Cerebral radioprotection by pentobarbital: dose-response characteristics and association with GABA agonist activity

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Pentobarbital reduces cerebral radiation toxicity; however, the mechanism of this phenomenon remains unknown. As an anesthetic and depressant of cerebral metabolism, pentobarbital induces its effects on the central nervous system by stimulating the binding of gamma-aminobutyric acid (GABA) to its receptor and by inhibiting postsynaptic excitatory amino acid activity. The purpose of this study is to investigate the role of these actions as well as other aspects of the radioprotective activity of pentobarbital.

Fischer 344 rats were separated into multiple groups and underwent two dose-response evaluations. In one set of experiments to examine the relationship of radioprotection to pentobarbital dose, a range of pentobarbital doses (0 to 75 mg/kg) were given intraperitoneally prior to a constant-level radiation dose (70 Gy). In a second series of experiments to determine the dose-response relationship of radiation protection to radiation dose, a range of radiation doses (10 to 90 Gy) were given with a single pentobarbital dose (60 mg/kg intraperitoneally). Further groups of animals were used to evaluate the importance of the timing of pentobarbital administration, the function of the (+) and (-) isomers of pentobarbital, and the role of an alternative GABA agonist (diazepam). In addition, the potential protective effects of alternative methods of anesthesia (ketamine) and induction of cerebral hypometabolism (hypothermia) were examined.

Enhancement of survival time from acute radiation injury due to high-dose single-fraction whole-brain irradiation was maximal with 60 mg/kg of pentobarbital, and occurred over the range of all doses examined between 30 to 90 Gy. Protection was seen only in animals that received the pentobarbital before irradiation. Administration of other compounds that enhance GABA binding (Saffan and diazepam) also significantly enhanced survival time. Ketamine and hypothermia were without protective effect.

Protection from acute radiation-induced mortality by pentobarbital in the rat model is a reproducible phenomenon and is associated with the GABA agonistic activity of the compound. This property of GABA agonists offers the potential for a novel approach to enhancement of the efficacy of radiation therapy in the treatment of brain tumors.

KEY WORDS · brain tissue · radiation therapy · pentobarbital · gamma-aminobutyric acid

RADIATION therapy is one of the cornerstones in the therapy of a wide range of brain tumors. When used in conjunction with surgery, it significantly prolongs the survival of patients with these tumors. Although its use confers benefits, it is truly a double-edged sword. The same ionizing process which injures tumor can injure the normal tissue surrounding the tumor.

Efforts to enhance the efficacy of radiation therapy have attempted to increase tumor radiosensitivity and, to a lesser extent, to decrease normal tissue sensitivity. Neither approach has improved the treatment of central nervous system (CNS) neoplasia. Because pentobarbital selectively decreases the metabolic activity of synaptically active tissue, and in view of reports of the ability of pentobarbital administration to offer protection from ischemic brain injury in animal models, we investigated pentobarbital as a potential radioprotectant. That investigation showed that, in an animal model, pentobarbital offers significant protection from the acute toxicity of high-dose single-fraction whole-brain radiation.

The purpose of the work described here was to better understand the characteristics of the radioprotection...
induced by pentobarbital. To accomplish this, two lines of investigation were undertaken. First, to evaluate the reproducibility of the radioprotective effect of pentobarbital and to assess the dose-response characteristics of this phenomenon, we investigated a range of radiation doses and pentobarbital doses in a rat model.

Second, based on the known pharmacological and physiological properties of pentobarbital, a four-part approach was designed to better elucidate the mechanism by which pentobarbital decreases radiation sensitivity. 1) An evaluation of the importance of the temporal relationship between irradiation and pentobarbital administration for reducing radiosensitivity was undertaken. 2) Pentobarbital as administered clinically is a racemic mixture of (+) and (-) isomers. The (-) isomer enhances gamma-aminobutyric acid (GABA) binding and function whereas the (+) isomer inhibits the postsynaptic conductance induced by excitatory amino acids. Therefore, the potential separation of the radioprotective properties between these two functional moieties was examined. 3) Binding of GABA to the GABA receptor is enhanced by the benzodiazepines, as it is by pentobarbital. We hypothesized that if the mechanism of radioprotection by pentobarbital is related to its GABAergic property, the benzodiazepines may also provide radioprotection. 4) Pentobarbital produces anesthesia and cerebral hypometabolism. To evaluate whether anesthesia or hypometabolism per se would be radioprotective, alternative modes of anesthesia and induction of hypometabolism were studied.

