Experimental delayed radiation necrosis of the brain

Part 1: Effect of early dexamethasone treatment

The authors have designed an experiment to detect a hitherto unrecognized interaction between high doses of the glucocorticoid, dexamethasone, and brain irradiation. Eighteen juvenile male rhesus monkeys received 1800 rads to the whole brain in 8.5 minutes. For 1 1/2 days before and 10 1/2 days after the irradiation, nine animals received approximately 2.9 mg/kg/day of dexamethasone intramuscularly in addition to irradiation, while the remaining nine animals served as the control group and received saline. All animals eventually developed a progressive neurological syndrome, and died of delayed radiation necrosis of the brain. The two groups were compared with regard to latency to onset of clinical signs, survival time, and number, distribution, and location of lesions of radionecrosis. Large doses of dexamethasone did not alter the susceptibility of the primate brain to delayed radiation necrosis. Detailed morphological study of the radionecrotic lesions supports the hypothesis that most, if not all, of the lesions develop as the consequence of injury to blood vessels.

Key Words • experimental radiation injury • dexamethasone • blood-brain barrier • brain edema • brain neoplasm

Delayed radiation necrosis of the brain is a dreaded, often disabling, and occasionally fatal complication of therapeutic irradiation of the cranium or its contents.2-5,9,17,22,24 The morphologically distinctive lesions of radionecrosis are thought to develop chiefly as the result of injury to blood vessels, and they characteristically become clinically manifest after a silent interval of months to years, the latency depending in large measure on the dose of radiation received.40 Delayed radiation necrosis of the brain continues to be an important clinical problem because radiotherapy is the most effective treatment available for patients with non-resectable brain tumors,37 and in such cases it ordinarily is prescribed up to and perhaps beyond the limit of tolerance of normal tissue.14 The recent spate of papers on the subject5,17,22,31,34 suggests that delayed radiation necrosis may be more prevalent than formerly believed. It seems useful, then, to learn more about those factors that may affect the susceptibility of brain to necrotizing doses of radiation. One potentially fruitful area for study relates to the interaction of drugs and ionizing radiation.

Glucocorticoids are widely used concurrently with radiotherapy for their putative salutary effect on intracranial hypertension and brain edema.8 They have been used extensively since 1961,11 when it was discovered that patients suffering from a variety of lesions of the brain, including neoplasms and trauma, recover more quickly if given pharmacological doses of a glucocorticoid such as dexamethasone.8,10,21,30 Although these clinical observations have been corroborated in the laboratory,6,19,20,22,26,27,32 the mechanism of action of glucocorticoid on the afflicted brain remains for the most part an enigma. Some of its beneficial effect is thought to derive from stabilization of membranes of capillary endothelium and parenchymal cells which, in turn, reduces brain edema and loss of intracellular potassium.19,22,26 It has also been suggested that glucocorticoid is effective because it protects the central nervous system (CNS) from free radical attack by intercalation into cellular and sub-
cellular membranes. This hypothesis is particularly relevant to the pathogenesis of delayed radiation necrosis of the brain since the biological effect of ionizing radiation is in large part related to the intracellular formation of free radicals. On the other hand, glucocorticoid may conceivably render the brain more vulnerable to radiation because it interferes with DNA synthesis and cell replication in normal and neoplastic CNS tissue. Confronted with the knowledge that both glucocorticoid and ionizing radiation affect DNA synthesis, as well as the permeability of cell membranes, we speculated as to whether they act synergistically or antagonistically on the brain when used together. Because this question could not be answered a priori, this is important from both a theoretical and a practical point of view, we designed the following experiment to explore the possibility of the existence of a hitherto unrecognized interaction between high doses of the glucocorticoid, dexamethasone, and brain irradiation.

