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EFFECTS OF COBALT-60 IRRADIATION TO THE REGION OF THE BRAIN OF THE BURRO

Clinical Signs and Symptoms

by

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ABSTRACT

Seven burros received 600r and four burros 200r of gamma rays from a bilateral cobalt-60 source to the region of the brain. Each burro had a paired control that was sham-irradiated. The principal target was the brain. Six out of seven burros receiving 600r died in the terminal phase of the hyperacute radiation syndrome. The animals that received 200r showed a few transient abnormal neurological signs. Irradiated burros exhibited abnormal neurological signs at relatively low doses of radiation to the region of the brain when compared to other irradiated mammalian species.

PUBLICATION REVIEW

This report has been reviewed and is approved.

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1. INTRODUCTION.

Radiosensitivity in the living animal can as yet only be measured by "biological dosimeters," such as lethality, carcinogenesis, cataract formation, blood cell changes, erythema, and other clinical manifestations. Neurological examinations comprise one method to determine the degree of radiosensitivity of the mammalian brain. Results of reported neurological examinations suggest that the brain is relatively unaffected by radiation in lower dose ranges. Neurological abnormalities occur in all mammalian species following sufficient higher doses of ionizing radiation. The dose rate and/or total dose required to produce neuromuscular disturbances under various experimental procedures in several species has been reviewed.[2]

The interest in effects of irradiation upon larger animals, whose body size approaches that of man, arose as a natural progression of similar interests in smaller mammals. Whole-body irradiation of large animals including the burro has been reported by Trum,[14] Trum and Rust,[3,15] and others.[2]

2. METHODS AND MATERIALS.

a. Irradiation facility and dosimetry.

The irradiation source, located in the university of Minnesota Gamma Irradiation Facility, was composed of ten 200-curie pencils of cobalt-60, a radionuclide which has two cascading gamma ray energies of 1.172 and 1.332 Mev.[11] The pencils were enclosed in stainless-steel tubes, silver soldered at each end. The effective length of each of these sources was 10 inches. To irradiate the burro, two carriages, containing two pencils each, were raised by remote control from a well of water measuring 5 feet in diameter and 17 feet deep. One carriage entered through the bottom of a concrete and lead collimator on the left of the burro and the other carriage entered a similar collimator on the right side. The carriages were placed so that the longitudinal axis of each pencil was parallel to the midline axis of the animal. The pencils were 85 cm from the midline of the animal's head to produce a solid field of flux (figure 1).

Radiation measurements were made by Victoreen Condensor r meters with cobalt-60 chambers, and a Baldwin-Farmer electrometer with ionization chambers. The delivered dose over a period of time to any point in the brain was within + 3 percent of the midline dose when measured in a paraffin and

