

## Interstitial delivery of dexamethasone in the brain for the reduction of peritumoral edema

RAFAEL J. TAMARGO, M.D., ALLEN K. SILLS, JR., M.D., CARLA S. REINHARD, M.H.S.,  
MICHAEL L. PINN, B.S., DONLIN M. LONG, M.D., PH.D., AND HENRY BREM, M.D.

*Department of Neurological Surgery, The Johns Hopkins Hospital, Baltimore, Maryland*

✓ Controlled-release polymers have facilitated the interstitial delivery of drugs within the central nervous system. In the present study, dexamethasone was incorporated into ethylene-vinyl acetate polymers, which were then implanted adjacent to a 9L gliosarcoma in the brain of Fischer 344 rats. The effect of interstitial delivery of dexamethasone on peritumoral edema was assessed and compared to the effect of dexamethasone delivered systemically.

Eighty-five rats underwent intracranial implantation of the 9L gliosarcoma. Five days later, the animals were randomly assigned to one of four treatment groups: Group 1 received intracranial implantation of controlled-release polymers containing dexamethasone; Group 2 received intraperitoneal implantation of controlled-release polymers containing dexamethasone; Group 3 received serial intraperitoneal injections of dexamethasone; and Group 4 received sham treatment. The animals were sacrificed 3 days after initiation of therapy and their brains were removed for measurement of the water content (edema) in the tumor-bearing and contralateral hemispheres. Brain and plasma samples were analyzed by reverse-phase high-performance liquid chromatography to determine the tissue and plasma concentrations of dexamethasone. Measurement of the release kinetics of dexamethasone from the ethylene-vinyl acetate polymers in an *in vitro* system showed that the drug was released in a controlled, tapering fashion. During the first 3 days of controlled release *in vitro*, 330  $\mu$ g of a total content of 7.5 mg of dexamethasone was released into the medium. Analysis of tissue for drug levels demonstrated, however, that the interstitial delivery of this fractional amount of dexamethasone within the brain resulted in levels 19 times higher than those achieved by administering the full dose of 7.5 mg systemically over a 3-day period. Conversely, the systemic administration of dexamethasone resulted in plasma levels 16 times higher than those measured in the interstitial delivery of dexamethasone in the brain. Brain-water content determinations showed that the interstitial controlled release of the fractional amount of dexamethasone within the brain was as effective in controlling peritumoral edema as systemic administration of the full dose by serial intraperitoneal injections.

The study demonstrates the following: 1) controlled-release polymeric carriers deliver biologically active dexamethasone in a sustained fashion; 2) very high concentrations of dexamethasone in brain tissue can be achieved using interstitial polymer-mediated drug delivery while minimizing plasma concentrations of this drug which are sometimes associated with serious systemic side effects; and 3) peritumoral brain edema can be effectively treated by the interstitial delivery of dexamethasone directly within the tumor bed.

**KEY WORDS** • brain tumor • edema • dexamethasone • polymers • drug delivery • rat

**V**ASOGENIC edema associated with brain tumors is effectively treated by the systemic administration of corticosteroids.<sup>8,9,13,24</sup> The extended administration of therapeutic doses of steroids, however, can be associated with serious side effects.<sup>14</sup> Controlled-release polymers implanted directly into the brain for interstitial delivery of drugs may provide adequate levels at the site of pathology yet minimize systemic exposure and side effects.<sup>12,22</sup>

In this study, dexamethasone was incorporated into controlled-release polymers which were then

implanted in the brains of Fischer 344 rats bearing intracranial 9L gliosarcomas. Ethylene-vinyl acetate copolymer, the prototype of the diffusion-regulated controlled-release polymer,<sup>11</sup> was used for local delivery of dexamethasone. This polymer is biologically inert<sup>10</sup> and has been used to deliver chemotherapeutic agents,<sup>26</sup> growth factors,<sup>17</sup> neurotransmitters,<sup>6</sup> and angiogenesis inhibitors<sup>23</sup> in a controlled fashion.