Materials and Methods

Nineteen juvenile male rhesus monkeys (Macaca mulatta), weighing 2.4 to 3.1 kg (mean 2.8 kg ± 0.19 SD), were used in this experiment. During the month before irradiation, they became acclimatized to their permanent cages. Detailed notes were made daily of each monkey's individual motor and behavioral characteristics, including aggressiveness in response to examiner, vocalization patterns, and reaction to being hand-fed bits of fruit. They were also periodically weighed, and blood was drawn for cytological and chemical analyses.

Dexamethasone Administration

One animal was chosen at random to serve as a control, and it received neither radiation therapy nor dexamethasone. The remaining 18 animals were then randomly divided into two groups of nine. One group received dexamethasone and the other group received normal saline as a placebo. Dexamethasone solution and saline were indistinguishable from each other and were identified only by code number. This concealed from observers the identity of the agent given to each monkey until after results were recorded, the experiment was ended, and the code for each animal was broken. Each monkey of the dexamethasone-treated group received 4 mg of dexamethasone intramuscularly twice daily, morning and night, for 12 days. Thereafter, over the ensuing 12 days, the daily dose of dexamethasone was gradually reduced to zero and then permanently discontinued. Control animals received at the same time equal volumes of saline.

Dexamethasone used in this study was subsequently shown to be biologically active by administering 4-mg aliquots of it intramuscularly twice daily to five additional healthy rhesus monkeys and recording overnight, after two doses and been given, a tenfold reduction in circulating serum cortisol.

Irradiation Procedure

Irradiation of the 18 animals was carried out on the second day of dexamethasone or saline administration, between 30 minutes and 2 hours after the third dose had been given.

A standard priming chair was modified to hold a collimator and lead body shield. In order to irradiate the entire brain of an alert animal, a collimator was used that also served to restrain the head. The collimator was a lead block, 7.6 × 10 × 20 cm in size, containing an aperture corresponding to the sagittal silhouette of the cranial cavity of a juvenile rhesus monkey. The animal's head was further restrained during the irradiation by a dental acrylic form molded in the shape of the monkey's left hemicranium.

The irradiations were performed with a linear accelerator at approximately 20 MeV with a beam current and pulse width adjusted so that the total dose of 1800 rads ± 2.0 SD was delivered to the whole brain in 8.5 min ± 0.30 SD. The electron beam was collimated to 4-mm diameter by a 10-cm cube of graphite and had 2.54 cm of lead on the output face to attenuate X rays produced in the graphite. The transmitted electron beam impinged on a 12.65-gm/sq cm tantalum target. The animals were irradiated unilaterally from the left side at a target-to-midsagittal distance of 1.5 meters. Dosimetry was performed before irradiation to establish dose rate and total dose. Each animal's exposure was monitored with an ionization chamber and current integrator in order to terminate exposure when the required dose had been delivered. Considering all sources of error, the dose each animal received varied less than 5% from the dose specified.

Clinical Follow-Up Review

After irradiation, the animals were returned to their cages, and observed and examined daily until they died or terminal inanition required that they be sacrificed. At monthly intervals they were sedated with ketamine, weighed, and blood was drawn for analysis. At 75, 106, and 136 days after irradiation, each animal's exposure was monitored with an ionization chamber and current integrator in order to terminate exposure when the required dose had been delivered. Considering all sources of error, the dose each animal received varied less than 5% from the dose specified.

Necropsy Protocol

Twelve of the 19 animals, including the non-irradiated, nontreated control, were anesthetized with ketamine, intubated, and placed on a respirator, and perfused with an intracardiac infusion of Karnovsky's...
solution in order to prepare the brain for both light and electron microscopic study. Five of these 12 animals, including the control, also received horseradish peroxidase intravenously 1 minute before perfusion for electron microscopic study of the blood-brain barrier. Five other animals were anesthetized with ketamine and sacrificed with a rapid intravenous injection of a saturated solution of magnesium sulfate. Their brains were removed immediately and fixed by immersion in buffered formalin. A few hours before sacrifice, most animals were given 150 mg of Evans' blue dye intravenously as a marker to aid in the macroscopic identification of areas of breakdown of the blood-brain barrier. The brains of two animals that died unexpectedly were fixed by immersion in buffered formalin.