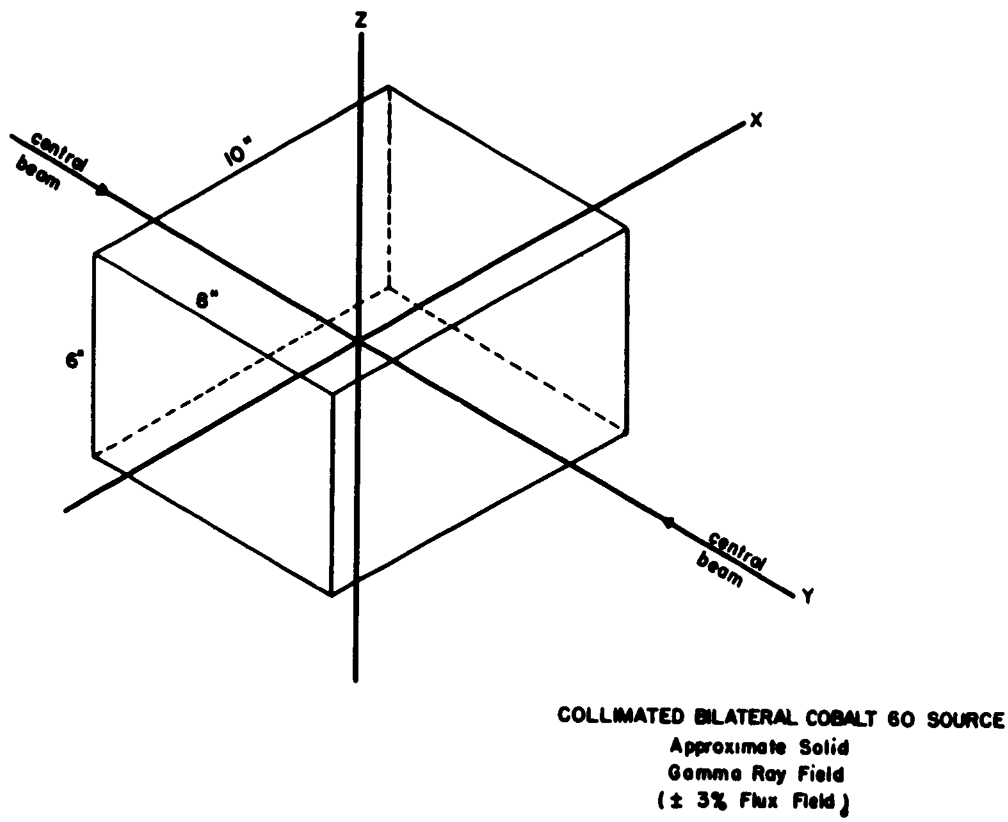

Figure 1. The xyz axes are shown in relation to the central base.

bone simulated burro-head phantom.[2]

The average rate of gamma-ray flux measured in air for the 600r group was 12.4r per minute and for the 200r group, 19.8r per minute. The gamma-ray flux was monitored during the irradiation of the burro with a remote area ionization chamber. The dose rate varied in the various groups because of radioisotopic decay between irradiation procedures. Excellent shielding was obtained by placing 3-inch steel bars in the lower front of the restraint box. This reduced the dosage to portions of the body other than the region of the head and the anterior cervical area, to less than ±6 percent of the delivered midline dose to the brain. Further shielding would have been difficult to achieve within practicalities of the experiment.

The burro irradiation cart was made of 3/8-inch exterior plywood and 2-inch angle iron (figure 2). A mandibular restraint board was constructed to conform to the angular regions of the mandible. One-inch cotton-web straps were secured on the board for placement behind the occipital crest and over the middle one-third of the maxillary region. The mandibular restraint board was adjusted to enable presentation of only brain region to irradiation. Once strapped in the restraint mechanism, the burro relaxed and offered little resistance. No anesthetic or tranquilizing drugs were necessary.

The mandibular restraint board could be moved forward or backward, up or down, or rotated on the horizontal axis, making it possible to fix the head in each axis of radiation as required (figure 1). Position on the X-axis was fixed by placed the burro's head so that the beam passed anterior to the frontal region and posterior to the occipital crest. The midline of the burro was positioned on the Y-axis equidistant from each source. The tissues at the midline, therefore, received a constant rate of radiation from each cobalt-60 source. Position on the Z-axis was adjusted so that the bottom of the collimated beam passed just above the eyes.

3. EXPERIMENTAL PLAN.

Twenty-two normal adult male burros were paired as closely as possible according to color, weight, height, disposition, and age. They were identified by a number from 1 to 100; each number followed by a P. Seven pairs

Figure 2. Burro head in place on the mandibular restraint board. The collimators are not properly adjusted.

were assigned to the 600r group and four pairs to the 200r group. One animal of each pair served as a control and followed the same sequence of experimental events except for the substitution of sham-exposure. The pairs are listed in table 1.

Surgical implantation of electrodes was performed on all pairs of burros as described by Usenik et al.[17] Whenever possible, surgery was performed on both members of a pair the same day. Some implantations, however, were performed as much as 2 weeks apart. These delays were beyond experimental control.

To acclimate the burros to their surroundings and to the methods of handling, each matched pair was placed in box stalls at the College of Veterinary Medicine facility of the University of Minnesota, 2 weeks before irradiation. Twenty-four hours before irradiation, each pair was transported from the St. Paul campus to the Gamma Irradiation Facility on the Minneapolis campus, 3 miles distant, where a complete simulation of the actual irradiation took place.