Traditionally, steroid therapy has been thought to be effective against vasogenic edema (associated with tumors and abscesses, for example) but not against cyto-

TABLE 1  
Summary of the experimental design\*

Treatment Group	No. of Rats	Intracranial Implant	Intraperitoneal Implant	Intraperitoneal Injection
Group 1 (intracranial DEX-EVAc implant)	16	DEX-EVAc polymer	pure EVAc polymer	saline solution
Group 2 (intraperitoneal DEX-EVAc implant)	16	pure EVAc polymer	DEX-EVAc polymer	saline solution
Group 3 (intraperitoneal DEX injections)	15	pure EVAc polymer	pure EVAc polymer	DEX solution
Group 4 (control)	17	pure EVAc polymer	pure EVAc polymer	saline solution

\* All animals were implanted with intracranial 9L gliosarcoma. DEX = dexamethasone; EVAc = ethylene-vinyl acetate copolymer.

toxic edema (as in ischemic insults and trauma). Higher levels of steroids in the brain, however, may have an impact on edema conditions previously refractory to systemic steroid therapy.

The release kinetics of dexamethasone from ethylene-vinyl acetate copolymer were studied *in vitro*, and brain and plasma levels of dexamethasone were determined by high-performance liquid chromatography. The response of peritumoral edema to various therapeutic manipulations was evaluated by determining the fractional water content of the brain samples.

#### Materials and Methods

##### Tumor Implantation

The 9L gliosarcoma<sup>2</sup> was propagated as a solid tumor in the flanks of adult male Fischer 344 rats. For intracranial implantation, tumor fragments were trimmed to pieces measuring approximately 2 × 2 × 1 mm. Eighty-five rats, each weighing about 200 gm, were anesthetized intraperitoneally with 3 to 5 mg/kg of a stock solution containing ketamine hydrochloride (25 mg/ml), xylazine (2.5 mg/ml), and ethyl alcohol (14%) in normal saline. The skin was prepared for this and all other surgical procedures by shaving and then washing with 70% ethyl alcohol and povidone-iodine solution. Using microsurgical technique, a midline incision was made and the periosteum displaced. A 3-mm burr hole was drilled over the left hemisphere with its center 5 to 6 mm behind the coronal suture and 3 to 4 mm lateral to the sagittal suture. The dura was opened sharply in a cruciate fashion and the cortex aspirated to expose the highly vascular sulcus between the thalamus and the superior colliculus. The bleeding was allowed to subside spontaneously, and the tumor fragment was then implanted into the brain defect. The wound was thoroughly irrigated and the skin closed with surgical clips. All animals were weighed after each procedure.

##### Polymer Preparation

Ethylene-vinyl acetate copolymer\* (40% vinyl acetate by weight) was washed extensively in absolute ethyl

alcohol to extract inflammatory impurities, mainly the antioxidant butyl hydroxytoluene (BHT). The presence of BHT in the ethyl alcohol wash was monitored spectrophotometrically at 230 nm, and the washes were continued until the absorbance fell below 0.03 unit.<sup>10</sup> The cleaned polymers were then vacuum-dried in a desiccator for 4 or 5 days.<sup>11</sup> Dexamethasone was incorporated into an ethylene-vinyl acetate copolymer matrix by solvent evaporation.<sup>19</sup> The pure polymer pellets were dissolved in methylene chloride (10% wt/vol), and enough solid particles of dexamethasone† were added to the ethylene-vinyl acetate copolymer solution in order to obtain a 50% mass fraction of dexamethasone. The suspension was poured into glass cylindrical molds (5 mm in diameter × 27 mm in height) precooled to -70°C. After 20 minutes, the solidified polymers were transferred to a -30°C freezer and allowed to dry for about 7 days. The 50% dexamethasone-ethylene-vinyl acetate copolymer cylinders were then cut to a uniform disc shape weighing 14.2 to 15.8 mg. These discs contained a dexamethasone dose of about 37.5 mg/kg. Control implants made of 100% ethylene-vinyl acetate copolymer were prepared by using the same procedure, except that no drug was added to the methylene chloride. Prior to implantation, the polymers were sterilized under ultraviolet light for 1 hour.

##### Reoperation for Polymer Implantation

On the 5th day after tumor implantation the animals were randomly assigned to one of the four treatment groups outlined in Table 1. For intracranial polymer implants the skin was reopened, the connective tissue overlying the burr hole was displaced, and either a 50% dexamethasone-ethylene-vinyl acetate copolymer or a pure ethylene-vinyl acetate copolymer disc was inserted into the defect within the cortex. The wound was thoroughly irrigated and the skin reclosed. For intraperitoneal implants, a midline abdominal incision was made and the appropriate polymer type inserted into the peritoneal cavity. The abdominal skin was closed with surgical staples.

\* Ethylene-vinyl acetate copolymer, Elvax 40P, supplied by DuPont, Wilmington, Delaware.

† Dexamethasone supplied by Sigma Chemical Co., St. Louis, Missouri.

