Treatment of experimental spinal cord compression caused by extradural neoplasms

YUKITAKA USHIO, M.D., ROSLYN POSNER, JAE-HO KIM, M.D., WILLIAM R. SHAPIRO, M.D., AND JEROME B. POSNER, M.D.

Laboratory of Neuro-Oncology, Sloan-Kettering Institute for Cancer Research, and the Departments of Neurology and Radiation Therapy, Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, New York

Epidural spinal cord compression was produced in rats by injection of Walker 256 carcinoma cell suspension anterior to the T-12 or T-13 vertebral body. The tumor grows through the intervertebral foramina to compress the spinal cord and produce paraplegia in 3 to 4 weeks. The effect of several treatments upon clinical signs was assessed. Dexamethasone caused a significant but transient improvement in neurological function. Radiation therapy likewise improved neurological function, and was more effective when given by a high-dose protracted course than when given either in a single dose or a low-dose protracted course. Laminectomy was not helpful in relieving neurological symptoms. Dimethyl sulfoxide did not relieve neurological symptoms. Cyclophosphamide was most effective in relieving neurological symptoms, and most of the animals that were treated with that drug when they were severely weak but still able to move their hind limbs recovered fully. Some animals that were totally paraplegic when treatment began recovered function after radiation therapy or cyclophosphamide treatment, but recovery was better if treatment was started when animals could still move their hind limbs. This animal model appears to be a useful way of studying the treatment of human spinal cord compression produced by epidural neoplasms.

KEY WORDS - spinal cord - laminectomy - radiation therapy - corticosteroid therapy - paraplegia - extradural tumor

Spinal cord compression by epidural metastasis is one of the most common and devastating neurological complications of systemic cancer. Opinion is divided concerning appropriate treatment for this disorder, but most of the literature recommends decompressive laminectomy, usually followed by radiation therapy. A few reports recommend radiation therapy without prior decompressive laminectomy. There is no controlled randomized study in the literature comparing the relative efficacy of these two treatment modalities, although a comparative study suggests that there is no substantial difference in outcome between patients who are irradiated without laminectomy and those who are irradiated following laminectomy. The lack of carefully controlled studies arises in part from the fact that patient variability is so great; for example, the epidural metastasis may be the only one or there may be widespread systemic illness. The vertebral body may be intact or may be collapsed.
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Metastasis may be to one or several segments. The tumor can arise from a number of primary sites that have variable responses to irradiation and chemotherapy. Whatever the treatment given, the outcome is frequently unsatisfactory. Most studies in the literature report that only about 35% of patients whose spinal cords are compressed by metastatic tumor regain ambulation, whatever the therapy. The best series in the literature yielded only a 50% ambulation rate after treatment.

Because controlled studies in humans are difficult to carry out, we developed an experimental model of spinal cord compression in the rat which mimics that of the human disease. It was developed by paraspinal inoculation of Walker 256 carcinoma cell suspension into adult Wistar rats. The tumor grows through the intervertebral foramina to compress the spinal cord and causes progressive weakness of hind limbs, leading to paraplegia in 3 to 4 weeks after tumor inoculation. In the current study, that experimental model was used to compare the efficacy of various treatment modalities directed against this neurological problem.

Materials and Methods

Details of the production of the model have been described previously. Walker 256 carcinoma is carried by serial subcutaneous transplantation in our laboratory. Seventeen days after subcutaneous inoculation, the tumor is removed and minced with fine scissors in Earle's basic medium and passed through first 40-mesh and then 80-mesh stainless steel screens under aseptic conditions. A concentration of $1 \times 10^6$ viable cells per 0.1 ml of Earle's medium is obtained using the trypan blue exclusion test for viability. Female Wistar rats weighing approximately 150 gm are anesthetized with sodium pentobarbital (50 mg/kg intraperitoneally). With a No. 25 needle, $1 \times 10^6$ viable cells are injected percutaneously anterior to the T-12 or T-13 vertebral body. The animals are observed daily after tumor inoculation and neurological symptoms are carefully recorded. Weakness of the hind limb is graded according to the following scale:

- 0 = normal
- 1 = slight weakness, with hip instability, observed only when the animal is running or jumping
- 2 = mild weakness, the animal is able to run
- 3 = moderate weakness, the animal is able to walk but not run
- 4 = marked weakness, the animal can stand but is unable to walk
- 5 = severe weakness, the animal cannot stand and there is only slight movement of the legs
- 6 = paraplegia, no movement.

Treatment was undertaken in one group of animals the day they developed Grade 4 weakness and in another group of animals the day they developed Grade 6 weakness. On the day that the desired grade of weakness was reached, the animals were randomized and treated by one of several modalities, as indicated in Table 1. To compare results, the first day of treatment was referred to as Day 1. There were at least nine animals in each treatment group that were compared with a control group of 34 untreated animals. For untreated animals, Day 1 was the day the animal reached Grade 4 (or 6) weakness. During and after treatment, the animals were graded daily with respect to weakness. The day of death was also recorded (Table 1).