Each fixed brain was weighed, photographed, serially sectioned in a coronal plane at approximately 5-mm intervals, and examined for evidence of gross abnormalities. Representative full-sized blocks from the entire intracranial neuraxis were embedded in paraffin and sectioned at 6 to 20 μ, depending on the type of stain required. Full-sized sections were mounted on oversized slides and were stained routinely with hematoxylin and eosin (H & E), luxol-fast blue for myelin, and the Woelke variant of the iron-hematoxylin method for myelin. The routine sections were screened, and selected blocks were subsequently sectioned and stained with a variety of methods including periodic acid-Schiff (PAS) and Alcian blue for mucopolysaccharides, Bodian and Bielschowsky stains for axons, Congo red stain for amyloid, Movat stain for various vascular components, Masson stain for connective tissue, von Kossa stain for calcium, and the mucicarmine stain for mucinous degeneration.

Specimens from animals given horseradish peroxidase before sacrifice were also prepared for electron microscopy. The results of these preparations will be reported elsewhere.

Data Analysis

Clinical criteria (presence of facial erythema, epilation of scalp, onset of behavioral changes and motor impairment, duration of neurological syndrome, weight profile, and survival time) and anatomical criteria (brain weight, evidence of atrophy, and the type, number, and distribution of radionecrotic lesions and hemorrhages) of radiation effect on brain were tabulated for each group, and the significance of the difference was tested with the Fisher exact test or the unpaired "t" test.

Results

Randomization resulted in two groups of nine monkeys that were identical in average weight.

Clinical Observations

During the first 24 hours after irradiation, a few animals of each group vomited once or twice, and three saline-treated animals were less active than usual. Thereafter, all animals of both groups appeared normal in all respects until the onset of the neurological syndrome to be described later. During the first 10 days after irradiation, eight of nine monkeys receiving dexamethasone and one of nine in the saline-treated control group developed erythema and desquamation of the face, which cleared in all animals by the 14th day after irradiation. This difference is statistically significant (p = 0.01, Fisher exact test). Epilation of the scalp usually began 2 to 4 weeks after irradiation and was usually complete by the end of the sixth week. However, three animals of the saline-treated group did not begin to epilate until approximately 7 weeks after irradiation. On the average, epilation of the scalp began by 24 days in the dexamethasone group and by 38 days in the saline group. This difference is statistically significant (p = 0.05, unpaired "t" test, Table 1 and Fig. 1).

During the first month following irradiation, all animals retained their appetite and accepted fruit avidly.
each time it was offered. Nevertheless all animals but one in the dexamethasone group lost weight in the first 10 days after irradiation (Fig. 2). At autopsy, mean weight loss of the dexamethasone group was 494 gm ± 267 SD, and of the saline group it was 433 gm ± 205 SD. This difference is not statistically significant (p = 0.58, unpaired “t” test).

Sooner or later, all animals developed a neurological syndrome characterized by anorexia, marked behavioral changes, and motor impairment.

Most striking, when it developed, was an inexorably progressive loss of coordination and strength of all four extremities, usually coupled with disequilibrium and a hunched-over posture. During the last week of life, the animals were listless, apathetic, and unresponsive to stimuli that would normally arouse them. They would often sit immobile on the bottom of the cage, unable even to grasp a piece of fruit. In their attempt to avoid capture, they would fall over, being unable to climb the side of the cage because of weakness and clumsiness of all limbs. The optic fundi of all surviving animals were examined under ketamine anesthesia at 75, 106, and 136 days after irradiation. Papilledema was not found at any time. Individual animals of both groups developed unique neurological signs. Some manifested myoclonic jerks of all muscle groups in response to sudden tactile or auditory stimuli. Others developed torticollis and retrocollis, truncal dystonia, and circus movements. The rate of progression of the neurological syndrome varied from animal to animal and ranged between 5 to 68 days from time of first clinical sign of radiation necrosis to death.