TABLE 2  
Results of analysis of dexamethasone levels in brain tissue and plasma by high-performance liquid chromatography\*

Treatment Group	No. of Rats	Tumor Hemisphere ( $\mu\text{g/gm}$ tissue)	Contralateral Hemisphere ( $\mu\text{g/gm}$ tissue)	Plasma ( $\mu\text{g/ml}$ )
Group 1 (intracranial Dex-EVAc implant)	6	$1.50 \pm 0.13$	$0.18 \pm 0.18$	$0.12 \pm 0.05$
Group 2 (intraperitoneal Dex-EVAc implant)	6	ND	ND	$0.25 \pm 0.12$
Group 3 (intraperitoneal Dex injections)	6	$0.08 \pm 0.03$	$0.02 \pm 0.02$	$1.91 \pm 0.19$
Group 4 (control)	3	ND	ND	ND

\* Values are expressed as mean  $\pm$  standard error of the mean. Dex = dexamethasone; EVAc = ethylene-vinyl acetate copolymer; ND = not detected.

### Dexamethasone Injections

The animals treated with systemic dexamethasone received six intraperitoneal injections of dexamethasone sodium phosphate $\ddagger$  (10 mg/ml) every 12 hours over the course of 72 hours. The total administered dose of 37.5 mg/kg was equal to the amount of drug present in the dexamethasone-ethylene-vinyl acetate copolymer matrices. The animals in the other three groups received intraperitoneal injections of the same volume of normal saline administered on the same schedule.

### In Vitro Release Study

Drug release was measured by incubation of 50%-loaded polymers at 37°C in 5 ml of 0.2 M sodium phosphate buffer (pH 7.4) with 0.01% sodium azide. The buffer was removed at specific times, replaced with fresh buffer, and the dexamethasone concentration determined in the old solution by spectrophotometry at 240 nm.

### Chromatographic Analysis

Eighteen animals, six in each treatment group, were used to measure the levels of dexamethasone in brain tissue and plasma obtained by each method of administration. The animals were sacrificed on the 8th day after tumor implantation, 2 hours after the last intraperitoneal injection of either dexamethasone or normal saline. Prior to sacrifice, the rats were anesthetized and blood samples collected in heparinized syringes. Plasma was obtained by centrifugation and stored at  $-35^{\circ}\text{C}$  until analysis. The brain was excised and the polymer removed. Each hemisphere was weighed and placed in a separate Potter-Elvehjem tube. The tissue was homogenized after enough normal saline was added to make 2 ml. Brain and plasma samples (1 ml each) were washed with heptane under alkaline conditions as described by Cham, *et al.*<sup>5</sup> The heptane layer was then discarded and 1  $\mu\text{g}$  of internal standard (prednisolone) was added to the aqueous phase. The samples were extracted with methylene chloride; the organic layer was transferred to a clean tube, dried at 45°C under a stream of nitrogen gas, and stored at 4°C. At the time of analysis, the extracted samples were reconstituted

with tetrahydrofuran and filtered; 25  $\mu\text{l}$  were then injected into the chromatography system. The analysis was performed with a Waters liquid chromatography system and a reverse-phase C18 Microbondapak column.<sup>§</sup> Column effluent was monitored at 254 nm. All separations were performed at ambient temperature. The isocratic delivery system for brain consisted of 60% sodium acetate buffer (2 mM, pH 4.8) and 40% acetonitrile at a flow rate of 2 ml/min. A continuous gradient of the same two eluents (20% to 60% acetonitrile in acetate buffer) was used as the mobile phase for the plasma samples at a flow rate of 1 ml/min. Dexamethasone standards (ranging in concentration from 0.1 to 5  $\mu\text{g/ml}$ ) were prepared in brain homogenate and plasma from untreated adult male Fischer 344 rats. Results were expressed as micrograms of dexamethasone either per gram of brain tissue or per milliliter of plasma.

### Brain Water Determination

On the 8th day following tumor implantation, the animals were anesthetized and then sacrificed by decapitation. The brains were removed and tumors excised by blunt dissection. Tumor was measured with calipers and the volume calculated by using the following formula:<sup>4,15</sup> tumor volume (cu mm) = length (mm)  $\times$  width<sup>2</sup> (mm)/2.

The cerebral hemispheres were placed in preweighed aluminum dishes. Each sample was weighed and the value recorded as the "wet weight." Each dish was then placed in a drying oven at 100°C for 24 hours, after which time the dish was reweighed and the value recorded as the "dry weight."<sup>13</sup> The fractional water content was then determined using the following formula, expressing the value as a percentage: tissue water content = (wet weight - dry weight)/(wet weight).