Results

Within 30 days after tumor inoculation 154 animals had developed Grade 4 weakness and were utilized in this study. Most of the animals developed Grade 4 weakness 13 to 22 days after the inoculation of tumor. The symptoms were steadily progressive in the untreated animals and 32 of the 34 control animals (94%) became paraplegic (Grade 6) by the fourth day after they had reached Grade 4. Once the animals became paraplegic, they remained so until death (Fig. 1).

The inexorable natural history of this experimental epidural spinal cord compression was considerably altered by treatment. The results of the various treatment modalities are described below.

Cyclophosphamide

This chemotherapeutic agent to which the Walker 256 carcinoma is known to be exquisitely sensitive was the most effective treatment of the spinal cord compression.
TABLE 1
Treatment of experimental spinal-cord compression

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Treatment</th>
<th>No. of Rats</th>
<th>Median Day of Death*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1†</td>
<td>control (no treatment)</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td>2†</td>
<td>cyclophosphamide 100 mg/kg IV x 1</td>
<td>11</td>
<td>&gt;61</td>
</tr>
<tr>
<td>3†</td>
<td>dexamethasone 10 mg/kg IM 2/day, 3 days</td>
<td>9</td>
<td>7,5</td>
</tr>
<tr>
<td>3†</td>
<td>dexamethasone 10 mg/kg IM 2/day until death</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>4†</td>
<td>dimethyl sulfoxide 40% solution 2.5 ml/kg 2/day, 1 day</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>5†</td>
<td>radiation (15 MeV Betatron) 1000 rads x 1</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>5†</td>
<td>radiation (15 MeV Betatron) 500 rads alternate days x 3, 5 days</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>5†</td>
<td>radiation (15 MeV Betatron) 200 rads daily x 8</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>6†</td>
<td>laminectomy</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>7†</td>
<td>combination 500 rads alternate days x 3, 5 days, + dexamethasone 10 mg/kg IM 2/day, 3 days</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>8‡</td>
<td>cyclophosphamide 100 mg/kg IV x 1</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>9‡</td>
<td>dexamethasone 10 mg/kg IM 2/day until death</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>10‡</td>
<td>radiation (15 MeV Betatron) 500 rads alternate days x 3, 5 days</td>
<td>9</td>
<td>19</td>
</tr>
</tbody>
</table>

*Median number of days after treatment was begun that death occurred in each group. Day animals reached 4 = Day 1.
†Treatment was started with the animals at Grade 4 weakness.
‡Treatment was started with the animals at Grade 6 weakness.

Fig. 1. The development of weakness in control animals and those treated with cyclophosphamide. Day 1 is the day the animals reached Grade 4 weakness. Closed circles indicate untreated animals, open circles, animals treated with cyclophosphamide 100 mg/kg intravenously. The vertical lines represent standard error of the mean. Control animals were significantly worse on Day 2 than they were on Day 1 ($p < 0.001$), and 94% were paraplegic by Day 4. The animals treated with cyclophosphamide did not change significantly until Day 7 (when dotted line became solid), but from that time on were significantly better than they had been before treatment. All of the animals regained ability to walk.
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(Fig. 1). When animals that reached Grade 4 weakness were treated with a single dose of cyclophosphamide (100 mg/kg intravenously), they became significantly better (p < 0.001) by Day 7 (that is, the seventh day after treatment) and continued to improve thereafter until they all became able to run (Grade 2). Ultimately, eight of 11 such animals were completely cured of tumor and fully regained motor function. Even if the treatment was delayed until the development of complete paraplegia (Fig. 2), seven of nine animals survived and five recovered sufficient motor function to walk; three could run. However, four of the seven animals were not cured of their tumor and eventually redeveloped paraplegia and died a median of 35 days after the treatment.

**Dexamethasone**

Three different experiments were performed. In 18 Grade 4 animals, dexamethasone 10 mg/kg intramuscularly was given twice daily for either 3 days or until death. Nine Grade 6 animals were treated with dexamethasone until death. The results with dexamethasone treatment of Grade 4 weakness are illustrated in Fig. 3. There was marked and immediate improvement of weakness so that animals were significantly better (p < 0.01) on the second day after treatment was begun. On that day, 14 out of 18 animals were able to walk or run. The effects, however, were transient. Both the animals in which steroids were discontinued on Day 4 and those in which steroid treatment was maintained started to deteriorate by Day 4 and eventually became paraplegic. If treatment was delayed until the development of paraplegia, only three of the nine animals improved, and that improvement persisted for only a few days (Fig. 2).