Materials and Methods

Animals

The experiments involved in this work utilized male Fischer 344 rats, each weighing 150 to 175 gm. The animals were maintained in accordance with the National Institutes of Health “Guide for the Care and Use of Laboratory Animals, Revised 1985.”

Radiation Procedure

A linear accelerator was used as a 15-mV source of x-irradiation. As in prior experiments each treatment was performed with a unilateral exposure of the whole brain, with lead shielding of the mouth, pharynx, and body at a source-to-target (midsagittal plane) distance of 86 cm and at a rate of 6 Gy/min. Anesthetized animals were treated on a circular Lucite platform on which they could be placed head first in a centrifugal fashion. Awake and lightly anesthetized animals were restrained in semiconforming Lucite cones, which held the animals in a fixed lateral decubitus position, with a nose hole for ventilation. The animals were observed on a video monitor and those that moved during x-irradiation, thus altering the radiation port, were not included in the calculations of the results. This accounts for the occasional nonuniformity of numbers in some of the groups. In all groups of animals survival was monitored for at least 30 days.

Dose-Response Studies

Varying Doses of Pentobarbital. Six groups of rats (10 in each group) were subjected to 70 Gy of x-irradiation 15 minutes after the intraperitoneal administration of graded doses of pentobarbital in 15-mg/kg increments, ranging from 0 to 75 mg/kg. Survival times were recorded.

Varying Doses of X-Irradiation. Eighteen groups of rats (nine or 10 in each group) were subjected to a single dose of x-irradiation ranging from 10 to 90 Gy in 10-Gy increments. Irradiation was delivered to rats while awake or under the influence of pentobarbital (60 mg/kg) administered intraperitoneally 15 to 30 minutes prior to irradiation. Survival times of each group were recorded.

Mechanism of Pentobarbital Radioprotection

Relationship of Radioprotection to Timing of Pentobarbital Administration. A group of eight rats was subjected to 70 Gy of x-irradiation. Immediately following completion of the x-irradiation they received pentobarbital (60 mg/kg intraperitoneally). Survival time was compared to the outcome after the same dose of pentobarbital was administered 15 to 30 minutes before x-irradiation and to survival time of control animals that were irradiated while awake.

Relationship of Protection to Action of Pentobarbital on CNS. Pharmacological quantities of purified (+) and (-) isomers of pentobarbital were not available to test the action of pentobarbital on the CNS. Therefore, alternative compounds that parallel the function of the (+) and (-) isomers were chosen. Alphaxalone, a steroid anesthetic, was used to mimic the function of the (-) isomer and was administered in a 3:1 mixture with alphadalone, an analogous steroid.* 2-amino-7-

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* This combination is marketed as the anesthetic Saffan by Pitman-Moore, Ltd., Middlesex, England.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Pentobarbital Dose (mg/kg)</th>
<th>Survival (days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16.7 ± 11.2</td>
</tr>
<tr>
<td>15</td>
<td>17.1 ± 7.9†</td>
</tr>
<tr>
<td>30</td>
<td>19.6 ± 9.4‡</td>
</tr>
<tr>
<td>45</td>
<td>19.3 ± 9.9‡</td>
</tr>
<tr>
<td>60</td>
<td>24.2 ± 9.3</td>
</tr>
<tr>
<td>75</td>
<td>19.5 ± 9.7‡</td>
</tr>
</tbody>
</table>

* Mean survival time ± standard deviation for 10 rats/dosage group, evaluated at 30 days after x-irradiation. Significance in comparison to 60 mg/kg was determined by the Wilcoxon signed-rank test: † p < 0.01; ‡ p < 0.05.
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FIG. 1. Relationship of survival time to the amount of pentobarbital given prior to x-irradiation. Survival curves are shown for groups of animals exposed to 70 Gy of single-fraction whole-brain x-irradiation following administration of 0 (awake) or 15, 30, 45, 60, or 75 mg/kg of intraperitoneal pentobarbital (PB). Significant enhancement of mean survival time as of 30 days after x-irradiation occurs in animals receiving a pentobarbital dose of 60 mg/kg as compared to animals exposed to brain irradiation while awake (p < 0.05). Smaller improvements in survival are seen with 15, 30, 45, and 75 mg/kg of pentobarbital as compared to that of awake animals, but these differences are not statistically significant.