To ensure experimental controls, each procedure of loading, transporting, unloading, securing and immobilizing, placement in the irradiation chamber, irradiating and sham-irradiating, etc., was duplicated exactly during the simulation runs and during the actual experiment. On the day of each actual irradiation, the principal burro received the predetermined dosage and his paired control underwent sham-irradiation. To further ensure that the control animal was not exposed to any significant residual radiation, the sham-irradiation process for the control was delayed nearly 1 hour in each case after the irradiated principal was removed from the chamber and returned to the St. Paul facility. The entire sequence of handling was identical for the members of each pair, for the pairs in each group, and between the groups.

TABLE 1

SCHEDULE OF BURROS IRRADIATED TO THE REGION OF THE BRAIN

BURRO	DOSE	DATE OF IRRADIATION	TIME	DEATH	CONTROL BURRO	DOSE	DATE OF SHAM-IRRADIATION	TIME	DEATH
50P	600r	7 Jul 61	0930	+ 26 hr	17P	600r	7 Jul 61	1100	*
29P	600r	20 May 61	1000	*	55P	600r	20 May 61	1100	*
62P	600r	15 Apr 61	0900	+ 19 hr	49P	600r	15 Apr 61	1000	**
57P	600r	29 Apr 61	1000	+ 28 hr	51P	600r	29 Apr 61	1100	*
46P	600r	17 Dec 61	0830	+ 125 hr	45P	600r	17 Dec 61	0930	**
41P	600r	21 Jan 61	1100	+ 22 hr	42P	600r	21 Jan 61	1200	**
18P	600r	25 Jun 60	1130	+ 33 hr	10P	600r	25 Jun 60	1230	**
80P	200r	13 Sep 61	1100	*	81P	200r	13 Sep 61	1200	*
70P	200r	6 Sep 61	1100	*	71P	200r	6 Sep 61	1200	*
77P	200r	30 Aug 61	1100	*	73P	200r	30 Aug 61	1200	*
64P	200r	23 Aug 61	1100	*	66P	200r	23 Aug 61	1200	*

*** Sacrificed after + 6 weeks.**

**** Used subsequently in another experiment.**

4. EXPERIMENTAL RESULTS.

a. Clinical Observations.

The radiation cutoff was very sharp on the vertical projection of the Z-axis since the tissues being irradiated were exposed essentially to a linear point source of cobalt-60. Effectiveness of this cutoff was demonstrated by the fact that blindness was not detected in the irradiated burros. Further evidence of the quality of radiation and dosimetry procedures utilized is found in the fact that epilation was not observed in any of the irradiated animals.

b. 600r Group.

Clinical observations in the 600r group were made constantly during a 48 hour post-irradiation period and three times daily thereafter. If an animal was still exhibiting symptoms after the 48 hour period, hourly observations were made until recovery or death. Any signs and symptoms indicative of neuropathic disturbances were noted. These will be discussed in detail. A plus sign denotes the time following the delivered dose of irradiation.

Animals receiving 600r cobalt-60 irradiation to the head exhibited mild ataxia, lasting no more than 5 minutes, when taken from the restraint box and led to the tying post. A few slight muscle tremors of the triceps occurred during this time.

Depression and anorexia were noted shortly after irradiation. Later in the post-irradiation period, when the animals desired to drink, they were apparently incapable of swallowing water. They would stand bobbing their muzzles in and out of the water pail. When there was a desire to eat, they failed to masticate and swallow hay, suggesting a pharyngeal paralysis. The control burro ate and drank normally during this period.

Burros 62P, 57P, and 29P showed paralysis of the lower lip as a prominent sign at +3½ hours. Later, burro 50P at +4½ hours and burro 41P at +7½ hours, exhibited lip paralysis. Lip paralysis persisted in six burros until exitus. Burro 29P exhibited paralysis of the lips until the +48½ hour, then continued gradually to make a clinical recovery.

