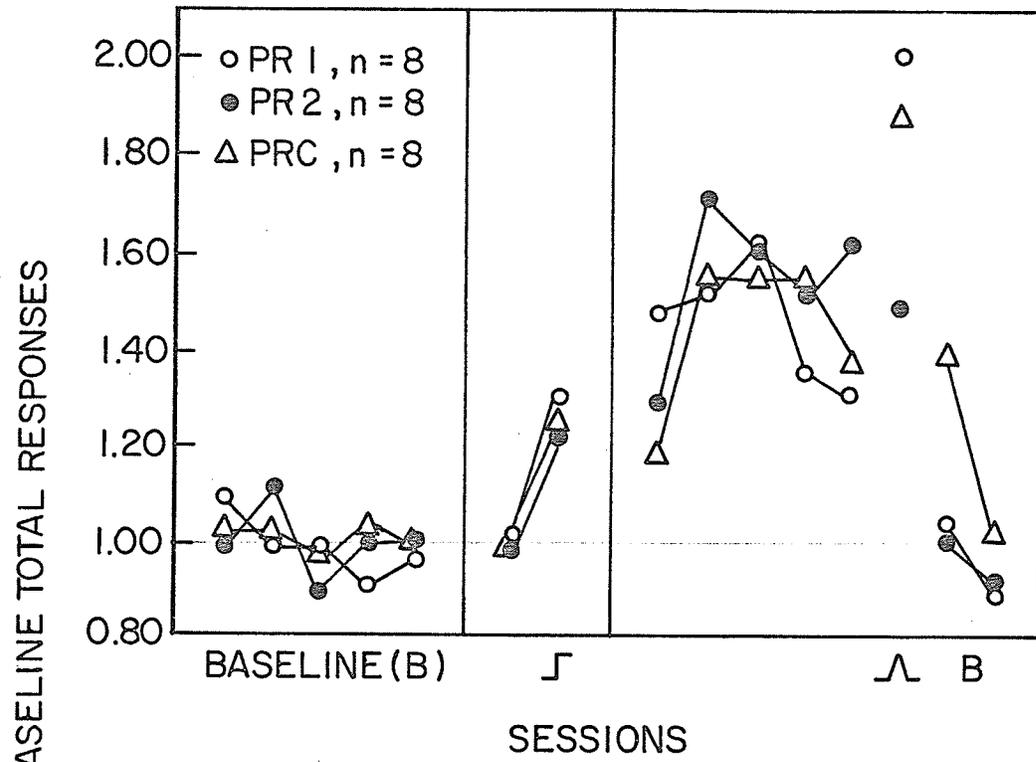


Figure 12b. The Ratios of Total Responses to Mean Baseline Total Responses during Baseline, Delay Step (r), Post-Step, Delay Impulse (A), and Return Baseline (B) Sessions for Neonatally Irradiated (NR1, NR2), RMF-exposed (NML, NMH) and Control (NRC, NMC) Groups.

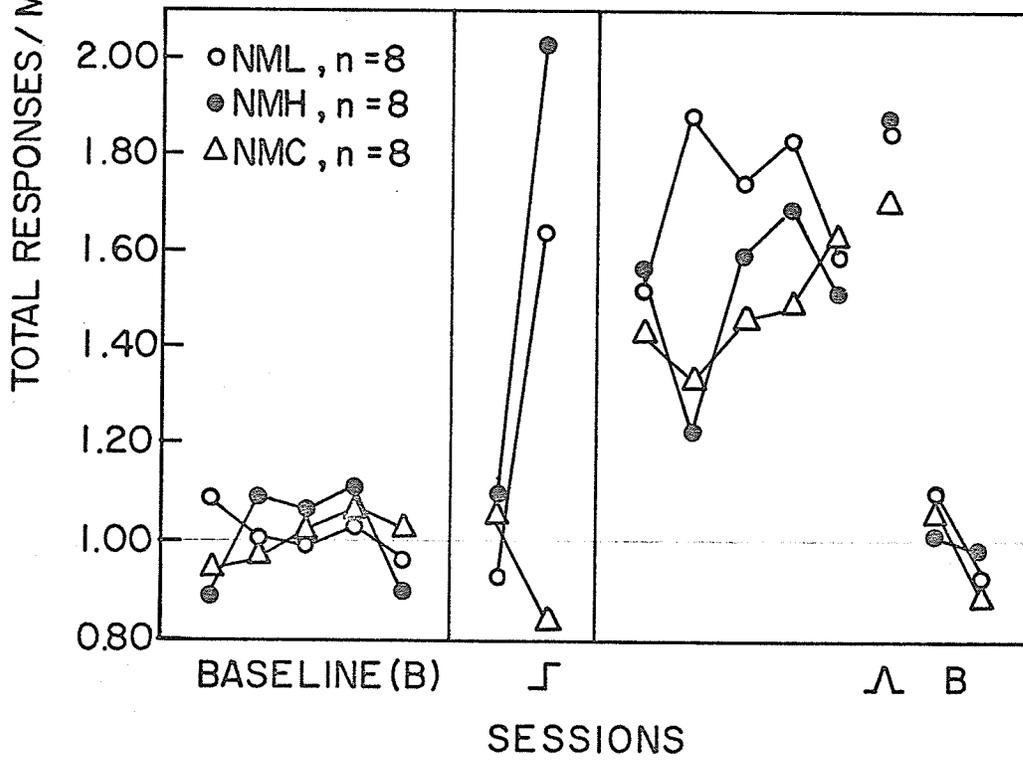
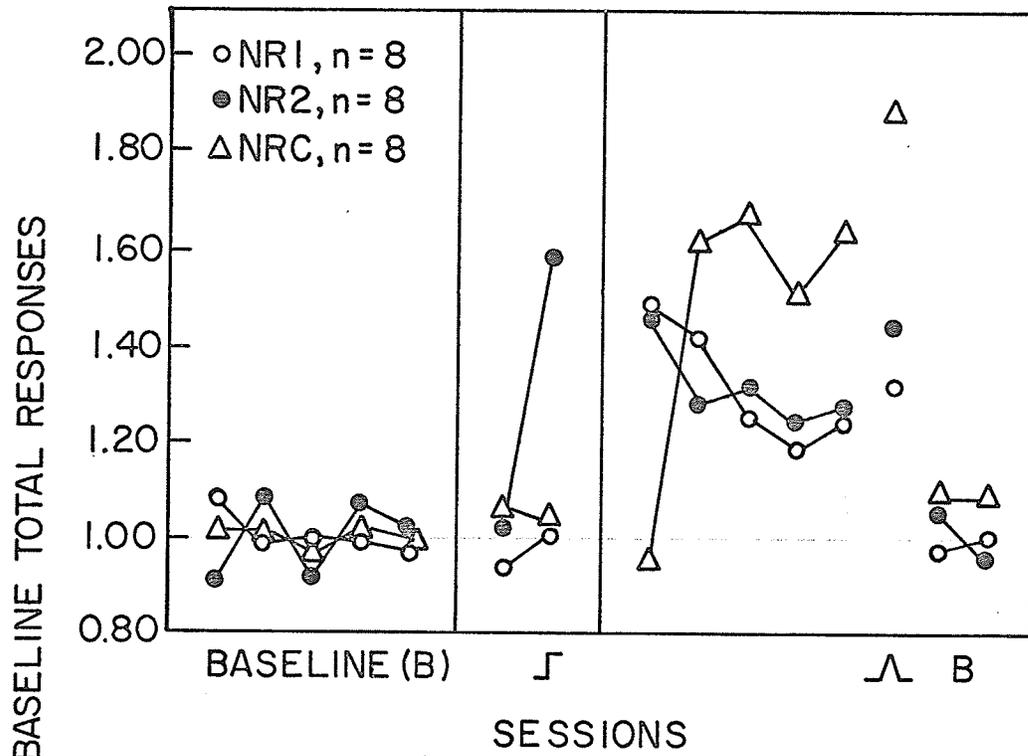


Table 11

Means (M) and Standard Deviations (SD) for Ratios of Total Responses to Mean Baseline Total Responses During the Fifteen Trials After the Institution of the Delay on Step-Day for Pre- and Neonatally Irradiated, RMF-Exposed and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal (P)					
N	8	8	8	8	8	8
M	1.30	1.22	1.25	1.20	1.28	1.21
SD	.24	.44	.46	.35	.51	.37
	Neonatal (N)					
N	8	8	8	8	8	8
M	1.01	1.59	1.00	1.63	2.04	.84
SD	.51	.66	.48	.84	.48	.56

Table 12

Degrees-of-Freedom (df) and t-test Values (t) for Ratios of Total Responses to Mean Baseline Total Responses During the Fifteen Trials after Step-Delay Institution for Pre- and Neonatally Irradiated, RMF-Exposed, and Control Groups

Groups	df	t	Groups	df	t
PR1:PRC	14	0.23	NML:NMC	14	2.20*
PR2:PRC	14	0.14	NMH:NMC	14	4.59***
PR1:PR2	14	0.40	NML:NMH	14	1.19
PML:PMC	14	0.06	NR:NM	30	2.26*
PMH:PMC	14	0.29	NRC:NMC	14	0.59
PML:PMH	14	0.35	PR1:NR1	14	1.42
PR:PM	30	0.28	PR2:NR2	14	1.27
PRC:PMC	14	0.20	PML:NML	14	1.30
NR1:NRC	14	0.07	PMH:NMH	14	2.92**
NR2:NRC	14	2.16*	PR:NR	30	1.67
NR1:NR2	14	1.95	PM:NM	30	2.83**
			PC.NC	30	1.84

*p<.05

**p<.01

***p<.001

exposed (NM) groups also had higher ratios than the neonatal irradiated (NR) groups ($p < .05$). Only the neonatal RMF-exposed (NM) groups had significantly higher ($p < .01$) ratios than their prenatal counterparts (PM). This was due mainly to the 3-30 gauss neonatal RMF-exposed (NMH) group's significantly greater ratio than the prenatal 3-30 gauss RMF-exposed (PMH) group ($p < .01$). No other group comparisons were statistically significant. Sample cumulative records for subjects from the neonatally 200 rad irradiated (NR2), 3-30 gauss RMF-exposed (NMH), and control (NRC) groups are presented in Figures 13a, 13b, and 13c, respectively. After the institution of the step-delay the vertical lines beneath the reinforcements (slashes), indicative of rapid responding or "bursts" during the delay period, are most pronounced in the RMF-exposed and irradiated rats. Such indices of rapid responding during the delay period are much reduced in the cumulative record of the control rat. Cumulative records of sample rats from the other twelve conditions are presented in the Appendix. Also, on step-day, there were no statistically significant differences between the groups with respect to changes from baseline total reinforcements ($F = 1.38$). A repeated measures analysis of variance of the average ratios of total responses to mean baseline responses during post-step days for the twelve groups did not show statistical significance ($F = 0.99$).

The average ratios of total responses to mean baseline total responses during the impulse-delay day for the twelve groups were

Figure 13a. Cumulative response graph over minutes for a rat that had been neonatally exposed to 200 rad of gamma-irradiation. Clusters of slashes (downward deflections of the pen) indicate reinforcements. Note the increase of near-vertical lines, indicative of "response bursting", i.e., short periods of very rapid responding, prior to reinforcement (beneath the slashes) after the introduction of the delay (τ).

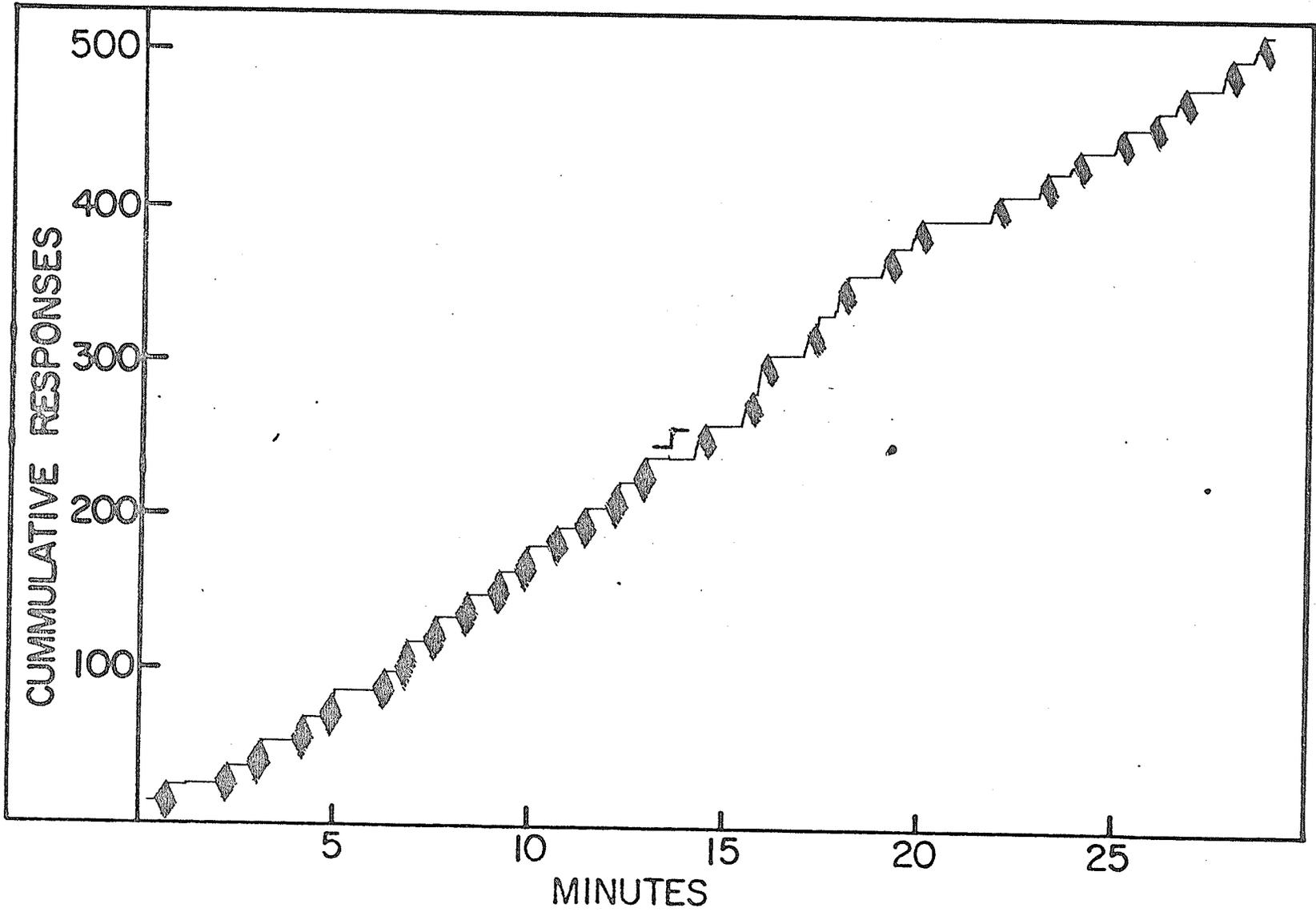


Figure 13b. Cumulative response graph over minutes for a rat that had been neonatally exposed to a 3-30 gauss RMF. Clusters of slashes indicate reinforcement. Note the increase of near-vertical lines, indicative of rapid responding or "response bursts", beneath the slashes after the institution of the delay.

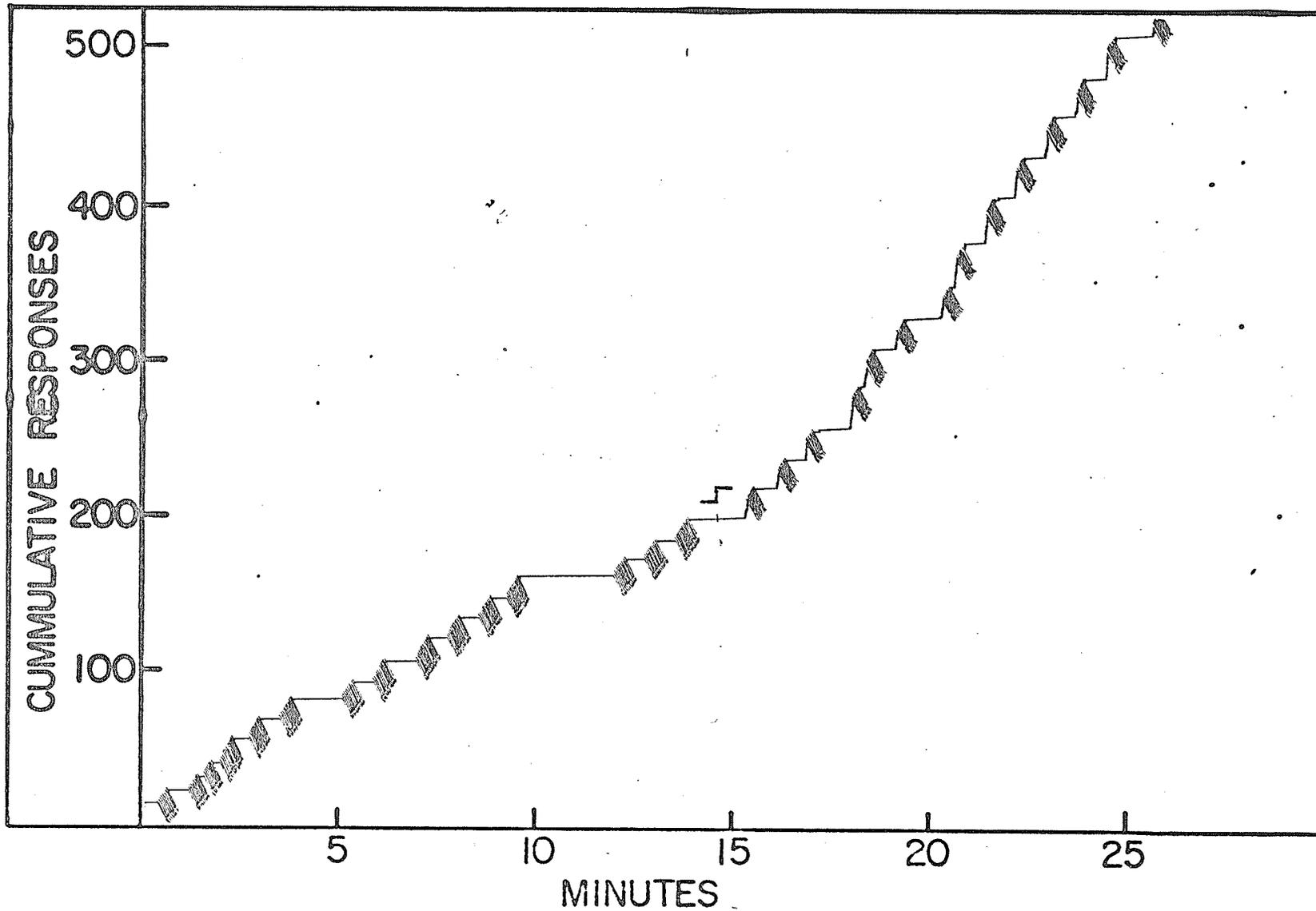
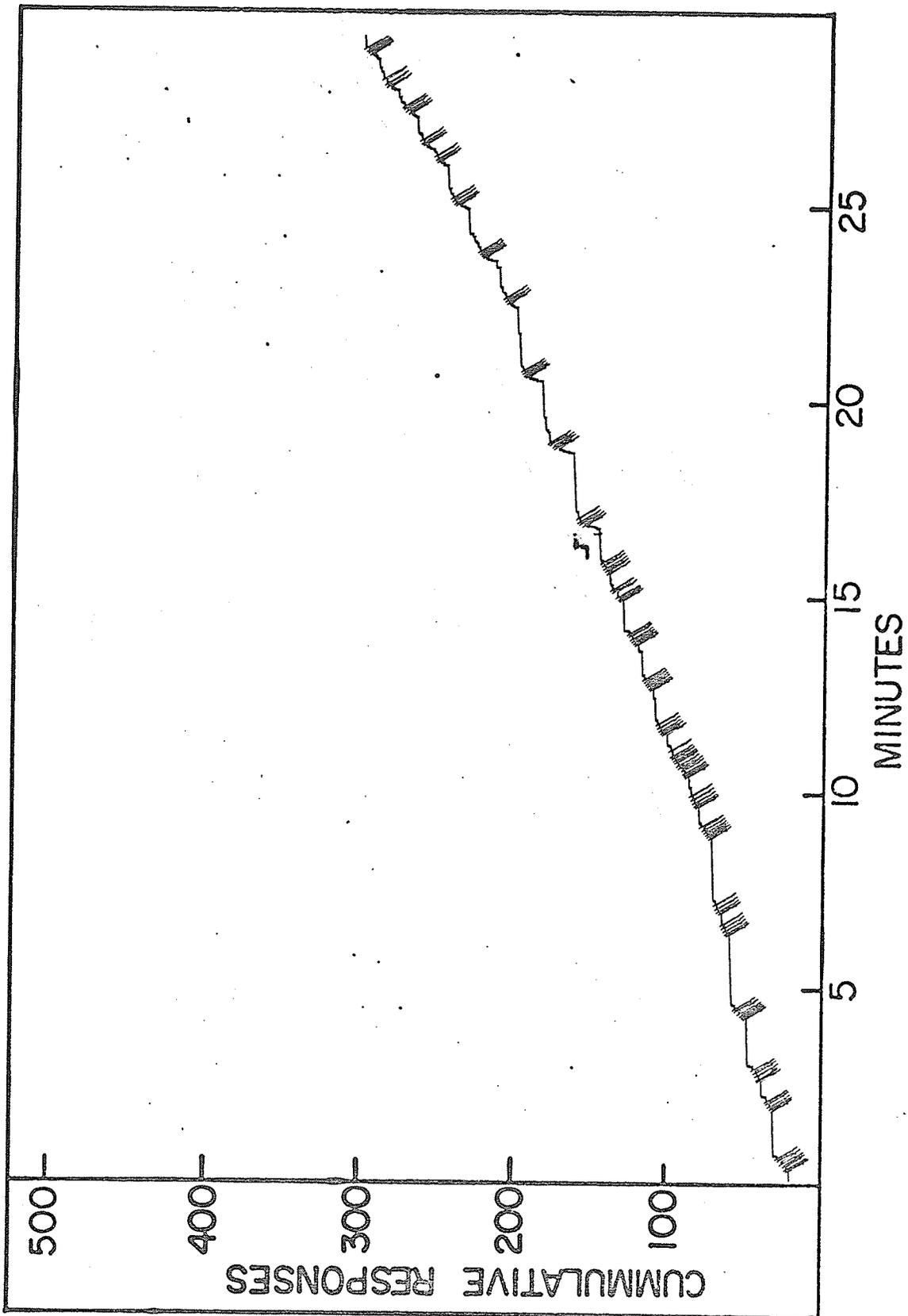