### Statistical Analysis

The brain edema values and the calculated tumor volumes were subjected to nonparametric, single-factor analysis of variance by the Kruskal-Wallis test and the Newman-Keuls nonparametric analog for multiple comparisons.<sup>28</sup>

<sup>§</sup> Model 6000A high-pressure pumps, WISP automatic sample injector, Model 440 ultraviolet absorbance detector, and Baseline computer software, all obtained from Waters Associated, Inc., Milford, Massachusetts.

$\ddagger$  Dexamethasone sodium phosphate supplied by Elkins-Sinn, Inc., Cherry Hill, New Jersey.

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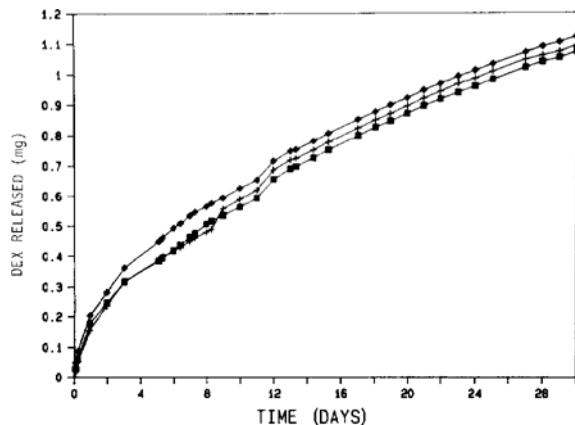


FIG. 1. Release of dexamethasone (DEX) from 50%-loaded (wt:wt) ethylene-vinyl acetate copolymer in sodium phosphate buffer over a 30-day period in rats. Data shown represent cumulative release profiles of three individual matrices.

### Results

#### In Vitro Release Kinetics

The release profile of dexamethasone from 50%-loaded ethylene-vinyl acetate copolymer implants was measured in phosphate buffer at 37°C for more than 30 days (Fig. 1). After 3 days (corresponding to the time the polymers were implanted *in vivo*), only 4.4% of the dexamethasone originally loaded into the ethylene-vinyl acetate copolymer matrix had been released (0.33 mg); after 17 days, only 11% had been released (0.83 mg).

#### Dexamethasone Levels in Brain Tissue and Plasma

Analysis by high-performance liquid chromatography showed that dexamethasone levels in the brain were highest in Group 1 rats (intracranial dexamethasone-ethylene-vinyl acetate copolymer implant) (Table 2). The concentration (mean  $\pm$  standard error of the mean (SEM)) in the ipsilateral hemisphere was  $1.50 \pm 0.13$   $\mu$ g/gm in the tumor-bearing hemisphere and  $0.18 \pm 0.18$   $\mu$ g/gm in the contralateral hemisphere. Group 3 rats (with intraperitoneal dexamethasone injection) had the highest concentration of dexamethasone in plasma ( $1.91 \pm 0.19$   $\mu$ g/ml), but had very low levels in brain tissue 2 hours after systemic injection of the last bolus dose of dexamethasone.

#### Tissue Water Content

All animals had large tumors at the conclusion of the experiment. The following volumes were calculated for each group (tumor volume expressed as mean  $\pm$  SEM): intracranial dexamethasone-ethylene-vinyl acetate copolymer,  $49.0 \pm 18.6$  cu mm; intraperitoneal dexamethasone-ethylene-vinyl acetate copolymer,  $68.6 \pm 13.4$  cu mm; control,  $69.5 \pm 14.2$  cu mm; and systemic dexamethasone injection,  $49.7 \pm 7.5$  cu mm (Fig. 2). The tumor-containing hemispheres in Group

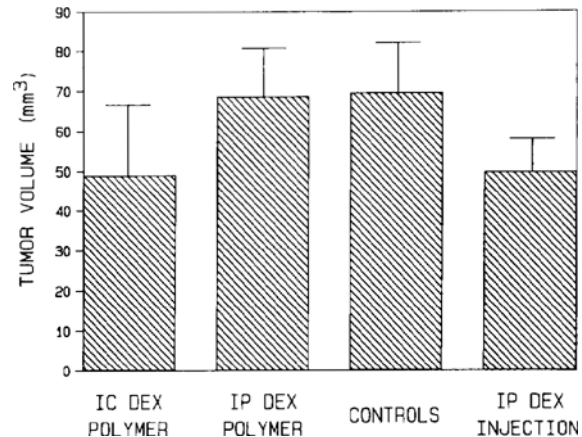


FIG. 2. Block graph depicting tumor volumes (mean  $\pm$  standard error of the mean) in the four treatment groups. All tumors were measured at the time of animal sacrifice. There were no significant differences in tumor size between the groups. IC = intracranial; IP = intraperitoneal; DEX = dexamethasone.