Although the lower lip was paralyzed, the animals went through chewing movements without the stimulation of food. Burros 50P, 62P, and 29P began the chewing movements at +3½ hours. EEG recordings under minimal-stimuli environmental conditions precluded earlier observations. Generalized muscle tremors were noted as early as +3½ hours (50P and 41P) and as late as +44½ hours (29P). Burros 18P and 57P exhibited similar symptoms and +5½ hours and +6½ hours respectively. Localized muscle tremors of the triceps, flank, gluteal group, and neck were observed from +3½ hours to +44½ hours in burros 62P and 46P respectively. These were differentiated from skin twitches which appeared in 29P at +8½ hours and disappeared at +28½ hours.

Relaxation of the penis was a consistent postirradiation sign. The burro normally drops the penis from the sheath and on stimulation quickly retracts it into the sheath. The irradiated burros, although nòt incapable of doing so, would fail to retract the organ into the sheath upon stimulation. This sign was exhibited by 62P at +4½ hours. At +5½ hours, 50P and 29P had similar responses.

Tail switching, which was a common finding in the higher-dose groups, was seen in burros 50P at +3½ hours, 57P at +9½ hours, and 29P at +17½ hours.

For the most part, the burros remained docile except number 62P, who became vicious at +6½ hours and remained so until death.

Depression was difficult to assess. Many times the animals would appear depressed but on closer examination were found to be physically incapable of holding up their heads for any period of time. Drooping of the ears was observed in burros 50P and 62P.

Head bobbing was common. The animal assumed a normal or slightly braced stance. The head dropped as in dozing; however, the burro did not appear to be sleeping. Burro 50P exhibited this at +3½ hours; burros 62P, 29P, 41P, and 57P showed head bobbing at about +13½ hours.

One of the early signs of impending ataxia was the constant shifting of weight. Burro 50P began shifting weight at +3½ hours, had a sawhorse attitude at +9½ hours and lay down at +19½ hours. Burros 18P, 29P, 62P, 41P, and 57P were observed shifting weight constantly. Knuckling over of the fetlocks of the hindlegs was commonly observed.

Severe ataxia was observed as early as 3½ hours post exposure (62P, 41P) following an apparent recovery from the initial mild ataxia immediately after irradiation. Hypermetria, stumbling, and hyperflexion of the hindlegs were exhibited by all irradiated burros.

Symptoms progressed until the animals could no longer stand. Once down, the burros would usually lie in a sternal position with their noses on the floor. Attempts to get them to stand once they were down were usually unsuccessful. Burro 62P assumed the sternal position as early as +17½ hours.

Shortly after assuming the typical postirradiation sternal position, the burros would lie in lateral recumbency. Sometimes they could be forced to sternal position, but would lie down after a very short interval. Burro 62P lay down at +17½ hours, 41P and 50P at +19½ hours, 18P at +24½ hours, and 57P at +32½ hours. Burro 46P arrived at lateral recumbency by +44½ hours and died at +5 days.

A thorough neurological examination during the period of recumbency was difficult because the animals resisted or were incapable of standing. The burros in lateral recumbency had diminished visual perception after light flashing, as measured by electroencephalograms. Blindness is not implied as it probably was not present. There was a loss of corneal and pinna reflexes. Near terminus in the 600r irradiated burros, signs and symptoms were characteristic of animals about to die a neuropathic death. Tonic-clonic convulsions, running movements, flaccid or tonic paralysis, or complete absence of spinal reflexes were observed 4 to 6 hours before respiratory death. The time of postirradiation death is listed in Table 1.

c. 200r Group.

Burro 64P exhibited no signs and symptoms indicative of irradiation damage.

Burro 80P exhibited chewing movements from +8½ hours to +19½ hours.

Burro 70P had a persistent hacking cough from +32½ hours to +34½ hours, and hiccups from +19½ hours to +22½ hours.

Burro 77P lay on his sternum with his nose off the floor at +18½ hours, +30½ hours, and +36½ hours.

5. DISCUSSION.

Mirand and Hoffman,[8] using a DBA strain of mice, found that 500r of X radiation was an MLD for head only or whole-body irradiation. A total dose of 1260r was needed for an MLD when the head was shielded. They concluded that the pituitary-adrenal axis accounted for the similarity in results and that the radiation alteration of this axis appeared to be reversible.