Figure 13c. Cumulative Response Graph Over Minutes for a Rat that had been Neonatally Exposed to Control Conditions. Clusters of slashes indicate reinforcement. Note that the vertical lines before reinforcement, indicative of "response bursts" in Figure 13a and 13b are minimal after the institution of the delay. The pattern of responding before and after the delay are strikingly similar.



2.03 (PRL), 1.48 (PR2), 1.88 (PRC), 1.36 (PML), 1.70 (PMH), 1.24 (PMC) 1.32 (NR1), 1.43 (NR2), 1.91 (NRC), 1.85 (NML), 1.80 (NMH), and 1.74 (NMC), and are presented in Table 13. These differences were found by analysis of variance not to be significant beyond the .05 level ($F = 1.08$). Differences in return baseline ratios for the groups were also not significant ($F = 1.07$).

The average body weights (Table 14) for the twelve groups during the week of the step-delay were 168 (PR1), 143 (PR2), 181 (PRC), 219 (PML), 206 (PMH), 193 (PMC), 171 (NR1), 169 (NR2), 215 (NRC), 198 (NML), 199 (NMH), and 199 (NRC), grams. These differences were found by analysis of variance to be significant beyond the .01 level ($F = 8.15$). Values of t-test comparisons of selected groups are presented in Table 15. In this week, the prenatally 200 rad irradiated group (PR2) weighed significantly less ($p < .01$) than their control group (PRC), while the 0.5-3 gauss RMF-exposed group (PML) weighed significantly more ($P < .05$) than their control group (PMC). As a result, the two prenatally irradiated groups (PR1 & PR2) weighed significantly less ($p < .001$) than the prenatally RMF-exposed groups (PML & PMH). Both 100 rad (NR1) and 200 rad (NR2) neonatally irradiated groups were significantly ($p < .001$) lighter than their control group (NRC), and the neonatally RMF-exposed groups (NML & NMH). However, the 200 rad prenatally irradiated (PR2) group still weighed less ($p < .05$) than its neonatal counterpart (NR2). The prenatal control groups (PRC & PMC) also weighed significantly less ($p < .05$) than the neonatal control groups (NRC & NMC).

Table 13

Means (M) and Standard Deviations (SDs) of Ratios of Total Responses to Mean Baseline Total Responses during Impulse-Delay Day for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed, and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	2.03	1.48	1.88	1.36	1.70	1.24
SD	1.04	.80	.87	.66	.49	.50
	Neonatal					
N	8	8	8	8	8	8
M	1.32	1.43	1.91	1.85	1.80	1.74
SD	.59	.21	1.13	.59	.59	.38

Table 14

Means (M) and Standard Deviations (SD) of Body Weights (in grams)
 During Step-Delay Week for the Twelve Pre- and
 Neonatally Irradiated, RMF-Exposed,
 and Control Groups

Measure	Condition					
	Irradiated			RMF-Exposed		
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	168	143	181	219	206	193
SD	39	20	23	23	16	18
	Neonatal					
N	8	8	8	8	8	8
M	171	169	215	198	199	199
SD	17	17	19	25	17	21

Table 15

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Body Weights During Step-Delay Week for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed and Control Groups

Groups	df	t	Groups	df	t
PR1:PRC	14	0.80	NML:NMC	14	0.09
PR2:PRC	14	3.53**	NMH:NMC	14	0.21
PR1:PR2	14	1.65	NML:NMH	14	0.10
PML:PMC	14	1.52	NR:NM	30	4.33***
PMH:PMC	14	1.28	NRC:NMC	14	1.76
PML:PMH	14	2.47*	PR1:NR1	14	0.18
PR:PM	30	5.95***	PR2:NR2	14	2.78*
PRC:PMC	14	1.17	PML:NML	14	0.78
NR1:NRC	14	4.85***	PMH:NMH	14	1.94
NR2:NRC	14	5.06***	PR:NR	30	1.58
NR1:NR2	14	0.23	PM:NM	30	1.93
			PC.NC	30	2.51*

*p<.05

**p<.01

***p<.001

The average differences in water consumption in the home cage during the weeks of baseline and step-delay for the twelve groups were found to be significant beyond the .01 level ($F= 3.16$). However, when the amount of water consumed in the home cage was adjusted for body weight, the differences were not significant ($F = 1.03$). The average water consumption in μl of water per gram of body weight for each of the twelve groups is presented in Table 16. The twelve groups averaged 70.1 (PR1), 75.8 (PR2), 71.4 (PRC), 56.8 (PML), 62.1 (PMH), 68.5 (PMC), 62.1 (NR1), 70.9 (NR2), 70.9 (NRC), 66.5 (NML), 60.1 (NMH), and 69.9 (NMC) μl water/gram of body weight

The average latencies i.e., time required to respond to the onset of the CS(tone), during the five baseline days before the institution of the delay on step-day, for the twelve groups are presented in Table 17. The groups averaged 1.7 (PR1), 2.2 (PR2), 1.1 (PRC), 2.3 (PML), 1.6 (PMH), 1.4 (PMC), 1.4 (NR1), 1.4 (NR2), 1.3 (NRC), 2.0 (NML), 1.1 (NMH), and 1.7 (NMC) seconds to respond to the onset of the CS. These differences were found by analysis of variance to be significant beyond the .01 level ($F = 4.10$). Values of t-tests for selected comparisons between groups are presented in Table 18. Prenatally irradiated 100 rad (PR1), 200 rad (PR2), and 0.5-3 gauss RMF-exposed (PML) groups had significantly ($P<.05-.01$) longer latencies than their controls (PRC & PMC). The prenatal irradiates (PR1 & PR2) also showed longer latencies than their neonatal counterparts ($p<.01$). The 0.5-3 gauss RMF-exposed groups (PML) had significantly ($p<.05$) longer latencies than the higher intensity group (PMH).

Table 16

Means (M) and Standard Deviations (SD) of Water Consumption During Baseline and Step-Delay Weeks, in μl of $\text{H}_2\text{O}/\text{gm}$ Body Weight, for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed and Control Groups

Measure	Condition					
	Irradiated			RMF-Exposed		
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	70.1	75.8	71.4	56.8	62.1	68.5
SD	12.0	15.0	15.9	12.4	14.7	14.9
	Neonatal					
N	8	8	8	8	8	8
M	62.1	70.9	70.9	66.5	60.1	69.9
SD	12.0	12.6	17.7	11.5	13.9	16.1

Table 17

Means (M) and Standard Deviations (SD) of Response Latencies (in Seconds) for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed, and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal (P)					
N	4	4	4	4	4	4
M	1.7	2.2	1.1	2.3	1.6	1.4
SD	0.3	0.5	0.2	0.3	0.5	0.1
	Neonatal (N)					
N	4	4	4	4	4	4
M	1.4	1.4	1.3	2.0	1.1	1.7
SD	0.1	0.1	0.3	0.9	0.3	0.3

Table 18

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Response Latencies for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed, and Control Groups

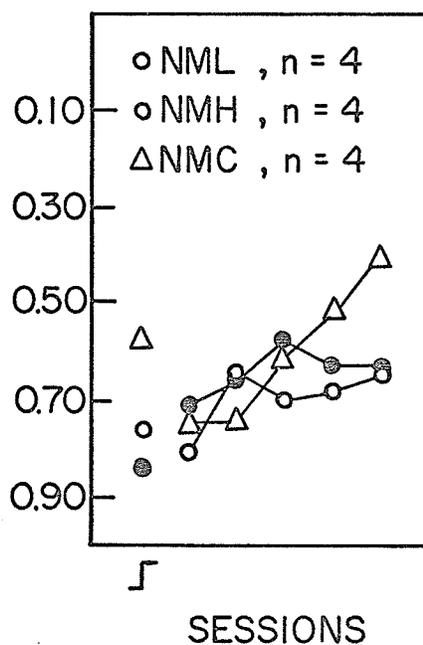
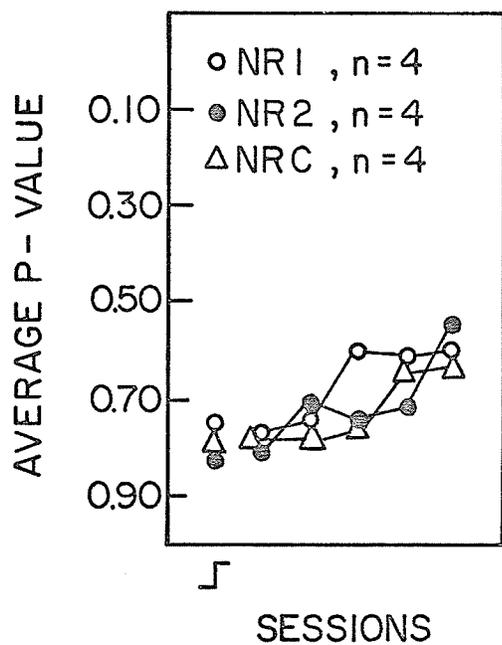
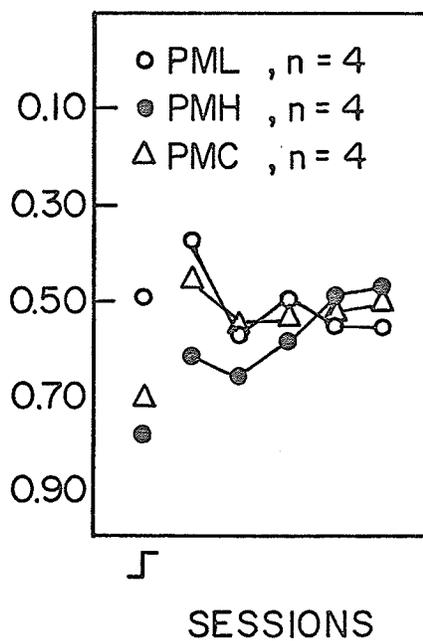
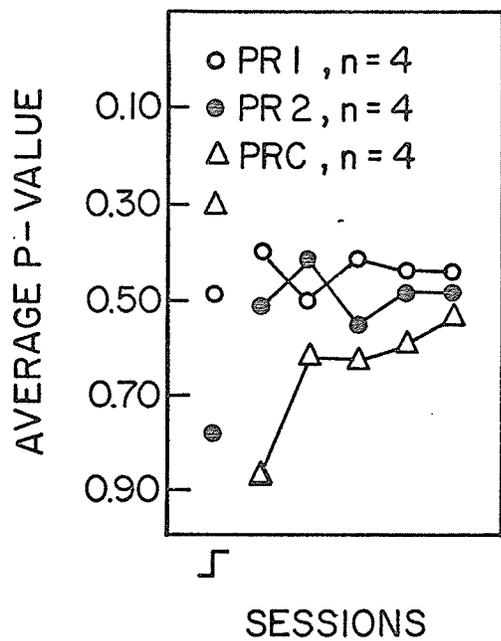
Groups	df	t	Groups	df	t
PR1:PRC	6	3.46*	NML:NMC	6	.55
PR2:PRC	6	3.85**	NMH:NMC	6	2.10
PR1:PR2	6	1.73	NML:NMH	6	1.77
PML:PMC	6	5.79**	NR:NM	10	.74
PMH:PMC	6	.96	NRC:NMC	6	1.92
PML:PMH	6	2.44*	PR1:NR1	6	2.29
PR:PM	10	.01	PR2:NR2	6	3.04*
PRC:PMC	6	.40	PML:NML	6	.65
NR1:NRC	6	.57	PMH:NMH	6	1.69
NR2:NRC	6	.74	PR:NR	10	3.28**
NR1:NR2	6	.75	PM:NM	10	1.13
			PC.NC	10	1.75

*p<.05

**p<.01

After the delay had been instituted on step day, the adjustment to the new schedule was measured by calculating P-values for each subject in the twelve groups. The P-value for a given session was determined by subtracting the actual response latencies from the "demanded" response latencies (9 seconds), and dividing the difference by the former. The average P-values for the twelve groups on the day of the delay step and on post-step days are presented in Figure 14. The values indicate that the groups were still responding at shorter latencies than "demanded" by the schedule. However, an analysis of variance on the step (J) day and on post-step days showed that the differences between groups were not statistically significant.

Figure 14. Average P-Values over Step and Post-Step Sessions for the Twelve Pre- and Neonatally Irradiated (PR1, PR2, NR1, NR2), RMF-exposed (PML, PMH, NML, NMH), and Control (PRC, PMC, NRC, NMC) Groups.



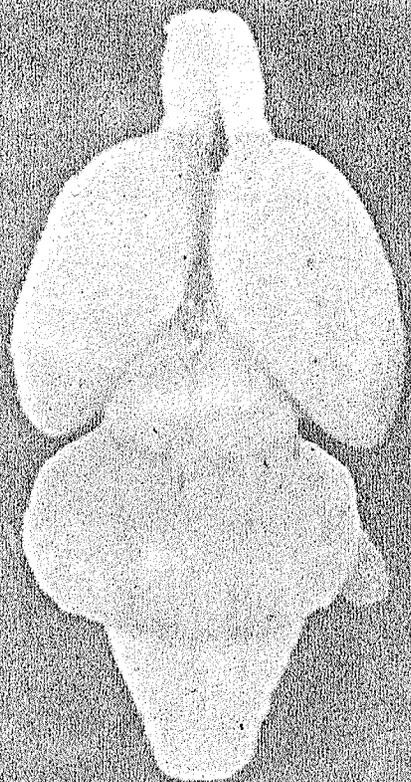
CHAPTER V

RESULTS: PHYSIOLOGICAL, CORRELATIONAL AND HISTOLOGICAL DATA

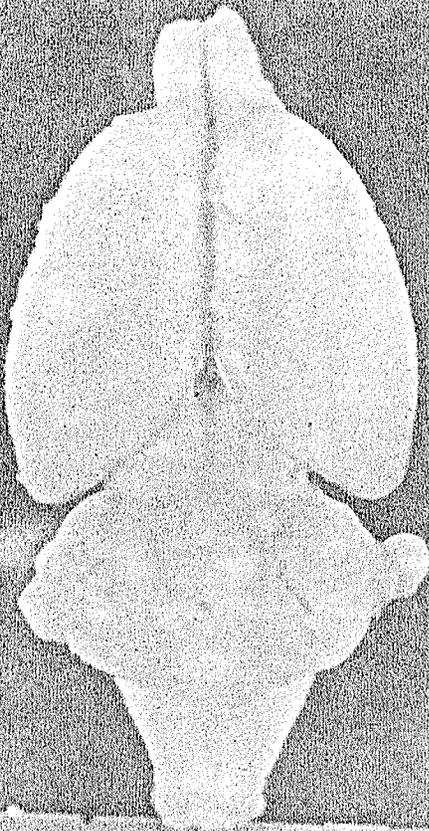
Photographs of sample brains from the twelve groups are presented in Figures 15, 16, 17 and 18. In Figure 15, the brains of rats that had been exposed on prenatal day 16 to either 200 rad (R14.3), 100 rad (R09.3) or control (RCon3.1) conditions, are shown. The reduction of forebrain (cerebrum) size, specifically rostral-caudal length, was most marked in the 200 rad animal. The cerebelli, on the other hand, with the exception of slight modification in shape of the lateral lobes, were not grossly affected by the two doses of irradiation. Figure 16 shows three sample brains of rats that had been prenatally exposed to either 3-30 gauss RMF (045.5), 0.5-3 gauss RMF (041.1) or control (038.7) conditions on days 13-16. No obvious or gross differences were noted in either the cerebellums or cerebrums, although the width of the latter structure was slightly larger in the 0.5-3 gauss brain.

Three sample brains of rats that had been neonatally exposed on day 4 (three days of age) to either 200 rad (R02.4) 100 rad (R01.9), or control (RCon.1) conditions are presented in Figure 17. No gross differences between the three brains were noted with respect to size or shape of the cerebrum. However, the cerebellum of the 200 rad brain was markedly shortened along the rostral-caudal axis, especially along the vermis. The vermal surface structure of the 200 rad brain was also severely jumbled and "granulated". No obvious differences

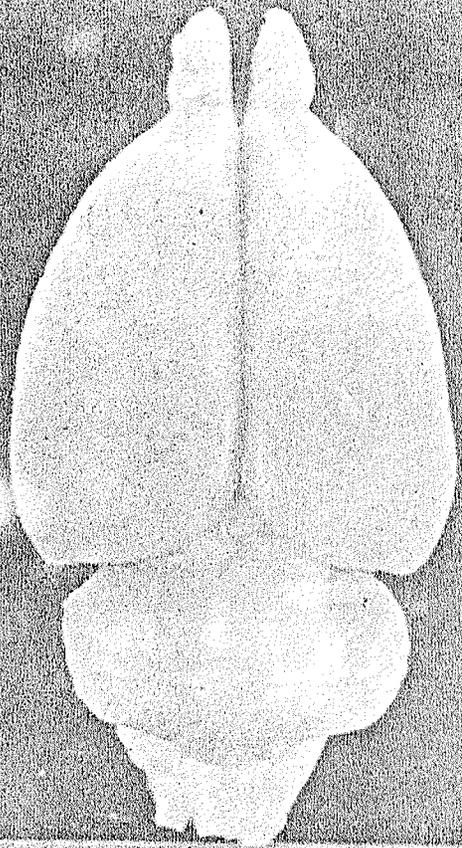
Figure 15. Sample brains from the prenatally irradiated and control groups. R 14.3 and R 09.3 had been exposed on prenatal day 16 to 200 rad or 100 rad of gamma-irradiation, respectively, while RCon 3.1 had been exposed to control conditions.