Data Analysis

Survival was compared by percentage and mean survival times evaluated 30 days after x-irradiation using the Wilcoxon signed-rank test for nonparametric data. Thirty days was chosen as the time for analysis of the data because 1) no deaths were observed after that interval in our previous studies and 2) in additional studies in this animal model we have determined that deaths from acute and early delayed toxicity consistently occur within this interval.

Results

Dose-Response Studies

Varying Doses of Pentobarbital. Survival of rats exposed to a uniform dose (70 Gy) of x-irradiation 15 to 30 minutes after pentobarbital improved with increasing doses of pentobarbital until 60 mg/kg was reached, at which optimal survival occurred. Animals receiving doses of 0, 15, 30, 45, or 75 mg/kg had significantly lower mean survival times as of 30 days after x-irradiation when compared to the group treated with 60 mg/kg (Fig. 1 and Table 1). Animals that received pentobarbital doses of 30, 45, or 75 mg/kg had increased mean survival times compared to animals irradiated while awake, but this difference was not significant (p = 0.17 in each case).

Animals receiving 15 or 30 mg/kg doses of pentobarbital were only mildly sedated and required restraint in the same fashion as awake animals. Rats that received 45 mg/kg remained still during x-irradiation and did not require restraint, but awoke sooner than those receiving 60 mg/kg. At doses of 75 mg/kg, animals remained anesthetized at least as long as those receiving 60 mg/kg.

Varying Doses of X-Irradiation. Exposure to x-
irradiation while under pentobarbital anesthesia significantly enhanced mean survival times compared to animals irradiated while awake with all doses from 30 to 90 Gy (Fig. 2 and Table 2). Only one death occurred in the group irradiated with 10 Gy while awake, and no deaths occurred in the 20-Gy groups. Thus at these low doses, no significant toxicity was noted, even in awake animals. As can be seen in Table 2, there was progressive radiation toxicity with increasing doses, whether the animals were awake or pretreated with pentobarbital. Nevertheless, animals irradiated under the influence of pentobarbital consistently had longer mean survival times.

**Mechanism of Pentobarbital Radioprotection Studies**

**Relationship of Radioprotection to Timing of Pentobarbital Administration.** Animals that received pentobarbital immediately after x-irradiation fared no better than the awake control group at the same x-irradiation dose (Fig. 3 and Table 3). This indicates that, by whatever mechanism pentobarbital imparts protection, the influence of the drug must be present during the ionizing insult for its protective effect.

**Relationship of Protection to Action of Pentobarbital on CNS.** After delivery of alphaxalone — the compound administered to simulate the function of the (-) isomer of pentobarbital — survival was enhanced to an extent statistically equal to that occurring with the
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FIG. 3. Evaluation of the importance of administration of pentobarbital before exposure to brain irradiation. There was a lack of radioprotection by pentobarbital when administered immediately after 70 Gy of x-irradiation, whereas survival time was enhanced when pentobarbital anesthesia was induced before radiation exposure.

TABLE 3
Investigation of the mechanism of pentobarbital radioprotection

<table>
<thead>
<tr>
<th>Group Description*</th>
<th>No. of Rats</th>
<th>Survival (days)t</th>
</tr>
</thead>
<tbody>
<tr>
<td>awake</td>
<td>10</td>
<td>16.7 ± 11.5</td>
</tr>
<tr>
<td>pentobarbital (60 mg/kg i.p.)</td>
<td>10</td>
<td>22.6 ± 8.6t$</td>
</tr>
<tr>
<td>postirradiation pentobarbital (60 mg/kg i.p.)</td>
<td>8</td>
<td>13.6 ± 10.1t$</td>
</tr>
<tr>
<td>Saffan (30 mg/kg i.p.)</td>
<td>10</td>
<td>25.6 ± 9.3t</td>
</tr>
<tr>
<td>2-APH (0.33 mM/kg i.p.)</td>
<td>10</td>
<td>18.1 ± 11.3t$</td>
</tr>
<tr>
<td>diazepam (5 mg/kg i.p.)</td>
<td>10</td>
<td>22.8 ± 9.9t$</td>
</tr>
<tr>
<td>ketamine (80 mg/kg i.p.)</td>
<td>8</td>
<td>10.1 ± 3.7t$</td>
</tr>
<tr>
<td>hypothermia (24.3°C ± 1.5°C &amp; x-irradiation)</td>
<td>10</td>
<td>9.4 ± 3.7t$</td>
</tr>
<tr>
<td>hypothermia (24.0°C ± 2.0°C) alone</td>
<td>10</td>
<td>30.0</td>
</tr>
</tbody>
</table>