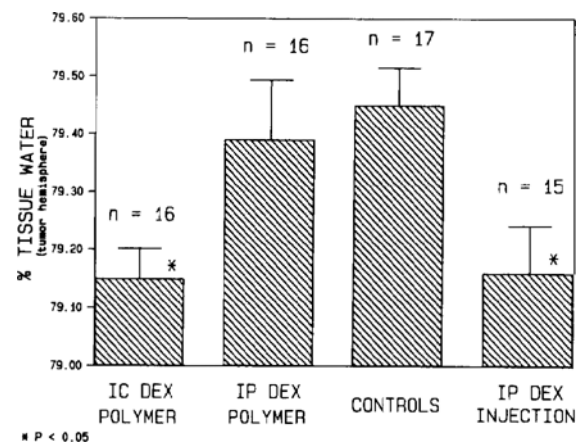


FIG. 3. Block graph showing the tissue water content (mean  $\pm$  standard error of the mean) of the tumor-containing hemisphere at the time of animal sacrifice. IC = intracranial; IP = intraperitoneal; DEX = dexamethasone; n = number of rats in each treatment group. Asterisks denote values significantly different from those of control animals ( $p < 0.05$ ).

4 rats (control) had the highest tissue water content ( $79.45\% \pm 0.07\%$ ) (Fig. 3). Group 1 (intracranial dexamethasone-ethylene-vinyl acetate copolymer implant) and Group 3 animals (intraperitoneal dexamethasone injection) showed significant ( $p < 0.05$ ) reductions in the water content of the tumor hemisphere ( $79.15\% \pm 0.05\%$  and  $79.16\% \pm 0.07\%$ , respectively) as compared to the control group. There was, however, no significant difference between these two treatment groups. The Group 2 rats (intraperitoneal dexamethasone-ethylene-vinyl acetate copolymer implant) had a mean tissue water content of  $79.39\% \pm 0.10\%$  in the ipsilateral hemisphere, which was not significantly different from that of the control animals.

## Discussion

### Study Rationale

Bioavailability of drugs to the central nervous system is limited by the blood-brain barrier.<sup>16</sup> To achieve therapeutic levels in the brain, some drugs must be administered systemically in doses that may be toxic to other organ systems. Current therapy for cerebral peritumoral edema necessitates the systemic administration of high doses of corticosteroids. Controlled-release polymers can be implanted in the brain to release drugs interstitially, thus circumventing the obstacle posed by the blood-brain barrier.

### Polymer Delivery of Dexamethasone

This study demonstrates that dexamethasone is released from the ethylene-vinyl acetate copolymer in a biologically active form and in a controlled fashion. The loading dose used in this experiment results in a slow, sustained delivery of dexamethasone whereby a smaller amount of drug is released each day, thus accomplishing a taper of this agent. Different polymer formulations and loading levels can be used to either accelerate or extend the release of the drug. In this study, only 330  $\mu\text{g}$  (4.4%) of a total dose of 7.5 mg dexamethasone was released from the polymer over a 3-day period *in vitro*. It can be assumed that the *in vivo* release of dexamethasone from the polymer into the brain and peritoneal cavity is either similar to or lower than that observed *in vitro*, given that the frequent buffer changes *in vitro* provide conditions resembling an "infinite sink" which enhance the kinetics of the diffusion-mediated release of dexamethasone but which may not necessarily be replicated in the rats. Thus, it can be assumed that only 330  $\mu\text{g}$  of dexamethasone was released in the brain or into the peritoneal cavity from the time the polymers were implanted in the rats to the time of their sacrifice. A full 7.5 mg dose of dexamethasone, however, was administered systemically over the course of 72 hours in the group receiving serial intraperitoneal injections. Despite systemic administration of a much larger dose, the concentration of dexamethasone in the brain tissue of this group was only 0.08  $\mu\text{g}/\text{gm}$  as compared to 1.50  $\mu\text{g}/\text{gm}$  in the group with intracranial dexamethasone polymers. Conversely, as a result of the systemic administration, the mean level of dexamethasone in plasma measured 1.91  $\mu\text{g}/\text{ml}$  while the mean level associated with the intracranial interstitial release of dexamethasone was 0.12  $\mu\text{g}/\text{ml}$ . Since higher levels of dexamethasone in plasma probably translate into a higher incidence of systemic side effects, this implies that the intracranial delivery of dexamethasone is probably safer than the standard systemic administration.