R14.3



R09.3



RCON3.1

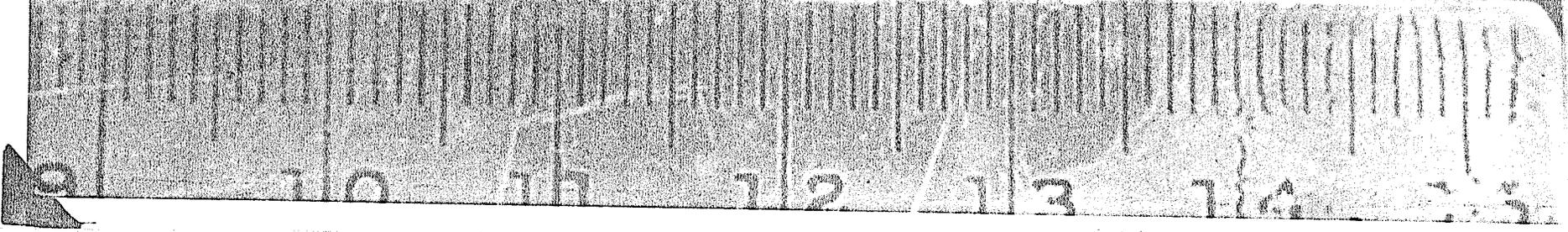
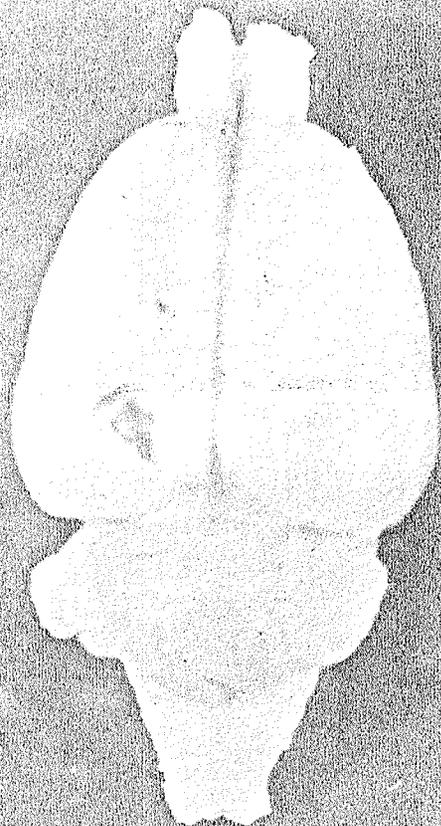
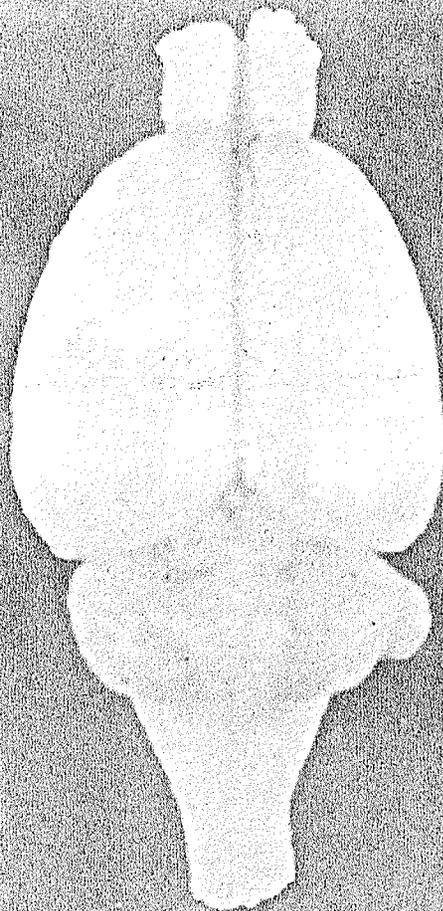


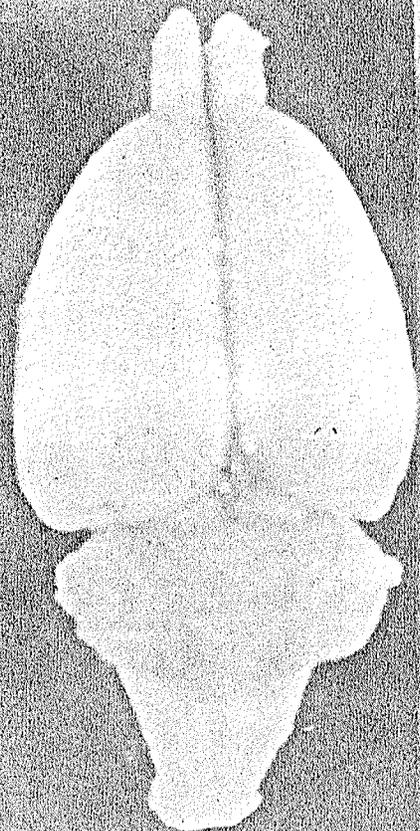
Figure 16. Sample brains from the prenatally RMF-exposed and control groups. Brains 045.5 and 041.1 had been exposed during prenatal days 13-16 to a 3-30 gauss or 0.5-3, 0.5H₃ gauss rotating magnetic field, while 038.7 had been exposed to control conditions.



045.5



041.1



038.7

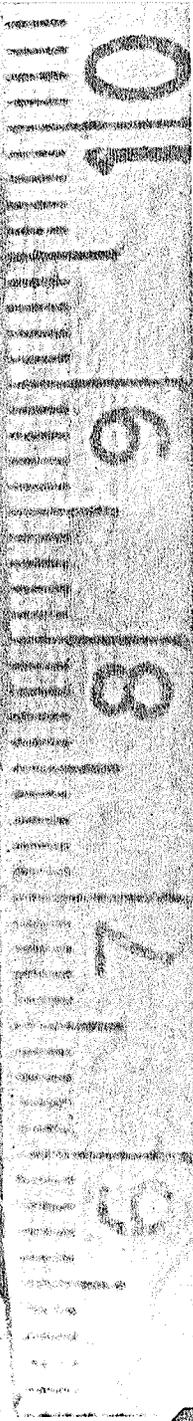
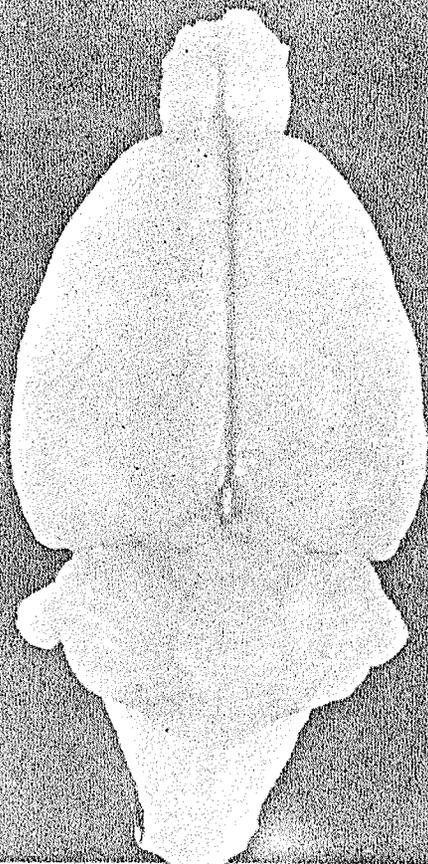
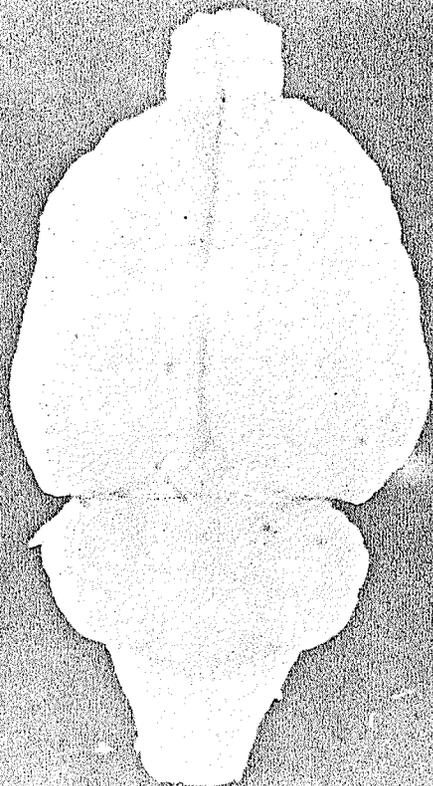
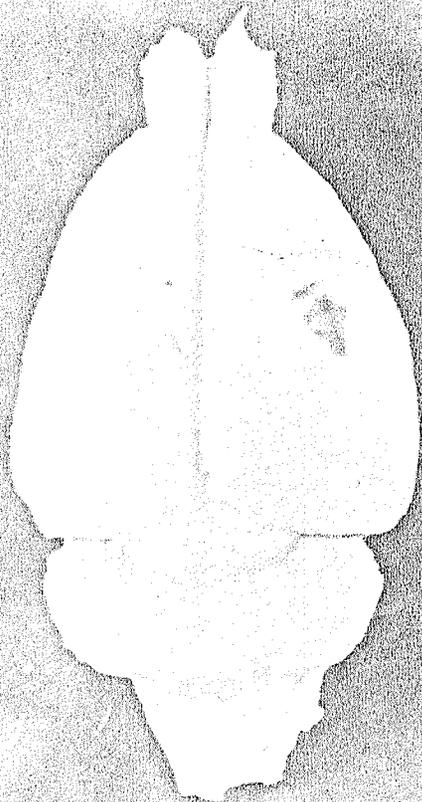


Figure 17. Sample brains for the neonatally irradiated and control groups. R 02.4 and R01.9 had been exposed to on postnatal day 4 (3 days of age) to 200 rad or 100 rad of gamma-irradiation, respectively, while RCon.1 had been exposed to control conditions.



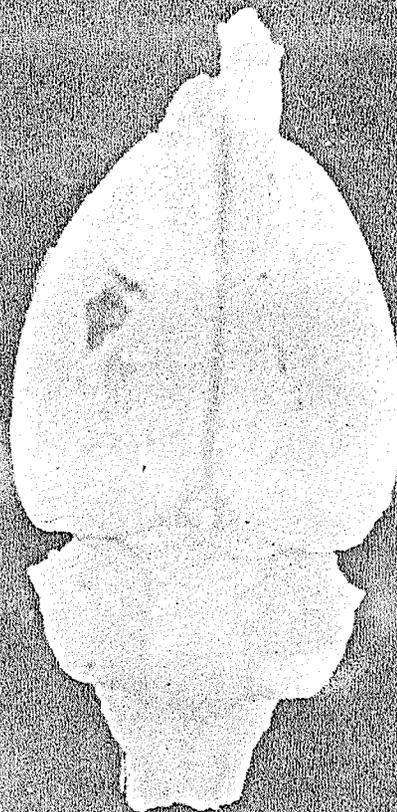
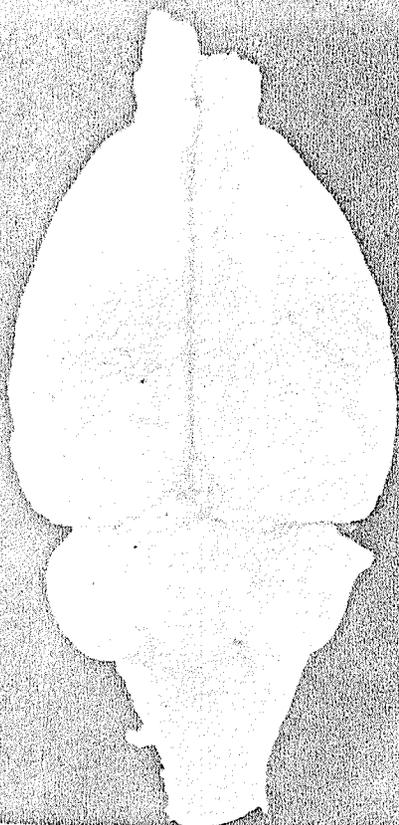
RO2.4

RO1.9

RCON.1

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Figure 18. Sample brains for the neonatally RMF-exposed and control groups. Brains 031.A.2 and 031.5 had been exposed during postnatal days 1-4 to a 3-30 gauss or 0.5-3 gauss, 0.5 Hz Rotating Magnetic Field, respectively, while 030.1 had been exposed to control conditions.



031.A.2

031.5

030.1



were noted between the 100 rad and control brain. In Figure 18, three sample brains of rats that had been exposed on neonatal days 1-4 to either a 3-30 gauss RMF (031.A.2), 0.5-3 gauss RMF (031.5) or control (030.1) conditions. No gross differences were noted between the cerebrums of the three samples. With respect to the cerebellums, there was a slight tendency for the 3-30 gauss cerebellum to be smaller both along the lateral and rostral-caudal axis. However, there were no obvious disturbances of surface structure. No gross differences were noted between the other RMF-exposed and control brain.

The average cerebral rostral-caudal lengths for the twelve groups are reported in Table 19. The groups averaged 13.4 (PR1), 11.5 (PR2), 16.5 (PRC), 16.0 (PML), 16.1 (PMH), 16.2 (PMC), 16.1 (NR1), 16.3 (NR2), 16.3 (NRC), 16.6 (NML), 16.1 (NMH), and 16.6 (NMC) millimeters for these lengths. An analysis of variance found the differences between the groups to be significant beyond the .01 level ($F = 45.77$). Values of t-tests for selected comparisons between groups are presented in Table 20. Both prenatally irradiated groups had significantly shorter cerebral lengths than their control (PRC) group ($p < .001$), the prenatally RMF-Exposed (PML & PMH) groups ($p < .001$) and the neonatally irradiated (NR1 & NR2) groups ($p < .001$). On the other hand, the groups exposed prenatally to the 0.5-3 gauss RMF (PML) had significantly shorter cerebral lengths than the 0.5-3 gauss neonatally RMF-exposed (NML) group ($p < .05$). No other differences were statistically significant.

Table 19

Means (M) and Standard Deviations (SD) of Rostral-Caudal Cerebral Lengths (in mm) for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed, and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	13.4	11.5	16.5	16.0	16.1	16.2
SD	0.4	0.9	0.5	0.6	0.2	0.9
	Neonatal					
N	8	8	8	8	8	8
M	16.1	16.3	16.3	16.6	16.1	16.6
SD	0.8	0.7	0.3	0.4	1.0	0.5

Table 20

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Cerebral Rostral-Caudal Lengths for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed, and Control Groups

Groups	df	t	Groups	df	t
PR1:PRC	14	8.32***	NML:NMC	14	0.11
PR2:PRC	14	9.20***	NMH:NMC	14	1.40
PR1:PR2	14	5.51***	NML:NMH	14	1.34
PML:PMC	14	0.02	NR:NM	30	0.57
PMH:PMC	14	0.01	NRC:NMC	14	1.48
PML:PMH	14	0.03	PR1:NR1	14	9.01***
PR;PM	30	8.20***	PR2:NR2	14	9.78***
PRC:PMC	14	0.73	PML:NML	14	2.46*
NR1:NRC	14	0.42	PMH:NMH	14	0.10
NR2:NRC	14	0.04	PR:NR	30	8.32***
NR1:NR2	14	0.011	PM:NM	30	1.50
			PC.NC	30	1.81

* $p < .05$

*** $p < .001$

The average cerebral widths for the twelve groups were 13.5 (PR1), 13.3 (PR2), 15.5 (PRC), 15.7 (PML), 15.5 (PMH), 15.3 (PMC), 15.2 (NR1), 15.0 (NR2), 15.6 (NRC), 15.7 (NML), 15.9 (NMH) and 15.6 (NMC) millimeters, and are presented in Table 21. These differences between the groups were found by analysis of variance to be significant beyond the .01 level ($F = 12.81$). Values of t-tests for selected comparisons between groups are presented in Table 22. Both prenatally irradiated groups (PR1 & PR2) had significantly smaller cerebral widths than their control (PRC) group ($p < .001$), the prenatally RMF-exposed (PML & PMH) groups ($p < .001$), and neonatally irradiated (NR1 & NR2) groups ($p < .001$). No other differences were statistically significant.

The rostral-caudal lengths for the vermis of the cerebellum for the twelve groups averaged 6.3 (PR1), 5.9 (PR2), 6.0 (PRC), 5.7 (PML), 5.8 (PMH), 6.0 (PMC), 5.3 (NR1), 4.2 (NR2), 5.9 (NRC), 5.8 (NML), 5.7 (NMH), and 6.0 (NMC) millimeters, and are presented in Table 23. These differences were found by analysis of variance to be significant beyond the .01 level ($F = 4.23$). Values for t-tests of selected comparisons between groups are presented in Table 24. Only the neonatally irradiated groups (NR1 & NR2) had significantly shorter vermis lengths than their control (NRC) group ($p < .001$), the neonatally RMF-exposed (NML & NMH) groups ($p < .001$), and the prenatally irradiated (PR1 & PR2) groups ($p < .001$). The latter significance was associated with the 200 rad neonatally irradiated group's shorter ($p < .001$) vermal lengths when compared with the 200 rad prenatally irradiated group.