* All groups received 70 Gy of single-fraction whole-brain x-irradiation. i.p. = intraperitoneally.
† Calculated as of 30 days following x-irradiation, survival times are given as means ± standard deviations.
‡ P < 0.05 as compared to the awake group, determined by the Wilcoxon signed-rank test.
§ P < 0.05 as compared to the pentobarbital group, determined by the Wilcoxon signed-rank test.

racemic mixture of pentobarbital (Fig. 4 and Table 3). 2-APH, which approximates the activity of the (+) isomer, imparted no protection as survival was not statistically different from that of awake animals. The animals that received alphaxalone were anesthetized while those receiving 2-APH were awake.

Relationship of Radioprotection to GABAergic Activity. Diazepam administration imparted protection statistically equivalent to that provided by a 60 mg/kg dose of pentobarbital (Fig. 5 and Table 3).

Influence of General Anesthesia on Radiosensitivity. The 80 mg/kg dose of ketamine used in this study rendered the animals anesthetized and immobilized during radiation treatment to a degree similar to that observed with the 60 mg/kg dose of pentobarbital. Following treatment, the animals in the ketamine group awoke sooner than the pentobarbital animals. The mean survival time of animals irradiated under the influence of ketamine was less than that of animals irradiated while awake, although the difference was not statistically significant (Fig. 6 and Table 3).

Influence of Cerebral Metabolic Activity on Radiosensitivity. The mean rectal temperature of the group of rats undergoing x-irradiation following induction of hypothermia was 24.3°C ± 1.5°C. As seen in Fig. 7, survival in this group was worse than in the awake control animals (p < 0.01). Clearly no benefit was derived from a nonspecific generalized decrease in cerebral metabolism. Animals exposed to a similar depth of hypothermia (mean rectal temperature 24.0°C ± 2.0°C) would
Fig. 6. Evaluation of anesthesia induced by ketamine, an agent that functions predominantly by mechanisms other than enhancing gamma-aminobutyric acid binding (a primary mode of pentobarbital action), on survival after exposure to brain x-irradiation. Ketamine does not provide radioprotection. In fact, survival times following radiation under the influence of ketamine are less than in animals irradiated while awake, but not to a statistically significant extent (p > 0.05).

without x-irradiation suffered no apparent ill effects, and all survived (Table 3).

Discussion
Dose-Response Characteristics of Pentobarbital Radioprotection

The purpose of this study was to evaluate the characteristics of the observed radioprotection by pentobarbital described in our initial report. 51 The first segment of the work reported here investigated the reproducibility and dose-response characteristics of these observations. It confirmed that the original findings were reproducible and that the effect occurred over a range of doses. As no significant protection was noted at doses of 100 Gy x-irradiation in the initial study, this and higher doses were not investigated in the present work.

At the two lowest doses, 10 and 20 Gy, it appears that early CNS radiation injury is relatively minor and the beneficial effects of pentobarbital on survival, apparent at higher doses, cannot be appreciated. In this model, the optimum enhancement of mean survival time occurred at an intraperitoneal dose of 60 mg/kg. Below that level, although some prolongation of survival was seen, it was not statistically significant. At the highest dose of pentobarbital administered, 75 mg/kg, a significant decrease was noted in survival times compared to those of animals receiving 60 mg/kg. This may be due to direct drug toxicity at this dose and to potential interactions with the radiation-induced toxicity.