There was no statistically significant difference between the two groups regarding latency to onset of the neurological syndrome, its rate of progression, or length of survival following irradiation (Table I, Fig. 1).

### TABLE 1

**Sensitivity of two groups of nine rhesus monkeys to 1800 rads delivered in 8.5 minutes to whole brain**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Saline-Treated</th>
<th>Dexamethasone-Treated</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>onset of epilation of scalp*</td>
<td>38 ± 13</td>
<td>24 ± 8</td>
<td>0.05</td>
</tr>
<tr>
<td>onset of behavioral change*</td>
<td>106 ± 32</td>
<td>108 ± 32</td>
<td>0.91</td>
</tr>
<tr>
<td>onset of motor impairment*</td>
<td>109 ± 23</td>
<td>109 ± 24</td>
<td>1.00</td>
</tr>
<tr>
<td>survival time*</td>
<td>137 ± 31</td>
<td>139 ± 37</td>
<td>0.87</td>
</tr>
<tr>
<td>duration of neurological syndrome†</td>
<td>27 ± 11</td>
<td>30 ± 22</td>
<td>0.71</td>
</tr>
</tbody>
</table>

*Days after irradiation, mean ± SD.
†Days from onset of clinical signs of radiation necrosis to death, mean ± SD.
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Anatomic Observations

Gross Morphology. The external surface of the brain of all 18 irradiated animals was indistinguishable from that of a normal nonirradiated animal. Mean brain weight of the saline-treated control group was 84 gm ± 10 SD, and for the dexamethasone-treated group it was 83 gm ± 5 SD. (The brain weight of a 3-kg juvenile male rhesus monkey averages 90 gm.) Coronal sections revealed mild to moderate ventricular dilatation in most animals of both groups. The largest ventricles were found in animals that survived longest or those that had large brain-stem hemorrhages. Examination with the unaided eye of full-section mounts through all levels of the brain, and prepared with H & E, luxol-fast blue, and Woelke myelin stains, assisted the interpretation of the changes observed grossly (Figs. 3, 4, and 5). A variety of lesions were distributed throughout the neuraxis and could be classified into three categories:

1. Widespread patchy mottling and rarefaction of the white matter of the centrum semiovale, cerebellum, and brain stem. This lesion was diffuse and not sharply demarcated from adjacent normal areas. The white matter of the internal capsule, striatum, and thalamus was also involved.

2. Soft, partially cystic, well demarcated areas of necrosis, particularly in the centrum semiovale and pons, that were situated most commonly within diffuse areas of rarefied white matter, and were stained intravitally with Evan's blue (Fig. 6).

3. Focal hemorrhages, ranging from minute, barely visible petechiae to massive hematomas at all levels of the neuraxis, chiefly involving the white matter (Figs. 5 and 6). The brains of all nine animals of the saline group and eight of the nine of the dexamethasone group had at least one ball hemorrhage visible grossly. Three animals in the dexamethasone group had large hemorrhages, 3 mm in size, in the basis pons that undoubtedly were the principal cause of their rapidly deteriorating clinical condition (Fig. 5).

There were no statistically significant differences in the gross morphological findings described above between the dexamethasone-treated group and the saline-treated controls.

Histology. The microscopic findings in the brains of the dexamethasone-treated and saline-treated animals will be described together because there were no statistically significant differences between the two groups as regards the type, number, and distribution of the lesions observed.