The early effects of head X irradiation in rabbits were studied by Gerstner and Kent.[3] The air dose was 300r/min at the base of the cerebral hemispheres and the center of the cerebellum. The actual tissue dose was 90 percent of the measured air dose. The animals were exposed to doses ranging from 4.2 to 9 kiloroentgens. The functional and structural alterations of the brain of 150 rabbits were studied. They found that radiation-induced changes formed two complexes. The first complex developed at 6 hours in animals receiving an X-ray dose of 4.2 to 6.0 kiloroentgens. This complex was independent of dose. The following were listed as being present in the first complex: Progressive apathy, transitory increase in blood specific gravity, transitory increase in brain gravity followed by a gradual decrease, and widely spread focal inflammatory reactions in the brain. The complex consisted of epileptiform seizures with subsequent ataxia or disturbance of posture. Histopathological examination revealed evidence of pyknosis of granule cells of the cerebellum.

The second complex was found to be dose dependent and appeared at an excess of about 6 kiloroentgens. The symptoms increased in severity with increases in dose. The complex consisted of epileptiform seizures with subsequent disturbance of posture and ataxia, accompanied by pyknosis of granule cells of the cerebellum.

Hansen et al.[4] reported that 250r (MTD) whole-body exposure of 1,000 KVP Xrays produced an LD-50/30 in beagles. The LD-50/30 for upper body exposure to 1,000 KVP X rays was found to be 1,775r (MTD). They concluded that the gram-roentgen dose necessary to produce an LT-50/30 was raised fourfold by shielding the lower portions of the canine body.

The vital centers in the medulla oblongata of dogs irradiated to the region of the head with 23,500r X radiation were directly damaged by the radiation.[9]

Disturbances of equilibrium and extensor rigidity were the chief neurological signs. The blood volume, arterial pressure, heart rate, and respiratory rate remained essentially unchanged until 1 hour before exitus. Death was due to respiratory paralysis from 14 to 28 hours post exposure.

The central nervous system irradiation syndrome in man is produced by an extremely high dose of irradiation delivered to the brain only, or to the whole body. Such a dose has a magnitude of several thousand roentgens. Once the syndrome appears in man, three processes of development are noted:[1] A prodromal phase of nausea and vomiting; then listlessness and drowsiness ranging from apathy to prostration; and finally a more generalized component characterized by tremors, convulsions, ataxia, and death. Cronkite[1] mentions that this was a laboratory curiosity until an accident at the Los Alamos Scientific Laboratory occurred. The victim received a dose of radiation high enough to cause disorientation from the moment of exposure and death within 36 hours.

Ross et al.[10] irradiated only the head of the monkey. They found that 3,000r of X radiation produced death in 3 weeks and 6,000r produced death in 2 to 3 days. No typical generalized symptoms of radiation sickness resulted except early blood changes in the 6,000r group. These changes were lympho- and eosino-penia and initial neutrophil rise followed by a fall. Grand mal type seizures were noted in both groups. Spasticity and paralysis were encountered in the 3,000r cases. General depression of activity progressed rapidly to preterminal coma in the 6,000r group. The same behavioral alteration appeared in the 3,000r group a few days before death. Pronounced cerebral edema was found on necropsy of the animals exposed to 6,000r. The investigators concluded that ionizing radiation can severely injure the brain if the dose is higher than that necessary to affect other organs.

Vogel et al.[18] used the monkey for head irradiation studies. Three groups of monkeys were irradiated with 10,000r at 1,000r/min from a cobalt-60 source. One group was irradiated to the head with the body shielded; another, to the body with the head shielded; and the third, to the whole body. The head and whole-body irradiation consistently induced meningitis, choroid plexitis, vasculitis, and pyknosis of the granule cells of the cerebellum. These brain lesions were seen only in the monkeys irradiated to the head and whole body. The head-irradiated animals had no cellular alterations in the body other than those in the brain. Vogel et al. concluded, "This observation suggests that damage of the central nervous system plays no role in the causation of the cytological alterations that occur in the gastrointestinal and hematopoietic organs after total head-body gamma irradiation."[18]

Langham et al.[7] reported on the hyperacute radiation syndrome as being due primarily to direct radiation damage of the central nervous system of mice and rats. However, these were total body irradiation trials. Four distinct clinical phases were observed after irradiation: (1) acute ataxic phase immediately after irradiation, lasting 5-10 minutes after exposure; (2) a lethargic or inactive phase; (3) an excited, hyperactive, convulsive phase; and (4) a terminal phase.