Table 21

Means (M) and Standard Deviations (SD) of Cerebral Widths (in mm)
for the Twelve Pre- and Neonatally Irradiated,
RMF-Exposed, and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	13.5	13.3	15.5	15.7	15.5	15.3
SD	0.5	1.0	0.3	0.4	0.4	0.3
	Neonatal					
N	8	8	8	8	8	8
M	15.2	15.0	15.6	15.7	15.9	15.6
SD	0.3	0.6	0.6	1.0	0.9	0.7

Table 22

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Cerebral Widths for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed and Control Groups

Groups	df	t	Groups	df	t
PRL:PRC	14	9.81***	NML:NMC	14	0.40
PR2:PRC	14	5.67***	NMH:NMC	14	0.79
PR1:PR2	14	0.54	NML:NMH	14	0.30
PML:PMC	14	1.88	NR:NM	30	0.98
PMH:PMC	14	0.90	NRC:NMC	14	0.72
PML:PMH	14	0.72	PR1:NR1	14	7.74***
PR:PM	30	9.28***	PR2:NR2	14	3.85**
PRC:PMC	14	1.61	PML:NML	14	0.25
NR1:NRC	14	1.46	PMH:NMH	14	1.13
NR2:NRC	14	1.77	PR:NR	30	7.09***
NR1:NR2	14	0.79	PM:NM	30	0.98
			PC.NC	30	0.71

**p<.01

***p<.001

Table 23

Means (M) and Standard Deviations (SD) of the Rostral-Caudal Lengths
for the Vermis of the Cerebellum for the Twelve Pre- and
Neonatally Irradiated, RMF Exposed,
and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	6.3	5.9	6.0	5.7	5.8	6.0
SD	1.6	0.4	0.2	0.2	0.3	0.5
	Neonatal					
N	8	8	8	8	8	8
M	5.3	4.2	5.9	5.8	5.7	6.0
SD	0.1	0.5	0.3	0.3	0.2	0.5

Table 24

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Cerebellar (Vermis) Lengths for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed, and Control Groups

Groups	df	t	Groups	df	t
PR1:PRC	14	0.60	NML:NMC	14	1.21
PR2:PRC	14	0.34	NMH:NMC	14	1.65
PR1:PR2	14	0.74	NML:NMH	14	0.29
PML:PMC	14	0.52	NR:NM	30	5.72***
PMH:PMC	14	0.36	NRC:NMC	14	1.64
PML:PMH	14	0.71	PR1:NR1	14	1.80
PR:PM	30	1.33	PR2:NR2	14	7.97***
PRC:PMC	14	1.06	PML:NML	14	0.62
NR1:NRC	14	5.77***	PMH:NMH	14	0.32
NR2:NRC	14	9.40***	PR:NR	30	4.09***
NR1:NR2	14	6.23***	PM:NM	30	0.28
			PC.NC	30	.02

***p<.001

The average lateral cerebellar widths for the twelve groups (Table 25), were 10.8 (PR1), 10.7 (PR2), 11.7 (PRC), 11.6 (PML), 11.5 (PMH), 11.5 (PMC), 11.7 (NR1), 11.8 (NR2), 12.1 (NRC), 12.0 (NML), 11.8 (NMH), 11.8 (NMC), millimeters. These differences were found by analysis of variance to be significant beyond the .01 level ($F= 8.51$). Values for t-test comparisons between selected groups are presented in Table 26. The prenatally irradiated groups (PR1 & PR2) had significantly shorter cerebellar widths than their control (PRC) group ($p<.05$, $p<.0001$, respectively), the prenatal RMF-exposed (PML & PMH) groups ($p<.001$) and the neonatally (NR1 & NR2) irradiated groups ($p<.001$). The prenatally 0.5-3 gauss RMF-exposed group (PML) also had smaller cerebellar widths than their neonatal (NML) counterparts ($p<.05$). Together the prenatally RMF-exposed groups (PML & PMH) displayed significantly ($p<.01$) shorter widths than the neonatally RMF-exposed (NML & NMH) groups. With respect to this brain dimension, the prenatal control groups (PRC & PMC) had significantly smaller widths than the neonatal (NRC, NMC) groups ($p<.05$).

The correlation coefficient matrices from comparisons between the four brain measurements: rostral-caudal cerebral length, cerebral width, rostral-caudal cerebellar (vermis) length, and cerebellar width, and five behavioral measurements for the twelve groups are presented in Table 27. The five behavioral measurements were: total response/mean total response ratios after the institution of the delay on step day, total responses on the first day of CRF, total responses on the

Table 25

Means (M) and Standard Deviations (SD) of Cerebellar Widths (in mm)
for the Twelve Pre- and Neonatally Irradiated,
RMF-Exposed and Control Groups

Measure	Condition					
	Irradiated		RMF-Exposed			
	R1	R2	RC	ML	MH	MC
	Prenatal					
N	8	8	8	8	8	8
M	10.8	10.7	11.7	11.6	11.5	11.5
SD	0.9	0.5	0.3	0.4	0.3	0.3
	Neonatal					
N	8	8	8	8	8	8
M	11.7	11.8	12.1	12.0	11.8	11.8
SD	0.1	0.3	0.4	0.5	0.3	0.3

Table 26

Degrees-of-Freedom (df) and t-test Values (t) for Selected Comparisons of Cerebellar Widths for the Twelve Pre- and Neonatally Irradiated, RMF-Exposed, and Control Groups

Groups	df	t	Groups	df	t
PR1:PRC	14	2.85*	NML:NMC	14	0.29
PR2:PRC	14	4.87***	NMH:NMC	14	1.41
PR1:PR2	14	0.25	NML:NMH	14	0.91
PML:PMC	14	0.67	NR:NM	30	1.94
PMH:PMC	14	0.19	NRC:NMC	14	2.41*
PML:PMH	14	0.36	PR1:NR1	14	2.96*
PR:PM	30	4.23***	PR2:NR2	14	5.36***
PRC:PMC	14	1.31	PML:NML	14	2.18*
NR1:NRC	14	3.01**	PMH:NMH	14	1.75
NR2:NRC	14	1.97	PR:NR	30	5.60***
NR1:NR2	14	0.87	PM:NM	30	2.84**
			PC:NC	30	2.54*

*p<.05

**p<.01

***p<.001

Table 27

Correlation Matrices Between the Four Brain and Five Behavioral Measures (See Text) for Prenatally Irradiated-Control, Prenatally RMF-Exposed-Control, Neonatally Irradiated-Control, and Neonatally RMF-Exposed Control Groups

Brain Measurements	Behavior Measurement				
	R	R _{CRF}	R _{SD}	R	T.A.
Prenatal Irradiated-Control (n = 24)					
Cerebrum:Rostral-Caudal (R-C)	.03	.68**	-.63**	.24	-.50*
Cerebrum:Width	.03	.56**	-.63**	.19	-.46*
Cerebellum (Vermis):R-C	.14	.26	-.17	-.06	-.33
Cerebellum:Width	.01	.54**	-.30	-.30	-.33
Prenatal RMF-Exposed-Control (n = 24)					
Cerebrum:Rostral-Caudal (R-C)	-.24	.13	.18	.03	-.15
Cerebrum:Width	.18	-.37	-.19	.22	.31
Cerebellum (Vermis):R-C	.04	.46*	.10	-.05	.32
Cerebellum:Width	.36	-.15	-.33	.13	-.15
Neonatal Irradiated-Control (n = 24)					
Cerebrum:Rostral-Caudal (R-C)	.14	.19	.52**	-.06	-.20
Cerebrum:Width	-.14	.01	.33	.35	-.51*
Cerebellum (Vermis):R-C	-.44*	.01	-.08	.16	-.20
Cerebellum:Width	-.08	.00	.32	.36	-.18
Neonatal RMF-Exposed-Control (n = 24)					
Cerebrum:Rostral-Caudal (R-C)	.24	.37	.06	.12	.39
Cerebrum:Width	.28	.26	.31	.18	.40*
Cerebellum (Vermis):R-C	-.26	.05	-.05	-.08	.26
Cerebellum:Width	.43*	-.06	.08	.08	.29

*p < .05

**p < .01

first day of S^D-S^A training, total response/mean total response ratios on the impulse-delay day, and total trial aborts on the first day of trial abort input. For analysis, as shown in the table, the two dose groups and their controls were grouped together for each major condition (prenatally irradiated, prenatally RMF-exposed, neonatally irradiated, and neonatally RMF-exposed conditions).

The prenatally irradiated, RMF-exposed, and control groups did not show a significant correlation with any of the brain measures and response ratios after the institution of the delay on step day. However, the neonatally irradiated and control groups showed a significant ($p < .05$) negative correlation (-.44) between this behavioral measure and the rostral-caudal length of the vermis of the cerebellum. In other words, a decrease of cerebellar (vermis) length was associated with an increase in total response/mean baseline total response ratios. The neonatally RMF-exposed and control groups only showed a significant ($p < .05$) positive correlation (.43) between cerebellar width and response ratios on step day.

The prenatal irradiated and control groups exhibited significant ($p < .01$) positive correlations with cerebellar width (.54), cerebral width (.56), and cerebral length (.68) and total responses on the first day of CRF training, but significant ($p < .01$) negative correlations with the latter two brain measurements (-.63, -.63) on the first day of S^D-S^A training. Total first day trial aborts showed a significant ($p < .05$) negative correlations again with cerebral length (-.50) and cerebral width (-.46). The prenatal RMF-exposed and control

groups showed only one significant ($p < .05$), positive correlation with total responses on the first day of CRF training (.46), with cerebellar (vermis) length.

Unlike the prenatal irradiated and control groups, the neonatally irradiated and control groups exhibited a significant ($p < .01$) positive correlation between cerebral length and total responses on the first day of S^D-S^A training (.52). A negative correlation ($p < .01$), however, was noted between cerebral width and trial aborts (-.51). The neonatally RMF-exposed and control groups only showed one other significant correlation ($p < .05$), which was between cerebral width and trial aborts (.40). None of the four matrices produced significant correlations between any of the brain measurements and response ratios on impulse delay day.

It is interesting to note that the irradiated and control groups, specifically the prenatal groups, displayed the largest number of significant brain-behavioral correlations. The prenatally irradiated and control groups had seven (7) significant correlations while the neonatally irradiated and control groups showed three (3) such correlations. On the other hand, the two prenatal and neonatally RMF-exposed groups showed only one (1) and two (2) significant correlations, respectively. Also, of the irradiated and control groups' 10 significant correlations, five (5) were negative, while the RMF-exposed and control

groups had only positive correlations.

Unstained tranverse sections (under 4 x magnification) of comparable areas of the anterior cerebellum from the neonatal control, 200 rad prenatally irradiated, 3-30 gauss neonatally RMF-exposed, and 200 rad neonatally irradiated groups are presented in Figures 19, 20, 21, and 22, respectively. Both the RMF-exposed and prenatally irradiated samples are similar to the control sample with respect to gross architecture, although the latter section shows slight changes in shape. The area and basic shape of the medullary layers (white areas) of the control, prenatally irradiated, and RMF-exposed samples are also quite similar. The neonatally irradiated sample (Figure 22), on the other hand, exhibits marked irregularities of the medullary layer, specifically in the vermis of the cerebellum. There is also an apparent reduction in the amount of inter-hemispherical white matter (fiber tracts) in the irradiated sample. Gross differences in the basic shape of the adjacent brainstem are only noticeable in the prenatally irradiated sample, where there is a slight change in shape. No differences were noticeable in the samples from the other eight groups.

Sample folial sections of the anterior vermis of the cerebellum from the neonatal control, prenatally 200 rad irradiated, 3-30 gauss neonatally RMF-exposed, and neonatally 200 rad irradiated groups are presented in Figures 23, 24, 25, and 26, respectively, under 100 x magnification. The sections have been stained with cresyl violet. In Figure 23, the control section, the orderly layers of the medullary

(white areas) and adjacent granular layer, Purkinje cell layer and molecular layer are noted. The Purkinje layer contains the single row of larger cells that lines the granular layer-molecular layer border (See Appendix). The RMF-exposed section (Figure 24) shows similar cytoarchitecture. The prenatally irradiated folia also shows comparable construction, but with a possible reduction in number of Purkinje cells. The above three samples are in marked contrast to the 200 rad neonatally irradiated sample (Figure 26). In this folial section, taken from the disturbed vermis, the molecular layer-granular layer interface is no longer as clear. There is an invasion of the granular layer into the adjacent medullary and molecular layers. In addition, the granular layer, as indicated by its lighter staining compared to that of the control section, is depleted in total cell number. It can also be seen, although more clearly under higher power of magnification (See Appendix), that the layer of Purkinje cells are markedly disarranged and are penetrating into the granular folial sections of other cerebelli from the remaining groups were not obvious. However, other sample sections are presented in the Appendix.

Figure 19. Tranverse section (4 X) of the anterior cerebellum and adjacent brainstem from a rat that had been exposed to neonatal control conditions.

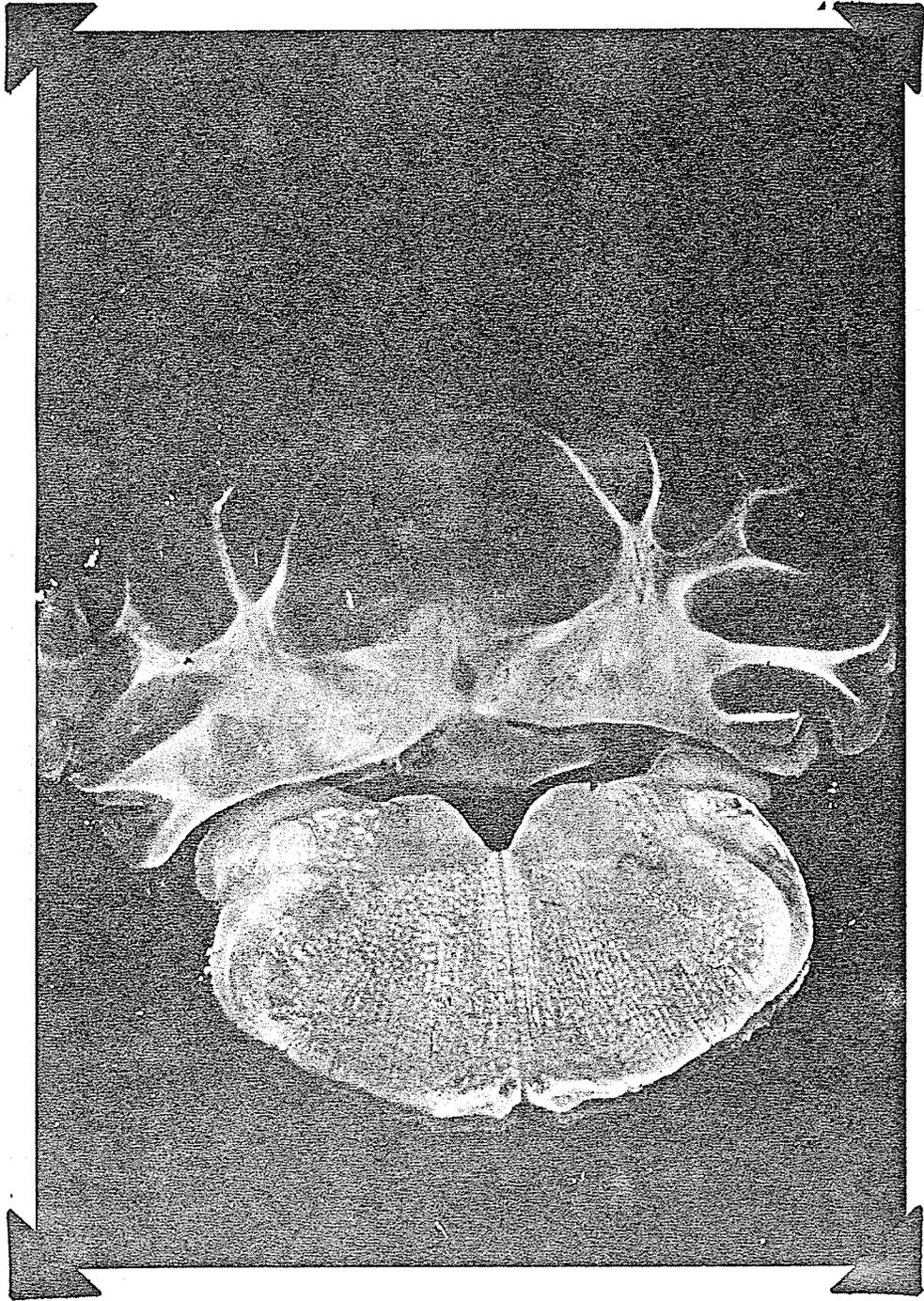


Figure 20. Transverse Section (4 X) of the Anterior Cerebellum and Adjacent Brainstem for a Rat that had been Exposed on Prenatal Day 16 to 200 rad of Gamma-irradiation.

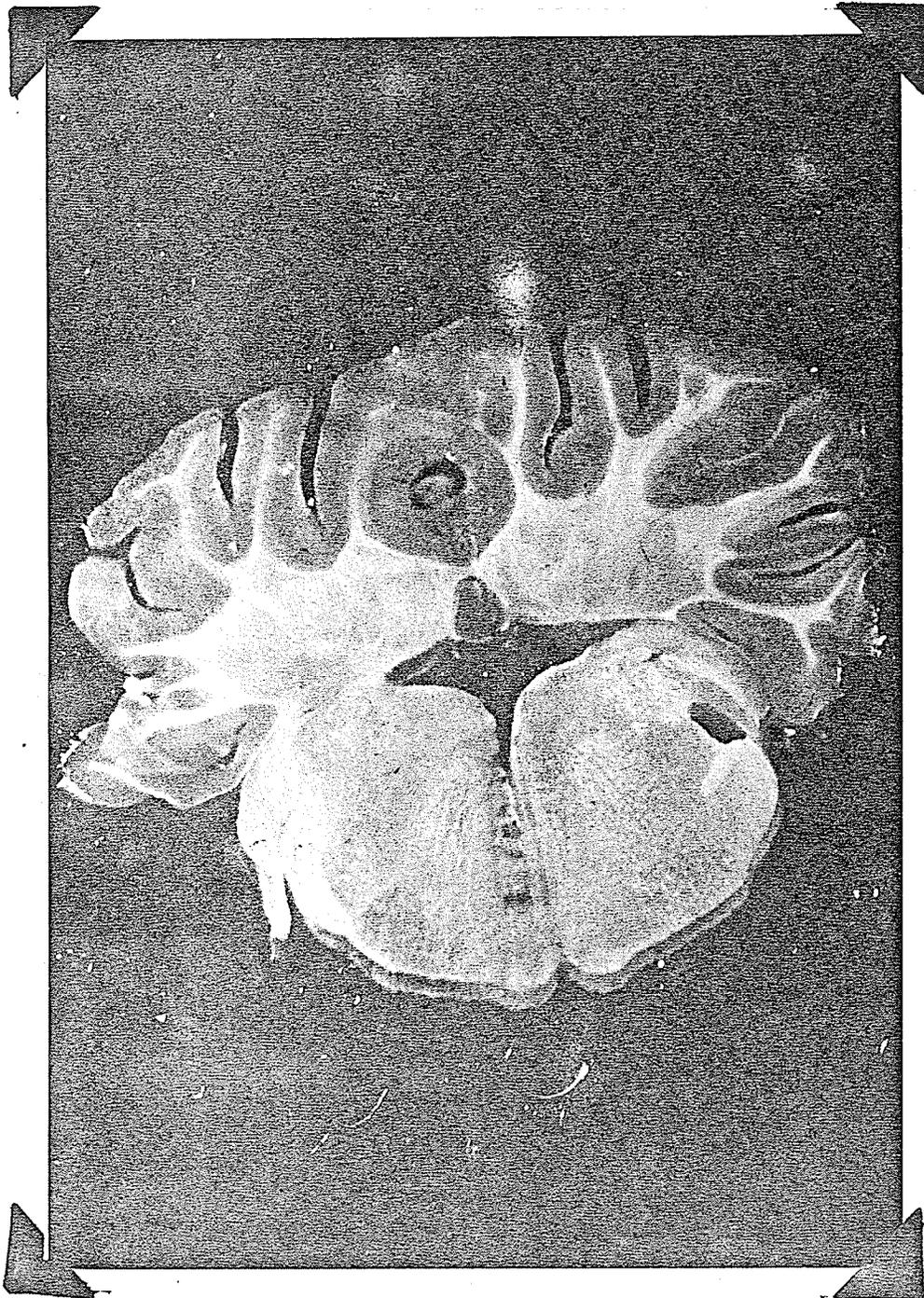


Figure 21. Tranverse section (4 X) of the anterior cerebellum and adjacent brainstem for a rat that had been exposed during postnatal days 1-4 to a 3-30 gauss, 0.5 Hz, RMF.