The three categories of tissue damage seen in the gross sections (that is, rarefied white matter, necrosis, and hemorrhage) were reflected at the cellular level. They are as follows:

1. The patchy rarefaction of white matter il-

![Fig. 3. Section of cerebrum showing multiple foci of necrosis. Woelke myelin stain, × 3. (AFIP neg. 79-3313)](image)

![Fig. 4. Section of pons showing multiple foci of necrosis in corticospinal tracts, brachium conjunctivum, and brachium pontis. Woelke myelin stain, × 4. (AFIP neg. 79-3331)](image)

![Fig. 5. Section of pons showing large perivascular hemorrhages and random foci of necrosis. H & E, × 4. (AFIP neg. 79-3302)](image)
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FIG. 6. Gross section of cerebrum showing a large hemorrhage on the right and focal necrosis with a small hemorrhage on the left (arrows). (AFIP neg. 78-7046)

Extensive demyelination and edema were accompanied by reactive gliosis characterized by randomly distributed gemistocytes. Comparison of control sections with abnormal sections prepared with Bodian and Bielschowsky stains for axons showed concomitant diffuse damage of axons throughout the white matter. This change was subtle and occurred in the form of moderate swelling and beading of many axons within the white matter of the entire neuraxis; randomly disseminated, large axonal bodies were also present within the white matter at all levels. These axonal changes may represent a secondary degenerative change due to edema and demyelination. Diffuse demyelination of cranial nerves was also seen, and was prominent in sections of the oculomotor nerve.

2. The most apparent lesions were small, well demarcated foci of necrosis that corresponded to various stages of white matter injury and resorption. The white matter within these areas showed a continuum of incomplete necrosis and partial resorption to foci of complete necrosis and cavitation (Fig. 7). Large, coalescent vacuoles, consistent in appearance with massive edema, were present within the necrotic

FIG. 7. Focal necrosis in descending tracts of the brain stem showing massive edema and partially calcified axonal bodies. H & E. Left: Low-power view. × 35. (AFIP neg. 79-3327) Right: High-power view. × 165. (AFIP neg. 79-3306)
areas, while milder degrees of vacuolization were seen at the margin where the lesion interfaced with normal parenchyma. Reactive gliosis and macrophage reactions of mild degree were present, with occasional foci of round cells. The degree of cellular response to injury within and around the necrotic areas was of mild intensity when compared to cellular reactions commonly seen in association with most other types of CNS injury, and was not commensurate with the degree of tissue damage. The remaining axons within the necrotic areas were grotesquely swollen and formed distinct axonal bodies, which were well illustrated with H & E, Bodian, and Bielschowsky stains (Fig. 7 right). Mucopolysaccharides were present within the necrotic areas. A variable amount of calcific material, ranging from minimal to massive, was deposited throughout the necrotic areas in the form of dystrophic calcification. It is our impression that the earliest stage of calcification began with deposits on the axonal bodies. These calcific deposits were composed of an admixture of polysaccharide and iron, as is true of various types of calcifications noted in other forms of brain disease. Areas of necrosis with dystrophic calcification and axonal bodies were present throughout the brain, and were particularly prominent in compact white matter such as in the corticospinal tracts of the brain stem.

3. The most significant underlying change seen at the microscopic level reflected abnormal vascular permeability due to radiation damage to small blood vessels within the white matter. Hemorrhages were conspicuous throughout the neuraxis, particularly in the white matter, and were in the form of either small, perivascular, petechial ball and ring hemorrhages, or massive perivascular hemorrhages (hematomas) with extension into the adjacent parenchyma. The perivascular relationship of both types of hemorrhage was seen repeatedly, and the degree of hemorrhage corresponded to the intensity of associated vascular damage. The petechial ball and ring hemorrhages often surrounded small vessels with morphologically intact walls at the light microscopic level; these hemorrhages probably reflect the process of diapedesis through abnormally permeable vessels. The areas of massive hemorrhage were clearly related to centrally located blood vessels with grotesque structural abnormalities. These vessels were arranged in groups, were greatly dilated and ballooned, and had thin walls consistent with dilated capillaries or small veins. At times, rupture of the dilated, thin-walled vessels was apparent, and the perivascular hematomas were frequently related to areas of rupture within these vessels. In other areas, occasional thickening and hyalinization of small vessel walls was seen, although such changes were not so striking as those seen in association with the delayed effects of radiation in the human brain. Endothelial swelling and proliferation were consistent and prominent features associated with white matter damage. The endothelial changes varied in degree, but were conspicuous throughout the white matter at all levels of the neuraxis, and were most prominent in the smaller vessels. Scattered vessels contained thrombotic material, but the minimal degree of thrombosis was not proportional to the severity of necrosis seen throughout the neuraxis. The walls of the vessels stained intensely with H & E and PAS, and delicate perivascular halos of PAS-positive material were seen in the parenchyma immediately adjacent to the vessels, indicating abnormal vascular permeability and transudation (Fig. 8). These findings were confirmed at the ultrastructural level.