### Critical Intracranial Steroid Levels

Despite a higher concentration of dexamethasone in brain tissue of the intracranial/interstitial delivery group, the effect on peritumoral edema in this group

was essentially identical to that achieved by serial systemic injections. This finding suggests that the anti-edema effect of dexamethasone probably peaks either at the lower concentration in tissue of 0.08  $\mu\text{g}/\text{gm}$  or below. Therefore, a dexamethasone-polymer formation could be designed to deliver a lower dose of dexamethasone interstitially, perhaps eliminating altogether the "leakage" of dexamethasone into the systemic circulation.

The optimal brain levels of dexamethasone needed to control peritumoral edema remain to be determined. Long, *et al.*,<sup>13</sup> have shown that increasing doses of dexamethasone are no more effective than smaller doses while Renaudin, *et al.*,<sup>18</sup> demonstrated a dose dependence in achieving edema control. Tracer studies suggest that extended brain and tumor exposure to high levels of corticosteroid may be advantageous since increased uptake of corticosteroids in the tumor and surrounding brain may eventually lead to reduction in peritumoral edema with further steroid therapy.<sup>20,24,25</sup> There is evidence that the clinical response to corticosteroid therapy paralleled the concentration of corticosteroid receptors in tumor and brain tissue.<sup>27</sup>

It is not surprising that the group treated with the intraperitoneal implantation of dexamethasone polymers did not show a significant reduction in peritumoral edema. The small dose of dexamethasone released into the peritoneal cavity was diluted by the large systemic volume of distribution, thus failing to reach detectable levels in the brain.

### Tumor Volumes

Although the differences in tumor volumes between the four groups were not significant, a trend may be apparent in the finding that both the group receiving the intracranial dexamethasone polymers and the group with intraperitoneal dexamethasone injections had somewhat lower tumor volumes. The tumors in the groups in which edema was not effectively controlled may have been slightly "swollen" because of the interstitial fluid, thus resulting in greater volume. Alternatively, dexamethasone may have a small cytostatic effect and impair tumor cell replication and growth. Nevertheless, the two groups used to answer the major question posed in this study, namely whether intracranial/interstitial delivery of dexamethasone is as effective as standard systemic administration of the same agent, had tumors of comparable size and showed comparable and significant reductions in peritumoral edema. Other factors known to influence the generation of peritumoral edema, such as proximity to the lateral ventricles and cell of origin,<sup>7</sup> were obviated by the experimental design.

### Polymer Characteristics

The ethylene-vinyl acetate copolymer has long been recognized as an effective carrier matrix with controlled-release properties. This polymer has been used

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clinically to release a variety of drugs.<sup>1-21</sup> More recent work has documented the advantage of this polymer for the release of biologically active compounds within the central nervous system.<sup>6,17,26</sup> Several studies from this laboratory have documented the efficacy of controlled-release polymers for the delivery of chemotherapeutic agents to intracranial neoplasms.<sup>3,22,23</sup>

## Conclusions

This study demonstrates that dexamethasone can be released in a controlled fashion by use of polymeric carriers. Interstitial cerebral delivery of dexamethasone results in extremely high levels of dexamethasone in the brain yet small amounts of the drug in the systemic circulation. The interstitial delivery of a fractional dose of dexamethasone directly within the tumor bed in the brain was as effective in reducing peritumoral edema as a much higher dose delivered systemically. Implantable polymers loaded with steroids may have numerous applications in neurological surgery, not only in tumor therapy, but also in other areas where steroids have proven to be advantageous.

## Acknowledgments

The authors thank Drs. Mark Saltzman and Michael Radosky for assistance with the chromatographic analysis, Peter Zage for technical assistance, and Dr. Pamela Talalay for reviewing the manuscript.

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Manuscript received August 24, 1990.

Accepted in final form December 19, 1990.

This study was supported in part by an Association for Brain Tumor Research fellowship in memory of Steven Lowe, National Institutes of Health Grants NS01058-01 and 5K08-NS01058, and American Cancer Society Grant IN-11W.

Address reprint requests to: Henry Brem, M.D., Department of Neurological Surgery, The Johns Hopkins Hospital, Meyer 7-113, 600 North Wolfe Street, Baltimore, Maryland 21205.