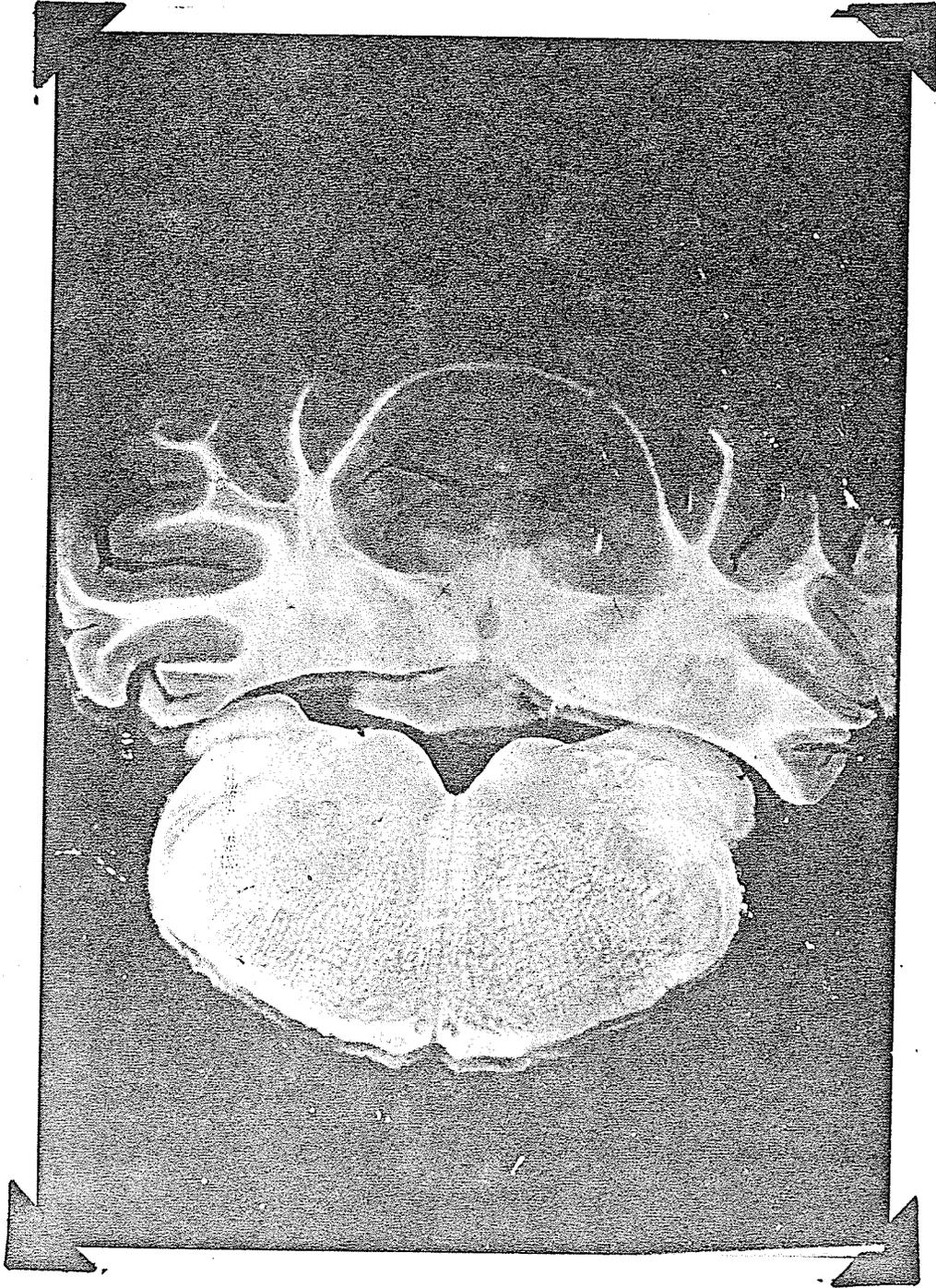


Figure 22. Transverse section (4 X) of the anterior cerebellum and adjacent brainstem for a rat that had been exposed on postnatal day 4 to 200 rad of gamma-irradiation.

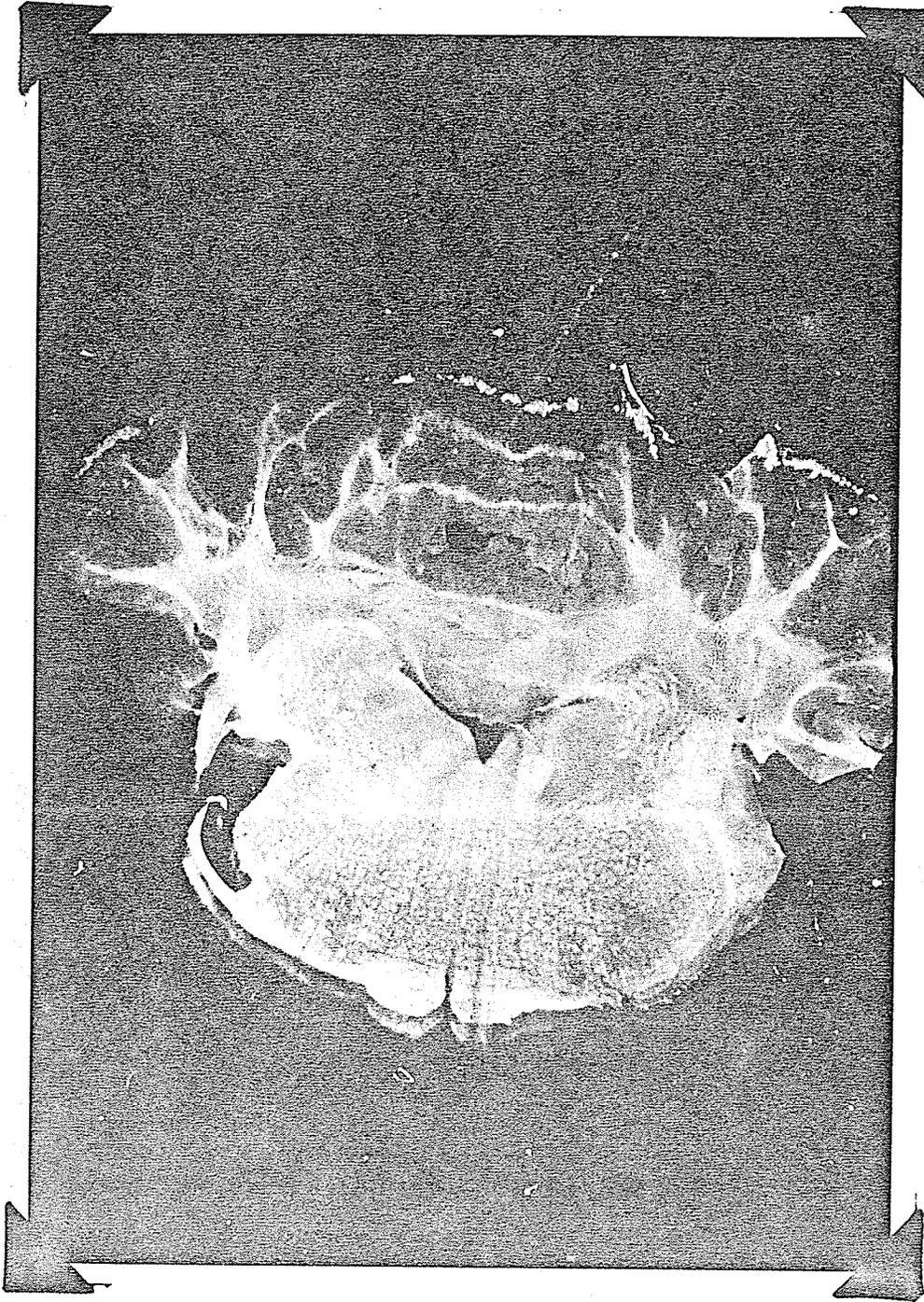


Figure 23. Section (100 X) through the anterior vermis of the cerebellum of a rat that had been exposed to neonatal control conditions

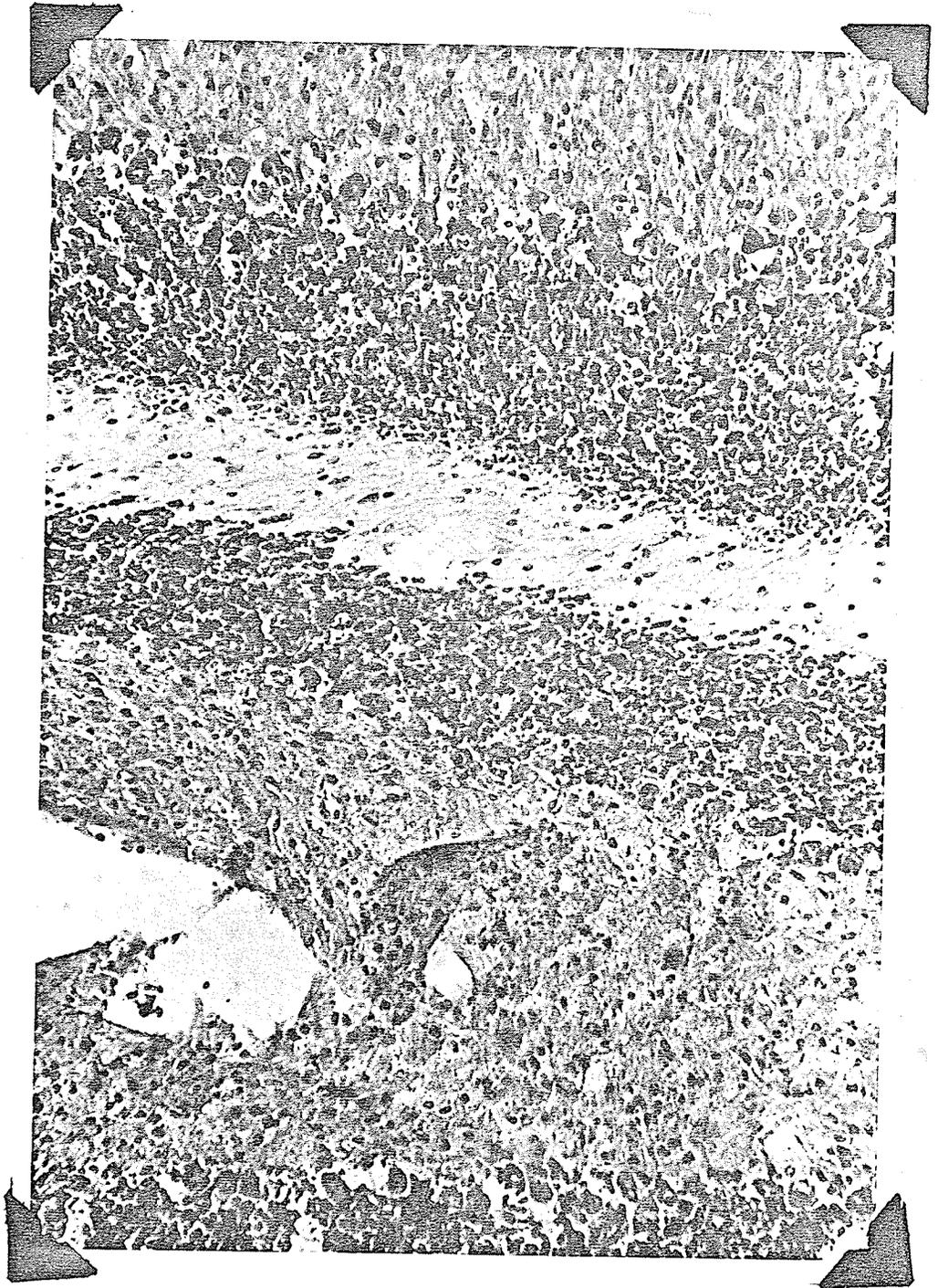


Figure 24. Section (100 X) through the anterior vermis of the cerebellum of a rat that had been exposed during postnatal days 1-4 to a 3-30 gauss, 0.5 Hz, RMF.

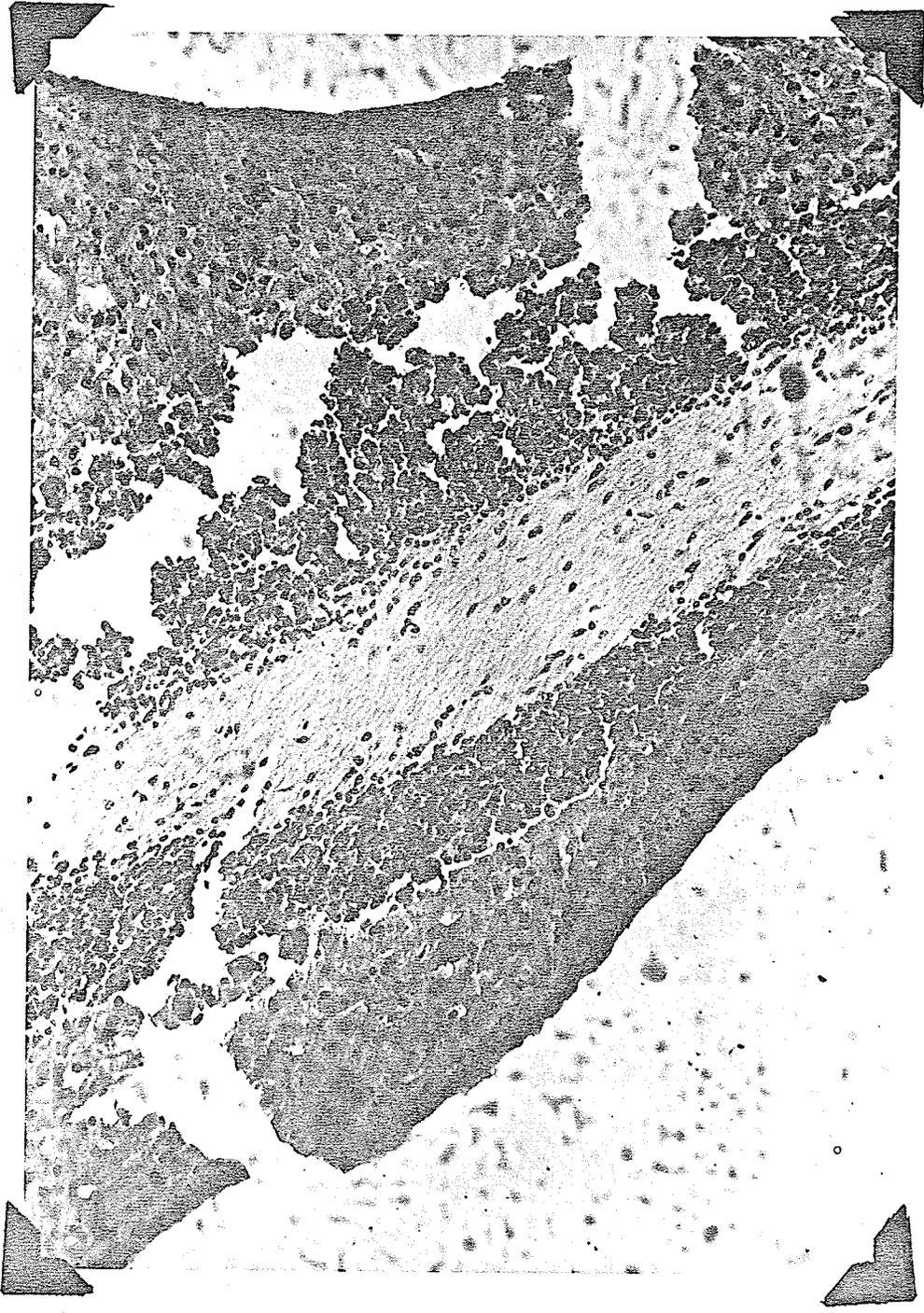


Figure 25. Section (100 X) through the anterior vermis of the cerebellum of a rat that had been exposed on prenatal day 16 to 200 rad of gamma-irradiation.



Figure 26. Section (100 X) through the anterior vermis of the cerebellum of a rat that had been exposed on postnatal day 4 to 200 rad of gamma-irradiation.



CHAPTER VI

DISCUSSION

The two behaviors of rapid responding during the delay period after its institution on step-day and increased frequency of inter-trial, non-reinforcement responding, were again noted in the present experiments. However, the relative occurrence of these two behaviors was markedly differentiated in the two populations of prenatally irradiated-RMF-exposed and neonatally irradiated-RMF-exposed groups.

The groups of rats that had been exposed to either 100 or 200 rad of gamma-irradiation on prenatal day 16 or to a 0.5-3 or 3-30 gauss Rotating Magnetic Field (RMF) during prenatal days 13-16 did not differ from their control groups with respect to ratios of total responses to mean baseline total responses after the institution of the delay on step-day. On the other hand, groups that had been exposed to 200 rad of irradiation on post-natal day 4 (three days of age) or to similar exposure intensities of the RMF during post-natal days 1-4, showed significantly greater ratios of total responses to mean baseline total responses to mean baseline total responses, than controls. This was interpreted as being associated with a relatively greater number of responses emitted during the delay period for the 200 rad irradiated and RMF-exposed groups.

That these differences were associated with some aspect of cerebellar change for both neonatally 200 rad irradiated and RMF-exposed groups, was suggested by the following data. First, the response

ratios on the day of the delay-step are significantly correlated with changes only in cerebellar and not cerebral measurements. The neonatally irradiated and control groups exhibited a significant negative correlation between cerebellar (vermis) rostral-caudal lengths and response ratios on step day, while the neonatally RMF-exposed groups displayed a significant positive correlation with cerebellar widths and response ratios on that day. Neither the prenatally Co^{60} irradiated or RMF-exposed groups showed a significant correlation with any of the measures and response ratios on step day. The reliability of the neonatal-effect of transient "bursting" is further supported since a dose relationship was shown. In both the neonatally irradiated and RMF-exposed groups, the higher intensity exposures were associated with more responding during the delay period.

The contribution of other "peripheral" factors to the increased responding during the delay for the neonatal 200 rad irradiated group and RMF-exposed groups (relative to controls), was also shown to be minimal. The possibility of differences in effective "thirst drive" due to some systemic modification following the radiation or RMF-exposures, seems unlikely. If such differences in effective water deprivation or "drive level" as it has been termed, existed, differential volumes of water intake between groups in the home cages might be expected. However, it was shown that once differences in weight were adjusted, the amount of water consumed per gram of body weight did not differ significantly between the experimental and control groups. Such lack of significant water consumption differences, was not isolated to

the home cage situation. Total reinforcements in the operant chambers on baseline days and step day again did not differ significantly between groups. Further precautions from the contribution of "drive level" to the rapid responding behavior were taken by exposing neonatally 200 rad irradiated and control groups to different levels of water deprivation. Again, there were no significant differences between the groups. The possible contribution of body weight to the responding during delay periods also seems minimal. Indeed, the neonatally 200 rad irradiated group weighed significantly less than their control group, a factor that may have produced some differential mechanical advantage between the two groups. On the other hand, the neonatally RMF-exposed groups which did not weigh significantly less than their control group, also showed significantly greater responding during the delay. The contribution of baseline activity to the rapid responding could not be responsible for this behavior either. The neonatally irradiated and RMF-exposed groups showed less activity than their controls in running wheel situations, although these differences were not statistically significant. In addition, these groups did not differ significantly from control groups with respect to mean baseline total responding.

If indeed, some process/es which occurred as a consequence of the experimental manipulations during the period of cerebellar development were responsible for the rapid responding during the delay period on step day, then one must ask why the prenataally exposed groups (who were exposed during the time of maximum forebrain, but minimum cerebellar development), also showed some evidence of such responding, although

they did not differ significantly from their control groups. The prenatally exposed groups, specifically the 200 rad irradiated group, showed some transient reactivity not only to the delay step but to changes in other schedules as well. These animals exhibited significantly greater number of total responses of intertrial, non-reinforcement responses on the days that the S^D-S^A and trial abort components of the paradigm were introduced more total responses on the days of extinction, and greater running wheel activity. The reports by Furchtgott and his associates who found transient changes in ambulatory behavior, heart rate, and exploration behavior in similarly irradiated rats, supports the above observations. It should also be pointed out that the prenatal control groups from both the irradiated and RMF conditions, unlike the neonatal controls, averaged almost the same ratios of responding as their experimental groups on step day. These findings suggest that some aspect of procedure may have been responsible for the small but notable increase. Hoffeld, McNew, and Webster (1968) have shown that the offspring of mothers who have only been handled and injected with distilled water ("controls") during mid-pregnancy (prenatal days 13-16) exhibited greater activity than offspring of mothers who had received similar treatment during other periods of pregnancy. Hence it could be argued that the small but notably increased responding on the step day for the prenatal irradiated RMF-exposed, and control groups, was associated with some other nonspecific type of factor.