Discussion

Large biologically active doses of dexamethasone (approximately 2.9 mg/kg/day) did not alter the susceptibility of the primate brain to delayed radiation necrosis. These results imply that the common clinical practice of using glucocorticoids together with radiation therapy to treat brain tumors neither protects normal brain from the deleterious effects of ionizing radiation nor increases the risk of developing delayed radiation necrosis.

It is worthwhile to compare some of our results to the careful study reported by Kemper, et al., especially in view of the fact that we irradiated a group of similar animals at similar dose levels. Comparison is most readily made to their group of four rhesus monkeys given 2000 rads to the whole brain at 200 rads per minute. Mean survival of these monkeys was 149 days. Mean survival of our 18 rhesus of similar size given 1800 rads at approximately 200 rads per minute was 138 days. The reason for the shorter mean

![Fig. 8. Abnormally permeable blood vessel showing perivascular transudate. H & E, ×120. (AFIP neg. 79-3297)](image-url)
survival of our animals given 200 rads less is not apparent. The discrepancy may be explained in part by natural variation in sensitivity of individuals of a species to irradiation, by the fact that all our animals were male, by the 5% error in delivered dose, and by other minor variables in method of delivery of irradiation. Another, and perhaps more important, factor to account for the apparent greater sensitivity of our animals to irradiation may have been a difference in criteria used to determine when to sacrifice an animal, which of course determines survival time as an end point. As noted, we made no effort to prolong survival by nursing the animal. The average latent period between irradiation and the onset of the neurological syndrome was more in harmony with relative doses, being 11 days longer in our animals (98 days versus 109 days).

The most prevalent lesion in our material, as well as that of Kemper, et al., was the sharply demarcated microscopic focus of necrotic tissue that had a predilection for white matter and spared the cerebral and cerebellar cortex (Fig. 7). However, there are some significant differences between the two studies that should be mentioned. First, hemorrhage was not a part of the pathological picture in any of their animals, whereas we observed both macroscopic and microscopic hemorrhages in the brains of all nine saline-treated control animals and eight of nine animals treated with dexamethasone. Second, we noted plasmatic transudates around some vessels in five animals, an observation not made by Kemper, et al. Third, widespread demyelination and gliosis of the centrum semiovale was another feature observed in some of our animals but not seen by Kemper, et al. Perhaps the natural biological variability in response to radiation, together with the small difference in radiation dose, account for the differing histological appearances between the two studies.

The considerable variation in latency and progression of the neurological syndrome among individual animals is worthy of note. Some of this variation may be attributable to differences in delivered dose since it may have randomly varied by 5% more or less than the specified dose of 1800 rads. Therefore, as much as 180 rads may separate animals receiving the highest and the lowest doses. On the other hand, biological variability in sensitivity to radiation is also important. Those constitutional factors that allow one animal to survive irradiation twice as long as another of the same species, sex, and age are not well understood.