As expected, animals receiving lower doses of pentobarbital were less sedated. Less sedated or awake animals, even when irradiated immediately after placement in restraints, may be subject to stress. In turn, the physiological alterations induced by stress may have an impact on radiosensitivity. 77 Looking at normal tissue, Keizer and van Putten showed a decrease in the radiosensitivity of rodent bone marrow stem cells in animals irradiated while awake and restrained, and speculated that this was due to induction of stem cell hypoxia during x-irradiation. Zanelli and Lucas demonstrated that, in awake immobilized animals, normal tissue is not subject to a significant decrease in blood flow or intravascular volume, whereas in tumors blood flow and volume are significantly decreased, potentially decreasing tumor radiosensitivity. Although none of these reports deals with normal brain, their findings suggest that the stress to which these animals were subjected either had no effect on the radiosensitivity of their normal tissues or was actually somewhat radioprotective. 34 The radioprotection of normal cerebral tissue induced by pentobarbital beyond that which might be induced by stress also strengthens the observations of this investigation.

Relation of Radioprotection to the Function of Pentobarbital

The mechanism of the radioprotective influence of pentobarbital is the subject of the second segment of this report. Pentobarbital is a frequently used anesthetic agent with CNS depressant activity. 2,3,5,39,43,55,58 It is used clinically as a racemic mixture of the (+) and (-) isomers. 31 In an in vitro investigation, Huang and Barker proposed that, upon binding its receptor, the function of the (-) isomer is to enhance the binding of GABA to its receptor. It was also proposed that the (+) isomer inhibits the postsynaptic conductance induced by the excitatory amino acids. Because isolated (+) and (-) isomers are not easily available in quantities necessary for in vivo experimentation, compounds with mechanisms of function that mimic the activities of the (+) and (-) isomers were used in this investigation.

Differential Radioprotective Effects of Agonists of GABA Binding and Inhibitors of Postsynaptic Conduction. Alphaxalone was chosen as an alternative to direct administration of the (-) isomer of pentobarbital.
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It is a progesterone analog, classified as a steroid anesthetic agent and marketed in a 3:1 mixture with alphadolone, another progesterone analog, as Saffan. The function of alphaxalone depends on enhancement of GABA binding and in that sense it is similar to the (-) isomer of pentobarbital. In rats receiving Saffan prior to a single 70-Gy fraction of whole-brain x-irradiation, the mean survival time as of 30 days after x-irradiation was actually better than in those receiving pentobarbital, although not to a statistically significant extent.

We chose 2-APH, a member of a class of novel anticonvulsants which are proposed to act by inhibition of the actions of the excitatory amino acids, to approximate the function of the (+) isomer of pentobarbital. 2-APH is a competitive inhibitor of glutamate binding at the NMDA (n-methyl-D-aspartate) receptor with less activity at the kainic acid and quisqualate receptors. It has physiological affects (it inhibits seizure activity in rodents) and distributes to the brain, even after intraperitoneal administration. Administration of known anticonvulsant doses of 2-APH (0.33 mM/kg) had no impact on radiation toxicity. This suggests that the inhibition of postsynaptic conductance by pentobarbital does not play a role in radiation protection. However, this statement must be qualified with the constraints realized in choosing 2-APH; that is, activity at other relatively unbound excitatory amino acid receptors may be important to radiation protection and would not be demonstrated by this compound. More broadly acting antagonists of excitatory amino acid function could possibly reveal some protective effect.

Because enhancement of the binding of GABA to its receptor appeared to be an important component of the radioprotective effect of pentobarbital, further attention was focused on the GABA receptor. The GABA receptor does not exist alone on the cell membrane. It is closely linked to the chloride ion channel and the benzodiazepine receptor. Modulation of any one of these components alters the others. As pentobarbital binding occurs, there is enhancement of GABA binding and subsequent opening of the chloride ion channel. This is one of the proposed mechanisms by which barbiturates affect neuronal activity. Benzodiazepine receptor binding also results in enhanced GABA binding and opening of the chloride ionophore. It was thus predictable that diazepam, by enhancing GABA binding (even though by a different mechanism than pentobarbital), may have a radioprotective effect. It must be kept in mind that the binding of the GABA receptor is not an end in itself. The subsequent opening of chloride channels and membrane stabilization likely lead to a cascade of events which explain the radioprotective effect of pentobarbital alphadolone, and diazepam.