Burros in the 600r group were extremely depressed shortly after returning from the radiation facility, i.e., in or for about 30 minutes after irradiation. Depression in the 200r group was of a transient nature. This depression appeared to be the second phase described by Langham.[7] Similar findings have been observed in burros receiving total-body irradiation. Trum et al.[13] reported apathy and malaise during the second day post-whole-body exposure in burros exposed to gamma radiation from tantalum-182 or from cobalt-60. Burros irradiated by neutron-gamma-radiation to the whole body appeared to be stupefied.[12] Kuhn and Brown reported depression within 2-6 hours following irradiation of the head of the burro.[6]

Signs and symptoms typical of the third phase were noted as early as 3½ hours post exposure in the 600r group. However the 200r group passed through this phase quickly, if at all, because hyperactivity, excitement, or convulsions were not observed. Kuhn and Brown[6] observed this phase within the first 12 hours postirradiation. These symptoms were seen by Trum in total-body irradiated burros during the first critical period of 2 to 5 days.[14]

Burros that died in the 600r group passed through these three phases and into the terminal one characterized by tonic-clonic convulsions, running movements, spastic or flaccid paralysis and coma. The burro that survived the dose of 600r did not enter into phase 4. Similar terminal symptoms were observed by Kuhn and Brown[6] no later than 80 hours postirradiation. Trum[14] observed burros that recovered spontaneously from a comatose collapse.

Langham et al.[7] reported that the exact physiological mechanism for the production of this syndrome is unknown. Kuhn and Brown,[6] however, state that, "The remarkable CNS symptoms are obviously keyed to early vascular changes which in turn are probably a result of nervous tissue damage or stimulation or both."

6. SUMMARY AND CONCLUSIONS.

Two groups of burros, containing seven and four animals respectively, were exposed to direct gamma radiation of the brain from a cobalt-60 source to determine levels of neurological damage in animals irradiated at 600r and 200r. Each irradiated animal in both groups was paired with a similar burro as a control which underwent sham-irradiation only. All other mechanics of the experiment except the sham-irradiations were identical for all animals. In all cases the brain was the target.

Six of the seven burros which received 600r of irradiation died within 125 hours. Observed syndrome of these fatalities included four basic progressive stages: (1) acute ataxia immediately after irradiation, (2) lethargy and depression, (3) hyperactive convulsiveness, and (4) terminal. Several specific symptoms of neurological damage were observed within each of the general stages. The four burros which received 200r exhibited only a few transient signs of abnormal behavior, and all four survived.

It was concluded from the experiment that irradiated burros exhibited abnormal neurological signs at relatively low dose rates of cobalt-60 irradiation to the brain as compared to other irradiated mammalian species studied in previous experiments.

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Seven burros received 600r and four burros 200r of gamma rays from a bilateral cobalt-60 source to the region of the brain. Each burro had a paired control that was sham-irradiated. The principal target was the brain. Six out of seven burros receiving 600r died in the terminal phase of the hyperacute radiation syndrome. The animals that received 200r showed a few transient abnormal neurological signs. Irradiated burros exhibited abnormal neurological signs at relatively low doses of radiation to the region of the brain when compared to other irradiated mammalian species.

1. Animals--effects of radiation
2. Bromedical studies
3. Brain--effects of radiation
4. Cobalt isotopes Co^{60}
5. Dosage rates
6. Nervous system--effects of radiation
7. Radiation effects

I. AFSC Project 7801
II. Ronald E. Engel, Capt USAF; Vaughn C. Moore, Francis A. Spurrell
III. In ASTIA collection

Air Force Special Weapons Center, Kirtland AF Base, New Mexico
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