The second behavioral observation that was replicated in the present study was the increased intertrial, non-reinforcement responding

noted earlier by Halasz, Hughs, Humpherys, and Persinger (1970) and especially Humpherys (1971). However, unlike those experiments, the present study found that both neonatally irradiated and RMF-exposed groups did not display greater intertrial responding than controls, as measured by either ratios of total responses to total responses during reinforcement periods or total number of trial aborts. In fact, the irradiated groups showed significantly less intertrial responding before the insertion of the trial abort and consistently less such responding after the trial abort was instituted. Similarly, the two neonatally irradiated groups, combined, had significantly fewer trial aborts than their controls on the first day of trial abort input. The neonatally RMF-exposed groups also showed no significant differences from their controls on these measures.

On the other hand, the prenatally irradiated groups, specifically the 200 rad group, exhibited significantly greater numbers of intertrial responses than the neonatally irradiated groups both before and on the day of trial abort input. These prenatally irradiated rats also averaged significantly greater number of trial aborts on the first day that this modification was introduced into the paradigm. The prenatal RMF-exposed groups, like their neonatal counterparts, did not differ from their control groups in any of these measures. Collectively, the above data suggest that greater intertrial, non-reinforcement responding is more a consequence of exposure to irradiation on prenatal day 16 than exposure on post-natal day 4. Such a relationship immediately implicates the reduction of cerebral (forebrain) size as the

critical brain correlate. This seems quite probable since only the correlations between trial aborts and cerebral sizes were significant for all groups. There were no significant correlations with cerebellar dimensions. Also, the number of non-reinforcement responses and trial aborts were dose dependent, the maximum values being exhibited by the group with the maximum forebrain reduction. The prenatally RMF-exposed groups, which did not show differences in these behavioral measures from their control groups, displayed, if anything, slightly larger cerebral sizes (widths). Similarly, both neonatally irradiated and RMF-exposed groups did not show greater numbers of intertrial responses or trial aborts relative to their controls, and, in addition, did not differ from their controls with respect to cerebral size.

These findings indicate that the significantly increased non-reinforcement responding of the irradiates in the Humpherys (1971) experiment was possibly a consequence of reduction in forebrain size. Since his subjects were irradiated with similar doses and received similar training procedures, the two studies appear to be at variance. However, unlike the present study, the above experiment involved a split-litter control technique, where the neonates were handled daily after the irradiation. Altman, Das, and Anderson (1968) have shown that handling during the first two weeks of life can significantly reduce the weight and size of the cerebrum. As a result, handling in conjunction with the irradiation, could have reduced the cerebral size to the threshold where non-reinforcement, intertrial responding increased in relative frequency.

Another contradictory result between the present study and the Humpherys experiment was that the latter did not show significantly greater responding for the irradiated subjects during a nine second delay period on the day it was instituted in a step-like fashion. The present study has indicated that such increases in responding during the delay period for both neonatally RMF-exposed and 200 rad irradiated groups were transient and did not reappear when another delay was instituted a week later. That these transients are extremely "delicate" and can be obviated by previous exposure to other schedules has been reported earlier. The neonatal irradiates in preliminary Experiment VI, along with their controls, had been exposed to extinction of the lever press response for water reinforcement. When a delay was instituted, in a manner similar to the one used in the main experiment of this study, the irradiates did not show responding during the delay period. In fact, both groups responded at values less than baseline, indicative of extinction. Hence, these findings suggest that exposure to extinction-like conditions reduce the rapid responding effect when the delay is inserted. In automated procedures, a failure in reinforcement delivery during training due to breakdowns in the apparatus, could simulate the extinction situation. An equally probable explanation for the differences between the Humpherys' experiment and the present study is that males were used as subjects in the former experiment while females were utilized in this study. That irradiated females show different behaviors than irradiated males in learning situations has been reported (Werboff, Havlena, & Sikov, 1962).

The possibility that the above behavioral phenomena are a consequence of some peculiarities in the irradiated groups can be considered to be minimal, since these animals displayed behaviors characteristic of irradiates in other similar situations. The observations that exposure on prenatal day 16 to ionizing radiation is associated with fewer responses on the first day of lever press training, more responses during extinction, and more non-reinforcement responses during training, have been reported by Furchtgott and Walker (1969) and Walker and Furchtgott (1970). Furchtgott and Walker, in addition, reported that day 16 X-irradiated rats received fewer reinforcements on the first few days of DRL training. These results are comparable to the increased ratios of total responses to reinforced responses and total trial aborts for day 16 gamma-irradiates after the institution of a second-order DRL (trial abort) into the paradigm. The longer response latencies of day 16 irradiated animals was also shown in the present study, and was in large part responsible for their lower (relative to controls) negative P-values, indicative of "better" adjustment to the nine second delay demand. Rat group that had been irradiated on fetal day 16 showed greater activity, again, a frequent observation in such animals (Furchtgott & Echols, 1958a). The decrement in running wheel activity for the neonatally exposed groups has also been reported elsewhere (Wallace & Altman, 1969).

One novel aspect of the present study was the comparison of rats that had been prenatally or neonatally exposed to a 0.5 Hz RMF with rats that had been irradiated during comparable periods of prenatal and neo-

natal development. In the preliminary experiments, it was found that, similar to prenatal irradiates, the prenatally RMF-exposed groups made fewer responses on the first day of acquisition but more responses during extinction than their control groups. However, these differences were not statistically significant. Further comparisons between measurements that were significantly different for the irradiated groups, i.e., baseline latencies, with corresponding measurements for the RMF-exposed groups indicated little behavioral resemblance. With respect to body weights, the prenatal RMF-exposed groups weighed significantly more than the prenatally irradiated groups. The high number of significant correlations between the four brain measurements and five behavioral measurements noted in the prenatally irradiated and control groups showed no similarity to the correlations of the prenatal RMF-exposed and control groups. By far the most obvious contrast between the two groups exposed to the two types of electromagnetic fields, was in actual brain sizes. Compared to controls, the prenatally irradiated groups showed markedly reduced cerebrums (forebrains), while the RMF-exposed groups showed, if anything, slightly larger cerebral sizes (widths) than their controls. Histologically, with the exception of possible reduction in the number of Purkinje cells in the prenatally irradiated group, no gross differences could be noted between prenatal RMF-exposed, irradiated, or control groups.

The neonatally irradiated and RMF-exposed groups showed much greater behavioral similarity. Neonatal exposure to these two types of electromagnetic conditions was associated with a similar lack of

statistically significant differences, when compared to respective control groups, in total number of responses on the first day of CRF training, during extinction and the first day of S^D-S^A training, and in average baseline latencies, P-values, and trial aborts on the first day that the latter modification was inserted. Similarly, the groups that had been exposed neonatally to the higher intensities of two types of electromagnetic conditions, showed comparably fewer intertrial non-reinforcement responses both before and after the institution of the trial abort. Unlike the neonatal irradiates, however, the RMF-exposed high intensity group's fewer non-reinforcement responses were not significantly different from controls. On the other hand, both neonatally irradiated groups along with the group exposed to the 3-30 gauss field has significantly fewer non-reinforcement responses than their respective prenatal counterparts.

After the impulse was instituted on step day, both RMF-exposed groups and the 200 rad irradiated group exhibited significantly greater responding than their controls. Again, in both situations, a dose-dependent relationship was noted. The groups that received the higher intensities of irradiation or RMF, exhibited the greatest relative responding, with respect to controls.

The neonatally RMF-exposed groups differed from the irradiated groups in their weights, cerebellar dimensions, cerebellar structure, and histology. While the irradiates weighed significantly less than controls, the RMF-exposed groups did not. Also, the rapid responding of the 200 rad group was definitely correlated with reduced cerebellar

length and deformation in the vermis. The 100 rad group which did show the significant reduction of vermal length but not the deformation were similar to controls in their responding during the delay period. Both RMF-exposed groups showed a positive correlation with cerebellar width but did not show any type of deformation of the cerebellum. Histological analysis of the RMF-exposed cerebelli was similar to that of the control rats, while the 200 rad animals showed deformation in the vermal layers, and a corresponding depletion and malformation of the granule cell layer, with accompanying disorganization of the Purkinje cells.

That the rapid responding during the delay period was associated with morphological deformation in the neonatally 200 rad irradiated group and no detectable deformation in the neonatally RMF-exposed groups, may at first appear puzzling. However, it should be pointed out that a frequent observation in the discipline of neurochemistry is that morphological changes may be associated with biochemical changes, but biochemical changes may not be associated with morphological changes. One class of biochemical candidates, that may have undergone change following both RMF and radiation exposure, are the thyroid hormones. These chemicals play a critical role in the biochemical differentiation and maturation of the brain (Garcia, Argiz, Pasquini, Kaplun, & Gomez, 1967).

As was noted previously, rats that had been exposed during their prenatal development, but removed at birth from a 0.5 Hz, 0.5-30 gauss RMF exhibited many of the symptoms of hypothyroidism. Neonatal

thyroidectomy and the consequent hypothyroid state, is associated with changes in the concentration of a number of brain chemicals (Krawiec, Garcia, Argiz, & Pasquini, 1969). Similar to irradiation, rats thyroidectomized at birth showed a decrease in AChE and ChE levels in the brain (Geel & Timiras, 1967) and are later more reactive to electroshock (Meisami, Valcana, & Timiras, 1970). Histological analysis, as reported by Hamburg (1970), indicated that thyroidectomy delays the migration of cells from the external granular layer and produces a hypoplasia of the dendritic spread of the Purkinje cells. Such delays in granule cells migration from the proliferative zone have also been shown to be a consequence of neonatal irradiation (Altman, Anderson, & Wright, 1969). More direct evidence that irradiation can produce a hypothyroid-like state was reported earlier by Cohan et al. (1969). They found that a 100 rad dose administered to the head only of neonatal day 4 rats, did not produce morphological changes in the cerebellum, but did retard the uptake of ¹³¹I-tri-iodothyronine (a thyroid hormone) into the brain. If RMF-exposure prevented the uptake of this chemical into the brain, then long lasting though subtle changes in the Purkinje cells or Purkinje cell-granule cell interactions, could have resulted. Such alterations would suggest that gross morphological deformation, as noted in the 200 rad animals, might not be a necessary antecedent condition for the observed behavioral changes on step day. Unfortunately, in this study neither biochemical changes nor dendritic architecture were studied.

The results of the present study can be shown to be compatible

with modern theory of the cerebellar cortex. It is well known that Purkinje cells receive afferent impulse from the inferior olive via the climbing fibers and from mossy fibers via the parallel fibers of granule cells. Marr (1969) has speculated that during learning the cerebrum organizes a given motoric movement, and in doing so causes the appropriate olivary cells to fire in a particular sequence, which in turn sends impulses to the corresponding Purkinje cells. The Purkinje cells are also exposed, via the mossy fiber input, to information about new physiological context in which the olivary cells were fired. The next time the context alone occurs, the mossy fibers activity stimulates the Purkinje cells, which in turn evokes the relevant elemental movements. In this way the cerebrum is free from the redundancy of repeatedly organizing precise elemental movements. Since the granule cells, due to the construction of their interface with the mossy fibers (glomeruli) are sensitive to small inputs, changes in different contexts in which a movement will occur, can be detected.

In the DCA situation, the neonatal RMF-exposed and irradiated rats did not show the greatest behavioral effects with just any change in schedule but with changes in the more complicated schedules to which definite learned movements had been associated. From Marr's theory one would argue that after repeated association of immediate onset of the CS with immediate availability of the reinforcement, the cerebellum began to initiate the responses which followed the onset of the CS. When the delay was instituted, the Purkinje cells of the "normal" control rats could detect the change in context via the intact mossy fiber-

granule-cell-parallel fiber circuit. That such delay or temporal discrimination behavior is mediated by the motor system has often been suggested (Laties, Weiss, Clark & Reynolds, 1965; Reynolds, 1966). On the other hand, the 200 rad irradiated rats with their depleted and deranged granule layer, would have been less sensitive to the subtle change in context, and would have continued to respond during the delay in the pattern to which they have been conditioned earlier. Hence the greatest differences in learned motor behavior between irradiated and control groups would not be during steady-state behaviors where the contexts from the mossy fiber input are synchronous with cerebral input, but during transient behaviors associated with schedule changes, where the context from the mossy fiber input varies from cerebral input.

However, merely scattering or disorganization of the granule cells was obviously not the only prerequisite for the responding through the delay period, since the RMF-exposed rats, with no obvious depletion, also showed such behavior. It can be assumed that the hypothyroid-like behavior of the RMF-exposed rats was also reflected in their biochemical characteristics. As was stated earlier both neonatal irradiation and thyroidectomy produced a decrease in ChE and AChE activity. Altman and Das (1970), have found that in the cerebellar (vermis) cortex, the strongest staining for the ChE occurred at the glomeruli, where the granule cells and afferent mossy fibers synapse. Disturbances of the biochemistry at this mossy-fiber-granule cell interface might reduce its efficiency at detecting small changes in contexts which in turn are sent to the Purkinje cells via the parallel fibers. As a result, when

the delay was instituted both neonatally irradiated and RMF-exposed groups would continue to respond with a type of "motor blindness" during the delay period, in a pattern similar to that which they displayed when the CS and reinforcement onset simultaneously. However, again within the logic of Marr's theory, as the cerebellum lost its responsiveness to the changed environment, the cerebrum would then take over the initiation of movements. If cerebral initiation was still dominant a week later when the second delay was instituted, rapid responding in the experimental groups would not be expected.

One interesting consequence of the above observations is that the responding during the delay period by RMF-exposed and 200 rad irradiated animals might only occur in a situation where an auditory stimulus is associated with the onset of reinforcement. This is especially probable since the cholinergic mossy fibers that deliver impulses to the granule cells are mostly associated with the acoustico-vestibular system (Altman & Das, 1970). Hence contexts propagated to the Purkinje cells by some other channel using a non-cholinergic transmitter, that was not affected by irradiation or RFM-exposure, might result in adaptation to delay inputs in a manner that was characteristic of the neonatal control rats in this study.

Before closing, it should be pointed out that the majority of the significant differences between the various groups tested in this study, did not occur during steady-state or maintained schedule, but during changes of schedules. The typical responses to these latter changes were specific but transient in nature. A systematic and controlled

investigation of such transient behaviors associated with schedule changes, may more clearly differentiate the consequences of exposure to many subtle, but socially relevant physical environmental variables.

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Figure 27. Cumulative response graph over minutes, before and after the institution of the delay (Γ) for a rat that had been exposed neonatally to 100 rad of gamma-radiation. Clusters of slashes indicate reinforcement.

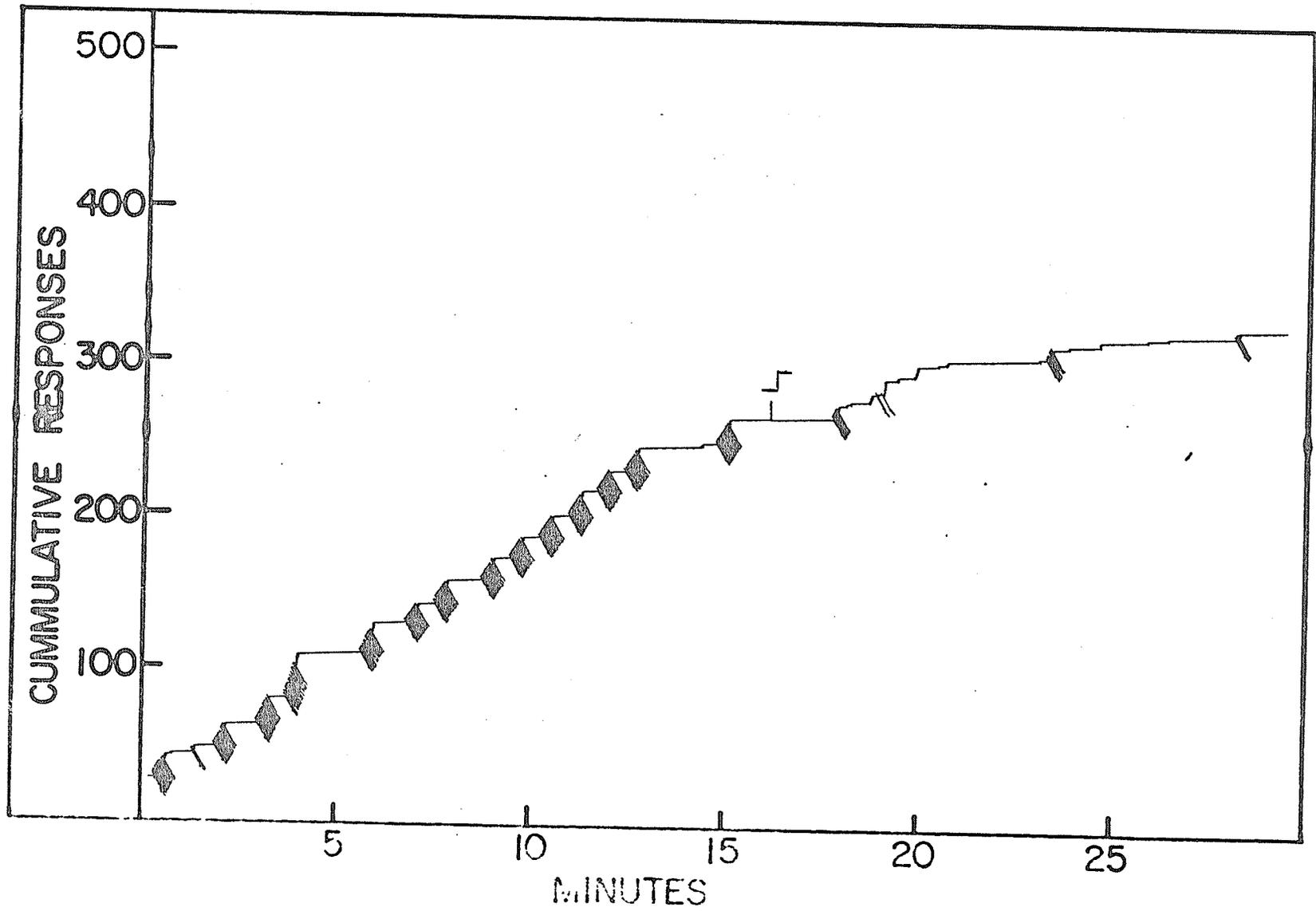


Figure 28. Cumulative response graph over minutes, before and after the institution of the delay (Γ) for a rat that had been exposed on prenatal day 16 to 200 rad of gamma-radiation. Clusters of slashes indicate reinforcement.