The Role of Alternative Modes of Metabolic Depression. Significant sedation occurred following the administration of pentobarbital, alphadolone, and diazepam, all of which had a radioprotective influence in the described model. 2-APH had no observable sedating effect and no radioprotective effect. Therefore the sedative- or anesthesia-inducing properties of enhancing GABA binding (the property of the (-) isomer of pentobarbital) are at least associated with the radioprotection described and may be inseparably linked to this effect.

The association between maximal radioprotection and the need for anesthetic doses of pentobarbital is relevant should consideration be given to the use of these findings clinically. The cardiac and pulmonary risks of the addition of anesthesia, potentially repeated daily, to a course of radiation treatment would have to be considered in light of the overall medical condition of the patient. On the other hand, repeated sedation to facilitate accomplishment of radiation therapy is commonly applied in young children to induce them to remain motionless and to maintain accurately positioned radiation ports during treatment. Among the compounds used for repeated sedation is ketamine, a dissociative anesthetic with little depression of cardiovascular function in quantities inducing useful sedation. Ketamine, as shown in original work and again here, does not impart radioprotection despite its ability to induce anesthesia. Thus, it cannot be assumed that general anesthesia induced by any mechanism is the basis of the protective effect we have observed with pentobarbital. The mechanism by which ketamine induces anesthesia is probably multifactorial and not so clearly dependent on modulation of GABA as are the barbiturates. It exerts a significant inhibitory effect on the synaptosomal accumulation and transport of 5-hydroxytryptamine. It has the same effect but to a lesser extent on norepinephrine and dopamine, and has little effect on GABA uptake. Ketamine also noncompetitively inhibits NMDA receptor-induced excitation. This has been explained as the result of an allosteric interaction with the ion channel that is linked to the NMDA receptor. This allosteric interaction with ketamine blocks the depolarization induced by binding of that receptor. From the data presented here it appears that those compounds that enhance GABA binding and initiate the subsequent cascade of events accompanying GABA receptor binding impart a radioprotective effect. Substances that we examined which alter neuronal function by other mechanisms, such as 2-APH and ketamine, did not offer radioprotection.

With pentobarbital anesthesia, overall cerebral metabolic rate is substantially lowered. The basal mitochondrial respiratory activity maintaining cellular integrity is little affected and most of the decrease is in synaptic activity. In order to establish whether hypometabolism in a general sense is responsible for decreasing brain radiosensitivity, the effect of x-irradiation in the presence of hypothermia was investigated. The decrease in metabolism which occurs with this manipulation does not exactly parallel that induced by pentobarbital. We were unable to substantiate a prior report...
by Hajduković, et al., of radioprotection in vivo following the induction of hypothermia. Although enzymatic function has been protected from radiation-induced disruption in vitro by decreases in temperature, it does not appear that this can be extrapolated to in vivo studies of the brain such as we have conducted. Induction of hypometabolism per se did not produce radioprotection, implying that the radioprotection observed with pentobarbital is unique to a specific mode of decreasing brain activity.

**Cellular Effects of Radiation: Potential Sites of Radioprotection.** These results do not provide a final answer as to the events that underlie the protection of the brain against early radiation damage by pentobarbital. There is an association between the enhancement of GABA binding to its receptor and longer survival after large-dose single-fraction whole-brain x-irradiation. How tissue protection results from this manipulation remains to be determined. The component of the brain on which this effect occurs is not readily evident, as GABA receptors reside on neurons, glia, and endothelia. On a subcellular level, many targets are available for the free radicals formed by ionizing radiation. The unsaturated bonds of membrane lipids may be involved in peroxidation reactions which alter membrane fluidity and receptor alignment. Sulfur-containing enzymes and proteins may undergo inactivation by cross-linking and nucleic acids may be subject to similar circumstances. Cellular carbohydrates may be oxidized, resulting in an alteration of receptor functions including those dealing with hormonal and neurotransmitter responses. As well as other possible mechanisms of action are under current consideration.

**Clinical Observations.** There is little doubt that radiation injury to normal tissues limits its use in the treatment of CNS tumors. Children with such tumors, especially in the younger age groups, suffer significant intellectual and endocrine injury from the doses necessary for tumor control and prophylaxis. In adults with primary cerebral tumors and metastases, except for selected cases, radiation therapy is only palliative. Thus, a method of enhancing the efficacy of radiation therapy, while maintaining its safety, would have significant clinical utility.

**Acknowledgment**

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