The relevance of this experimental model to the clinical syndrome of delayed radiation necrosis may be questioned, since our animals received irradiation in one dose over an 8.5-minute period whereas therapeutic irradiation is performed clinically over 4 to 6 weeks in 20 to 30 divided doses. Apart from Kramer’s opposing viewpoint, the literature supports the view that lesions of the brain produced by a single dose of radiation and those produced by multiple fractionated doses are identical entities in terms of fundamental radiobiology as well as pathogenesis and morphology. Indeed, according to Zeman and Samorajski, fractionation is merely a special way to reduce dose rate. Berg and Lindgren found that delayed radiation lesions of the rabbit brain after fractionated exposures were essentially the same as after a single exposure. More recently, Caveness’ group has confirmed this in the primate.

The histological appearance of the lesions in our animals differs in some respects from that which is commonly observed in humans. This can be ascribed to the difference in relative age of human subjects and our adolescent monkeys. As noted by Zeman and Samorajski, plasmatic infiltration of blood vessels and the secondary microthrombosis are usually not seen in children and young animals. In addition, radionecrosis in humans generally evolves over 2 years or more, and the chronicity of the process gives rise to a histological picture that is different from the more acute process seen in our animals.

The pathogenesis of delayed radiation necrosis of the brain remains the subject of continuing controversy and debate. One widely held view is that most, if not all, of the lesions develop as the consequence of injury to blood vessels. According to this hypothesis, ionizing radiation damages stem cells that supply mature endothelial cells to replace those lost through natural attrition. This sets the stage for progressive failure of the microcirculation of the brain that leads to a break in the blood-brain barrier, chronic vasogenic edema and demyelination, petechial hemorrhages, and thrombosis. The parenchyma may also show a broad spectrum of secondary ischemic changes from reactive gliosis to frank infarction. The morphology of the lesions observed in this study supports this hypothesis, the main propositions of which are summarized in Fig. 9.

We must be cautious in extrapolating the results of this experiment in which a single-dose regimen of dexamethasone was challenged by a single dose of radiation. There are obviously limitless different combinations of the two, and conceivably a change in one or both variables may reveal an interaction between the two not detected in this study. Although possible, this seems unlikely. In retrospect, the doses of dexamethasone and radiation seem a suitable compromise. The dose of dexamethasone was relatively massive compared to that commonly used clinically; it was biologically active and yet without demonstrable toxicity. The dose of radiation allowed survival for a reasonable period with a sufficiently variable latency that should have revealed a clinically significant interaction between dexamethasone and irradiation had one existed.

As previously noted, large doses of glucocorticoids have been shown to ameliorate the effects of many forms of brain and spinal cord injury, both clinically and in the laboratory. Treated animals
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PETECHIAL HEMORRHAGE
HEMORRHAGE IN stressful PLASMA INTO BLOOD VESSEL WALL WITH STRUCTURAL WEAKENING

RADIATION → ENDOThELIAL CELL DAMAGE → ABNORMAL VASCULAR PERMEABILITY (Blood Brain Barrier) (Dyschoria)

ENOSLUTION OF PLASMA INTO WHITE MATTER WITH INCOMPLETE DEMYELINATION (secondary demyelination)

Fig. 9. Hypothetical sequence of events that lead to delayed radiation necrosis of the brain.

sustain less damage and recover more quickly than untreated controls. The failure of dexamethasone to have a similar beneficial effect on radiation-induced injury of the brain is consistent with the view that radiation injures the brain by a mechanism that is fundamentally different from the mechanism by which other physical agents act. 29 However, since dexamethasone was given to these animals for only a short time and was permanently discontinued after 3 weeks, the results of this experiment do not eliminate the possibility that dexamethasone may exert a beneficial effect on the brain once radionecrosis has become clinically apparent. This hypothesis, supported by some clinical evidence, 7,17,20 deserves additional experimental study.

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Address reprint requests to: Albert N. Martins, M.D., Neurosurgery Service, Walter Reed Army Medical Center, Washington, D.C. 20012.