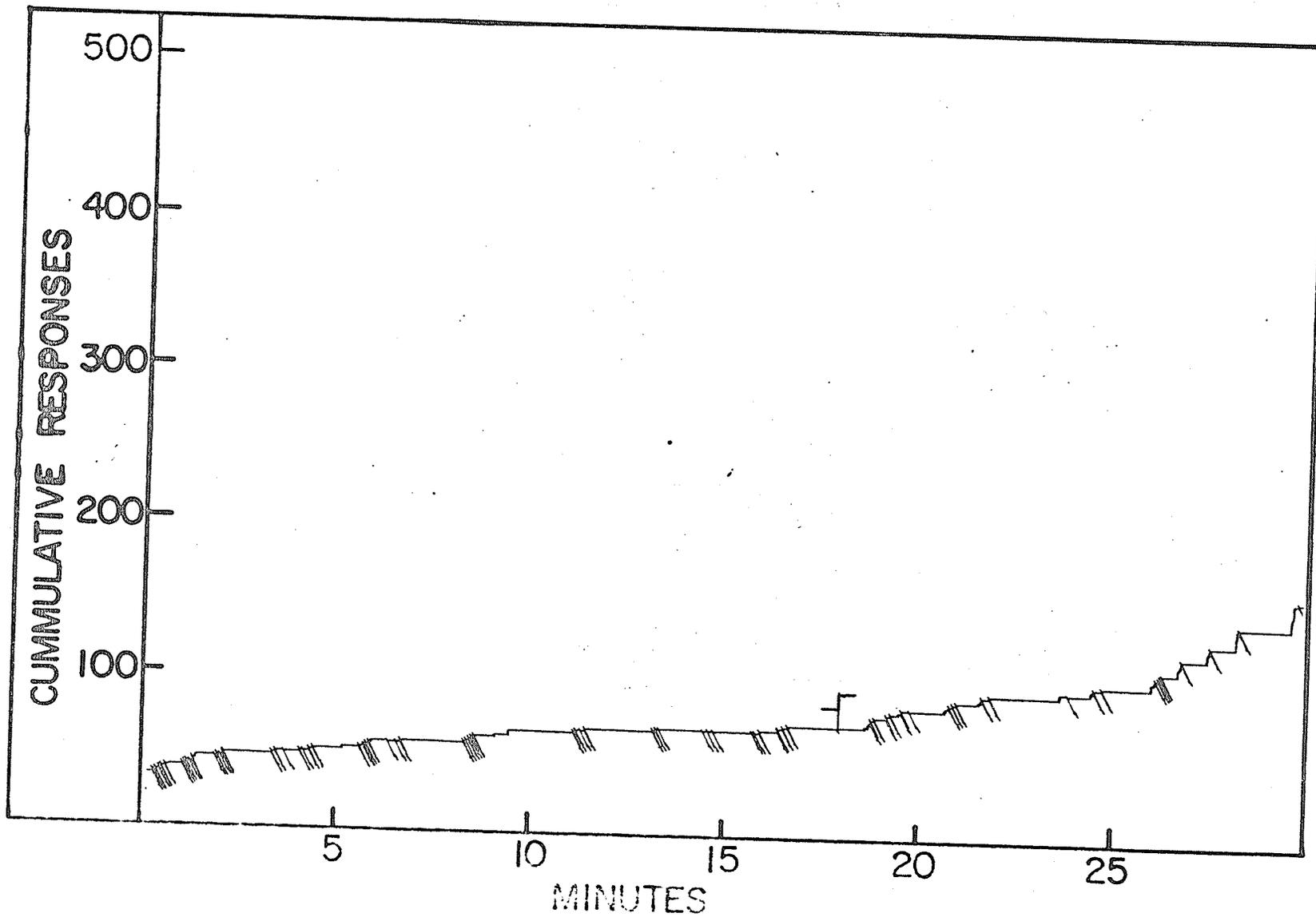


Figure 29. Cumulative response graph over minutes, before and after the institution of the delay (Γ) for a rat that had been exposed during prenatal days 13-16 to a 3-30 gauss Rotating Magnetic Field. Clusters of slashes indicate reinforcement.

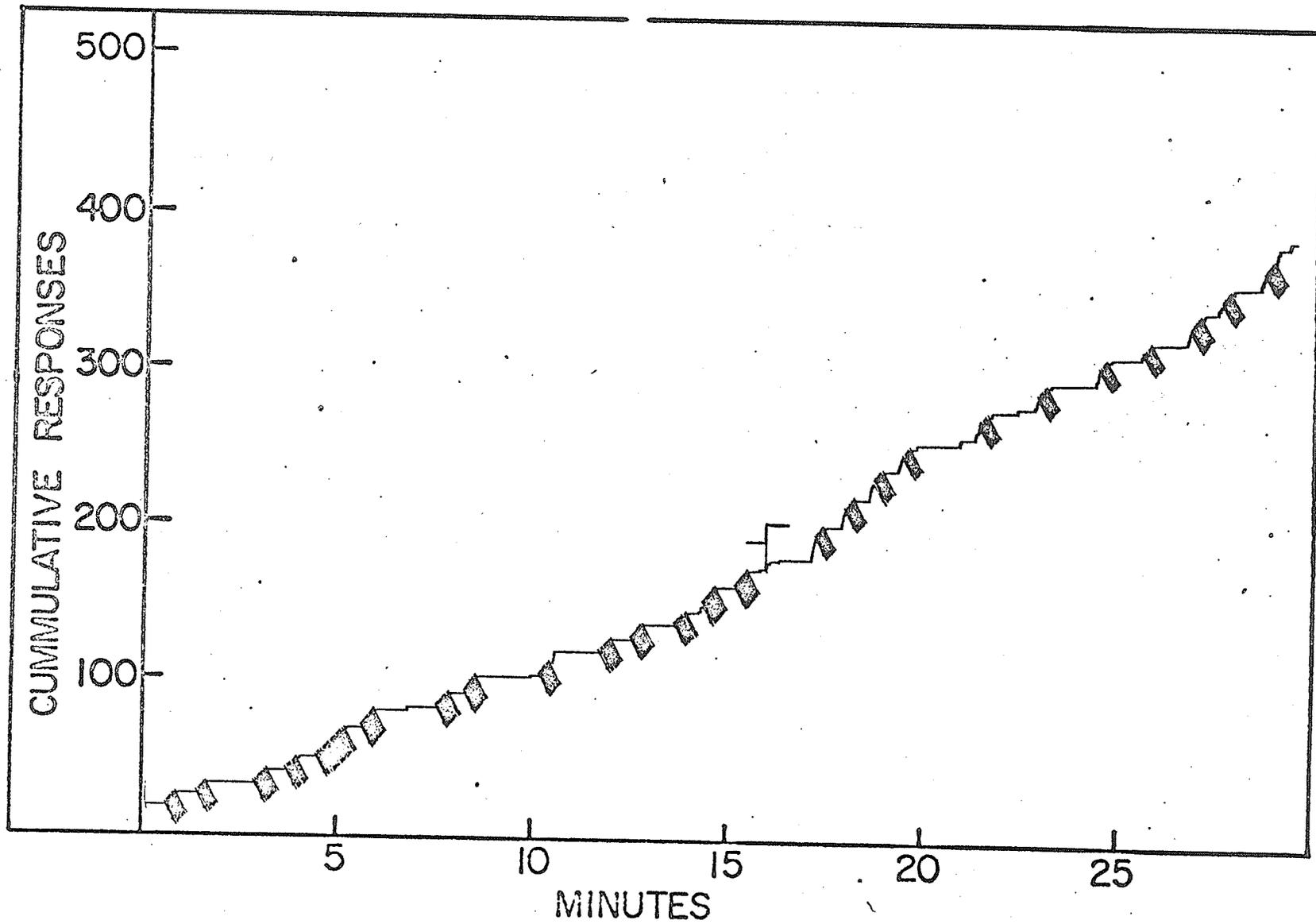


Figure 30. Cumulative response graph over minutes, before and after the institution of the delay (Δ) for a rat that had been exposed to prenatal control conditions. Clusters of slashes indicate reinforcement.

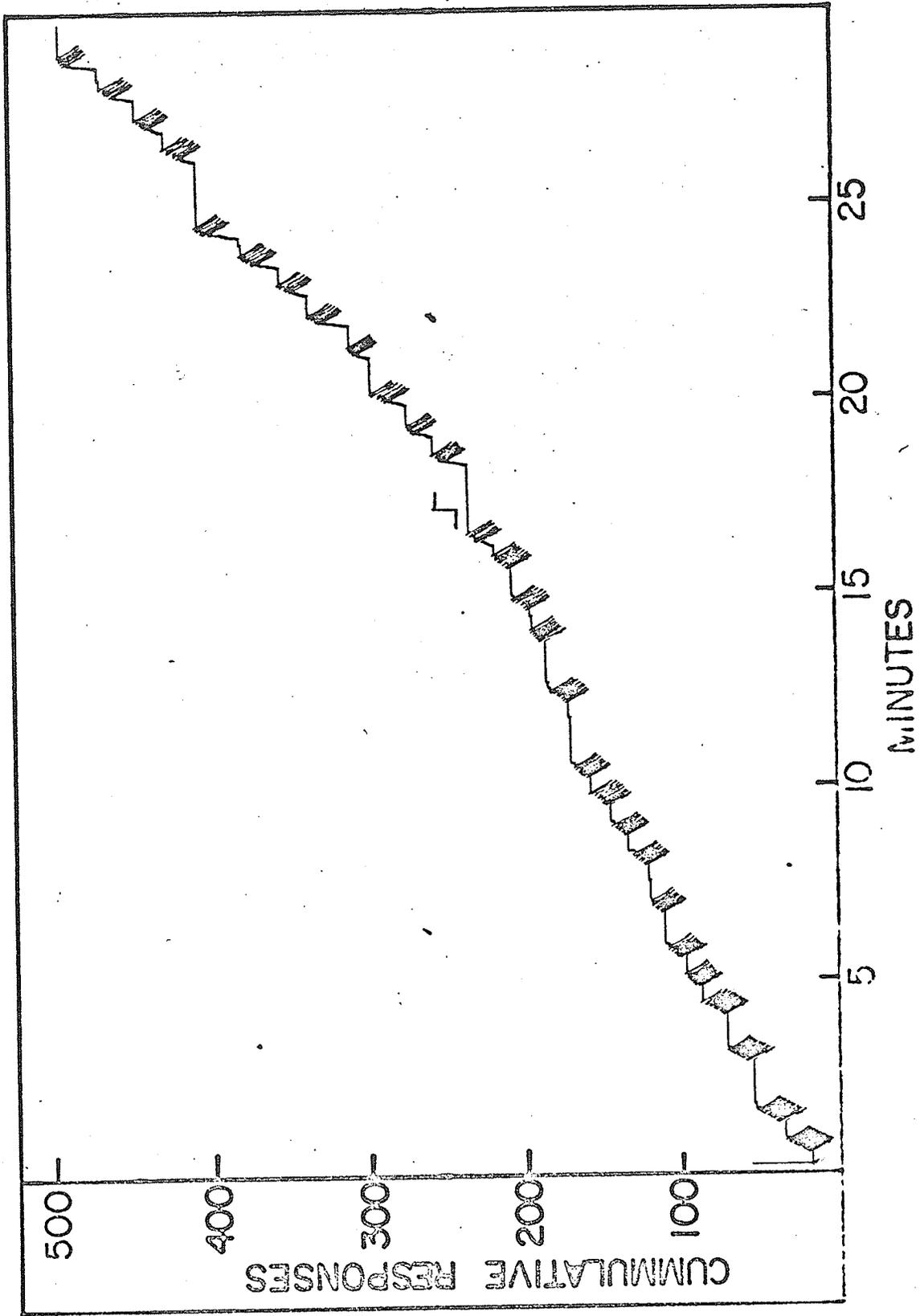


Figure 31. Section (400 X cresyl violet stain) through anterior vermis of cerebellum of rat exposed neonatally to control conditions. The Purkinje cells (larger cells) form a single straight row between the granular layer (upper part of picture) and molecular layer (lower part of picture). The medullary (white) layer can be seen in the upper left hand corner.

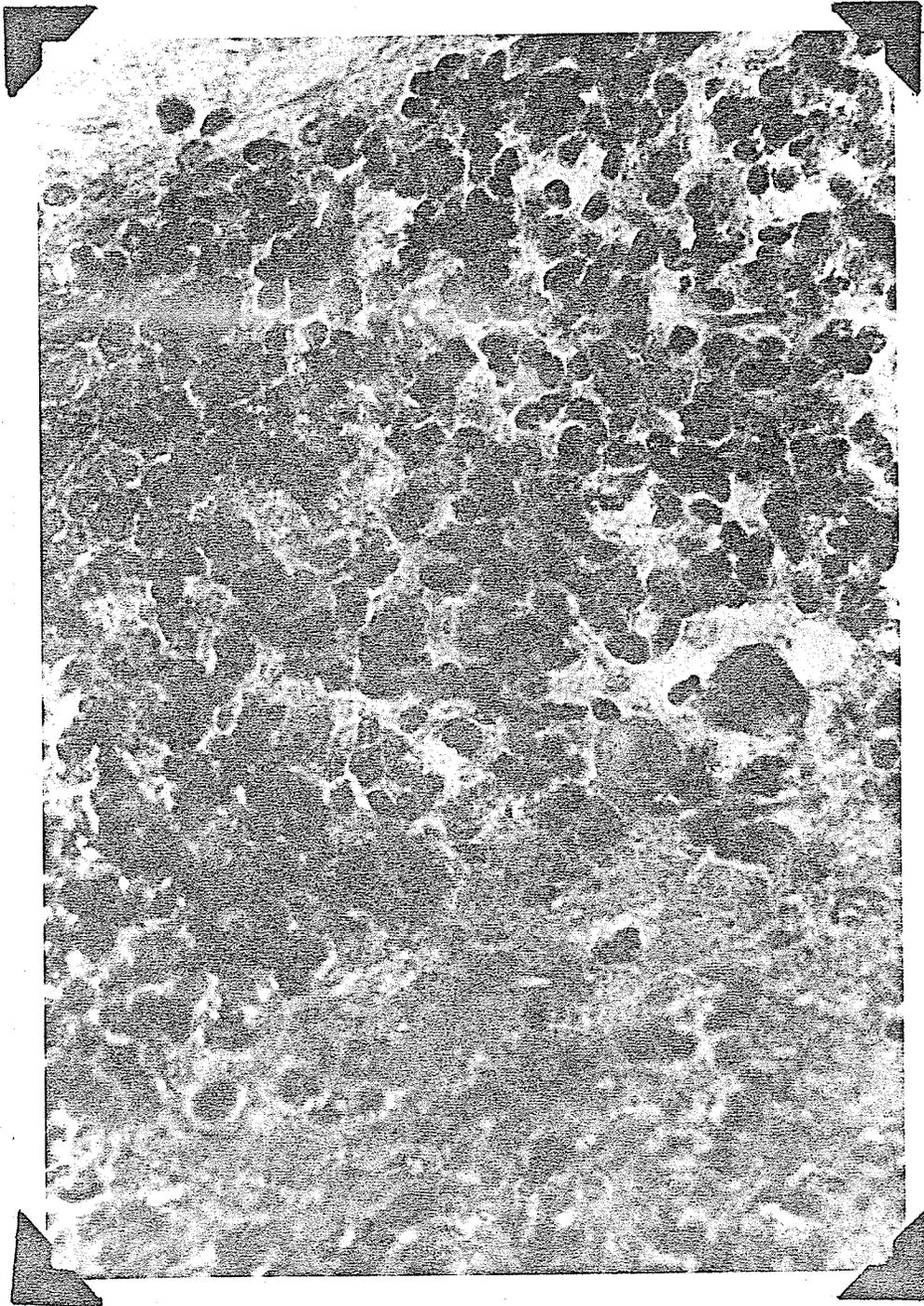


Figure 32. Section (400 X; cresyl violet stain) through anterior vermis of cerebellum of rat exposed neonatally to a 3-30 gauss Rotating Magnetic Field. Note that the Purkinje cells are borderin the molecular layer-granular layer interface, similar to the control section (Figure).

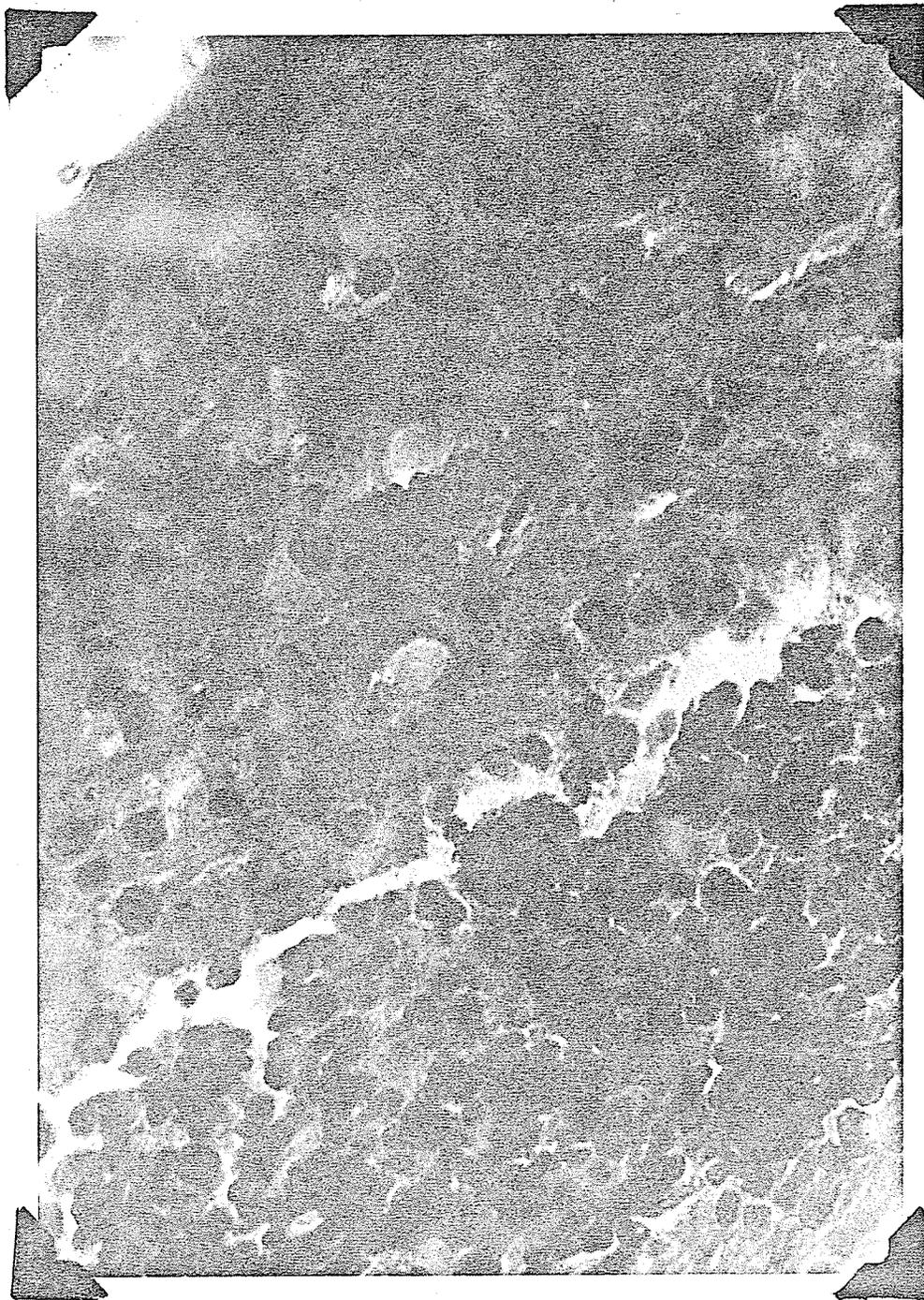


Figure 33. Section (400 X cresyl violet stain) through anterior vermis of cerebellum of rat exposed neonatally to 200 rad of Co⁶⁰ radiation. Note the intermingling of Purkinje cells (larger cells), and granule cells in this molecular layer.

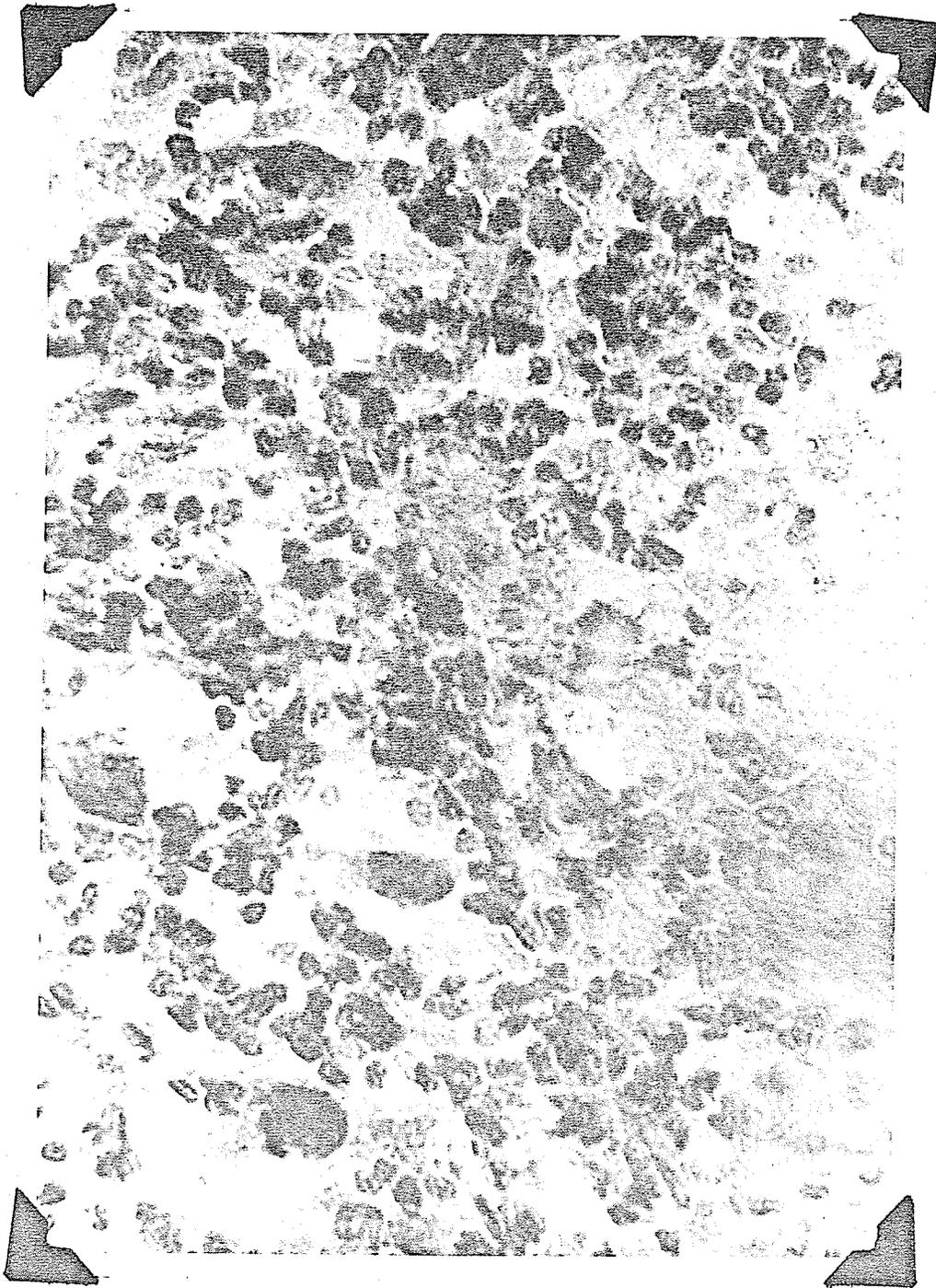


Figure 34. Section (400 X cresyl violet stain) through anterior vermis of cerebellum of rat exposed on prenatal day 16 to 200 rad Co⁶⁰ radiation. The grayish area is the molecular layer while the darker layer is the granular layer. The Purkinje cells which lie along the interface of the two layers stained lighter and are reduced in number (in this photograph).

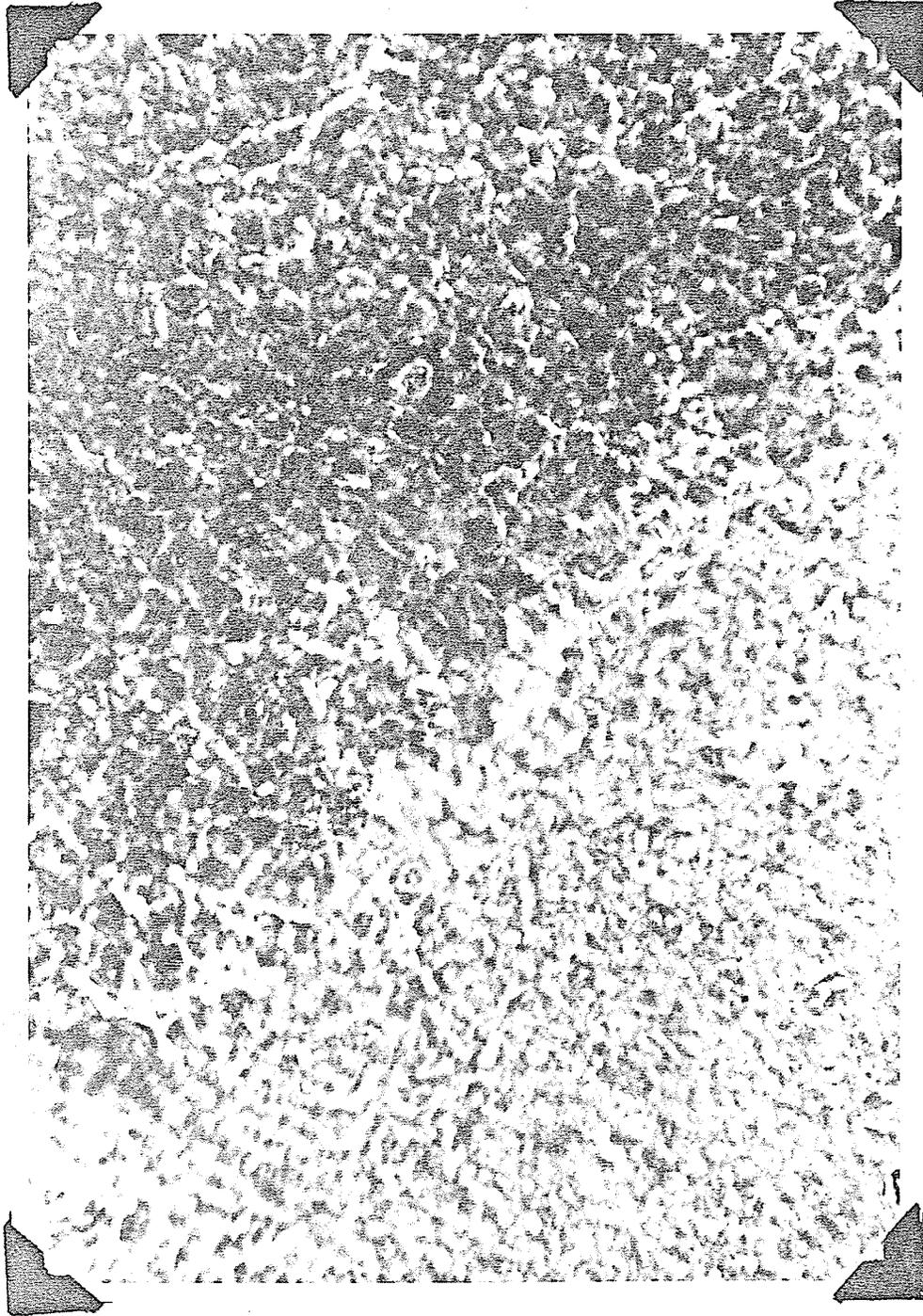


Figure 35. Section (100 X; cresyl violet) through the cerebellum of a rat that had been exposed on post-natal day 4 to control conditions.

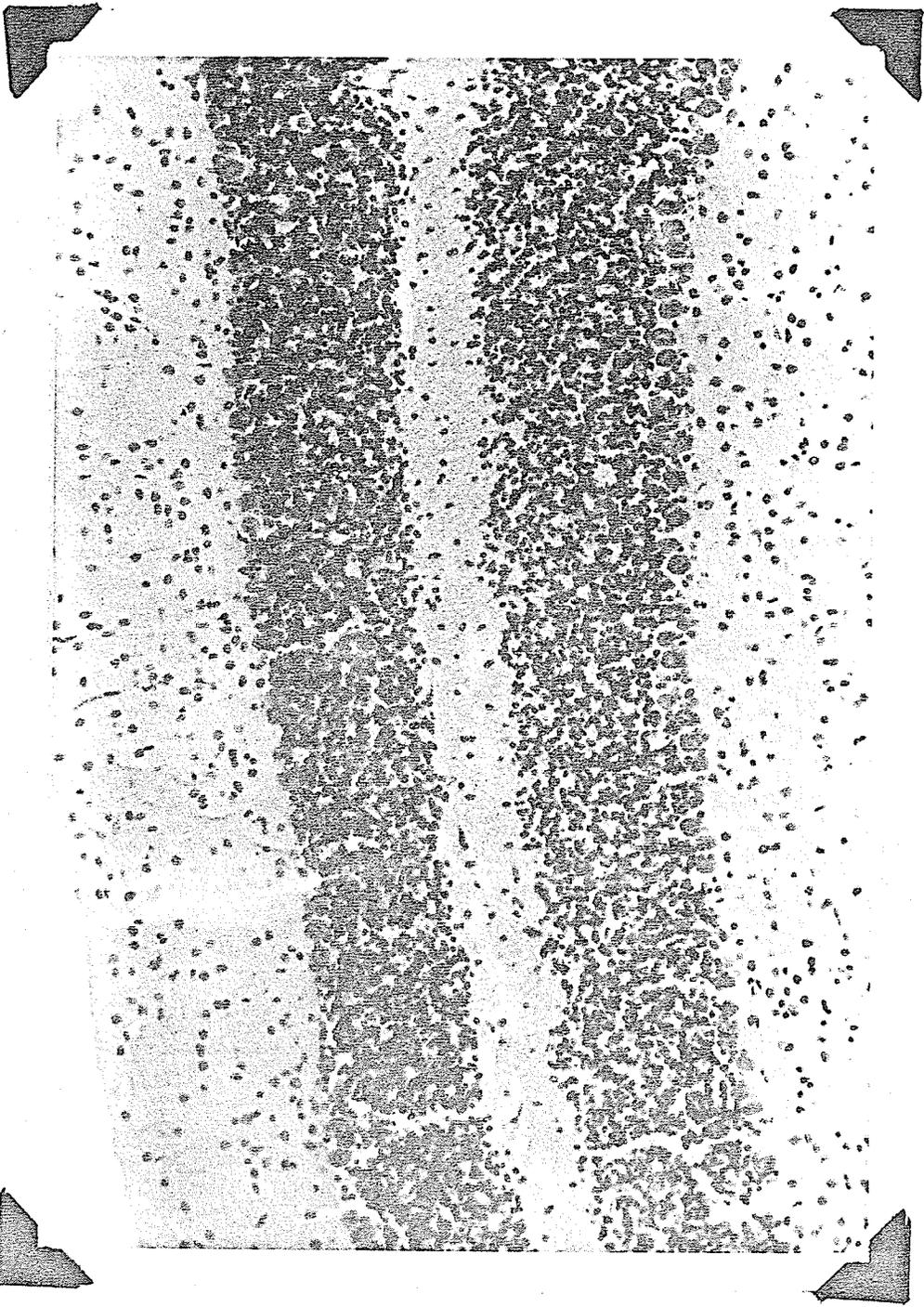


Figure 36. Section (100 X; cresyl violet) through the cerebellum of a rat that had been exposed on post-natal day 4 to 200 rad of gamma-radiation.

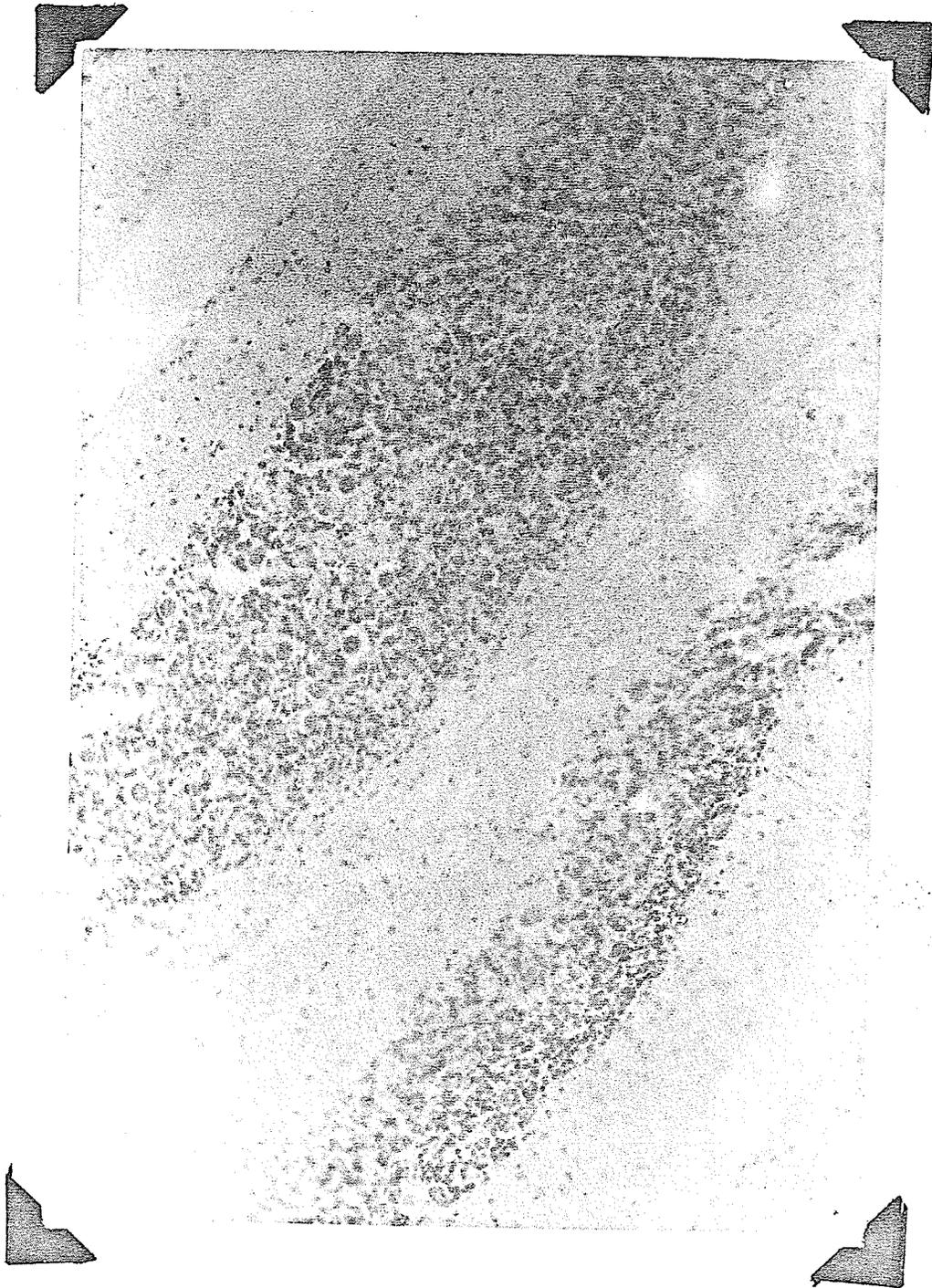


Figure 37. Section (100 X; cresyl violet) through the cerebellum of a rat that had been exposed during post-natal days 1-4 to a 0.5 Hz, 0.5-3 gauss Rotating Magnetic Field.

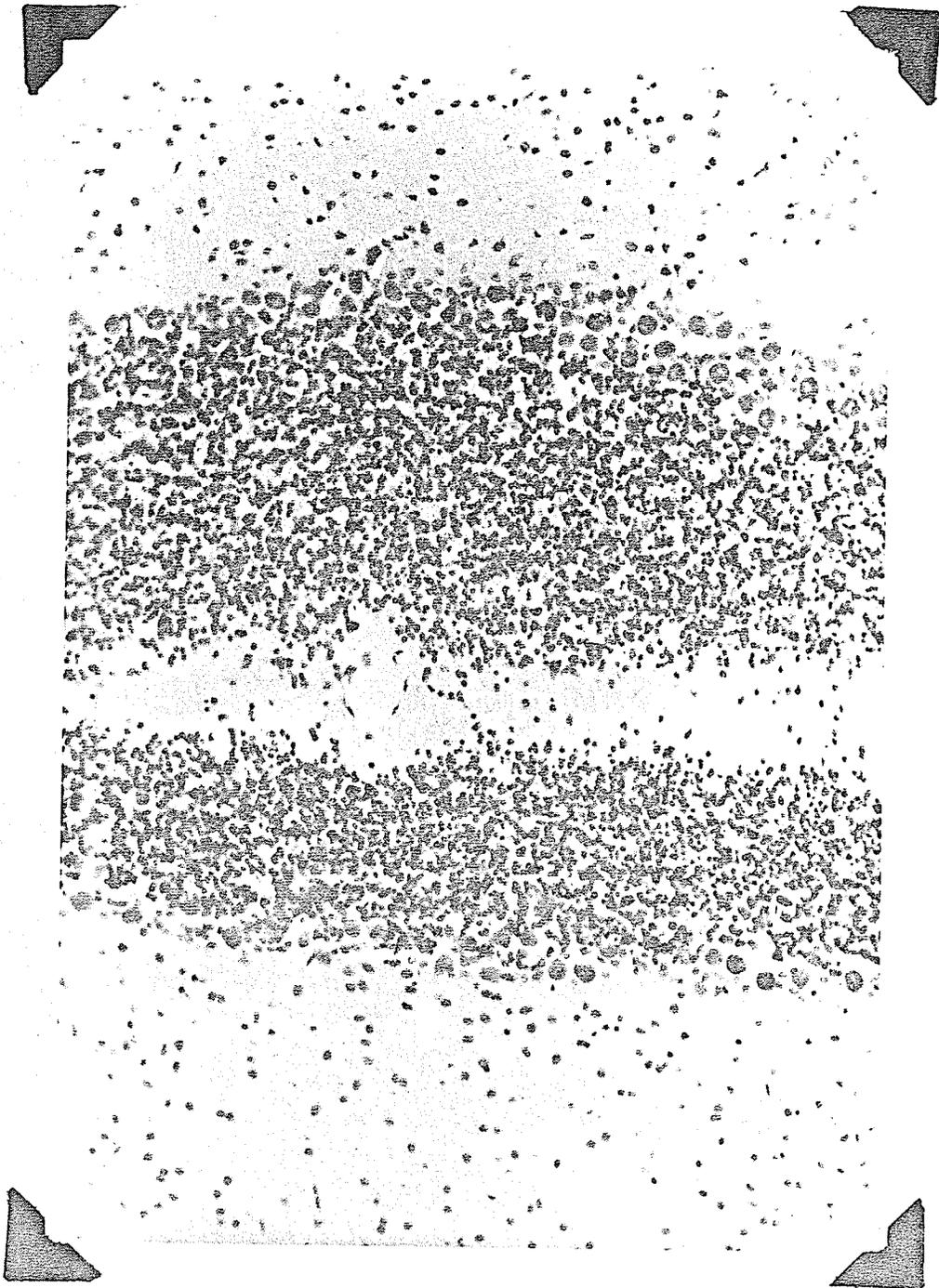


Figure 38. Section (100 X; cresyl violet) through the cerebellum of a rat that had been exposed on post-natal day 4 to 100 rad of gamma-radiation.



Figure 39. Section (100 X; cresyl violet) through the cerebellum of a rat that had been exposed on prenatal day 16 to 200 rad of gamma-radiation.