**Dimethyl Sulfoxide**

Dimethyl sulfoxide was tried because of its reported salutary effects in paraplegia following spinal cord trauma. No effect on clinical symptomatology was noted in nine animals. The progression of the paraplegia was identical with that in the control animals.

**Radiation Therapy**

Radiation therapy has been reported to be successful in the treatment of both human and experimental spinal cord compression. Three different dose schedules were utilized...
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Dexamethasone 10 mg/kg IM bid □9 3.
Control, N = 34

Dexamethasone 10 mg/kg IM bid
until death. N = 9

FIG. 3. The effects of dexamethasone on paraparesis from epidural spinal cord compression. All animals were treated the day they reached Grade 4 weakness. Animals treated with dexamethasone for 3 days (open circles) improved initially, but all became paraplegic by the seventh day. The animals treated with dexamethasone in the same dose until death (open triangles) also improved initially, and by the eighth day were substantially weaker than they had been when treatment was started, and most were paraplegic by Day 9.

(Table 1). All animals were treated with electron beams of 15 MeV (Betatron) at a depth of 3 cm. When a single dose of 1000 rads was given on the day the animals developed Grade 4 weakness, they improved significantly by the sixth day (p < 0.05) and remained improved for a further 3 days (Fig. 4). Six of nine animals regained the ability to walk. However, by the ninth day all the animals began to deteriorate again, and by Day 19 they were significantly worse than they had been on Day 1 (p < 0.025). Animals treated

FIG. 4. The effect of several dose schedules of radiation therapy on paraparesis. Three different radiation modalities were evaluated: 1000 rads in a single dose (open triangles) produced significant improvement by the sixth day, but animals had relapsed by the 19th day. Radiation therapy 200 rads a day for 8 days (open circles) never produced significant improvement over the day treatment was started, although a few animals regained the ability to walk. Radiation therapy of 500 rads every other day for 3 doses (closed triangles) produced significant improvement by the 11th day, and improvement was sustained much longer than with the single dose of 1000 rads. The vertical lines are standard error of the mean.
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with fractionated doses of 500 rads every other day for three doses initially showed no response and continued to deteriorate at the same rate as untreated animals (but not faster). However, after the second treatment (when they had received 1000 rads total dose), they started to improve and by Day 11 were significantly better (p < 0.05) than on Day 1 (Fig. 4). They remained so until Day 19. Six of seven surviving animals regained the ability to walk or run. The effect persisted in this group of animals longer than with a single dose of 1000 rads. However, six of seven animals ultimately became paraplegic and died by 60 days following the onset of treatment. When the radiation dose was 200 rads daily for 8 days, the animals initially showed no response and, like control animals, were significantly worse (p < 0.001) by Day 2 (Fig. 4). Most of the animals remained paraplegic during the course of treatment. Two died before treatment could be completed. The surviving animals started to improve at about the eighth day, but the clinical course was variable. One rat remained paraplegic while two regained the ability to walk, which remained for more than 10 days. Thus, the best initial improvement was observed with a 1000-rad single dose, but relapse occurred rapidly. Poor initial improvement was observed with standard doses of radiation therapy, that is, 200 rads daily for eight doses, although the few animals who did regain ability to walk maintained it for the longest period of time. Overall, the best fractionation schedule was 500 rads every other day for three doses, which gave improvement as good as the 1000 rads in a single dose, albeit somewhat delayed, and a duration of improvement considerably longer than with a single dose.

The best radiation therapy fractionation, that is, 500 rads every other day, was combined with dexamethasone 10 mg/kg twice a day for 3 days. The first dose of dexamethasone was given 5 to 6 hours before the first radiation dose. Some animals were already stronger when radiation was started. Animals improved rapidly and remained significantly improved until Day 12 (Fig. 5). Seven out of 10 animals became able to run, and the other three regained the ability to walk. As in the radiation group alone, there was a relapse so that by the 13th day animals were not significantly better than when treatment was begun, and by the 23rd day they were significantly worse than Grade 4.

Animals irradiated after they had reached Grade 6 weakness with doses of 500 rads every other day for three doses also improved significantly, but less so than those irradiated at Grade 4 weakness (Fig. 2). Surprisingly,
three of the nine animals regained the ability to walk, but, like the animals in the prior irradiation groups, the symptoms recurred and they subsequently became paraplegic.

Laminectomy

Laminectomy was performed at five vertebral levels, centered on the level of tumor invasion at T-12 or T-13, under a dissecting microscope. Two of nine animals regained the ability to walk after surgery, and remained improved for several days (Fig. 6). In the remainder of the animals, however, there was continued progression of neurological symptoms, and they became paraplegic. Similar laminectomies performed...
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in animals without tumor did not produce adverse effects.

When animals undergoing decompressive laminectomy were treated with dexamethasone as well, with the first dose 3 to 4 hours before surgery, they did better than when laminectomy alone was carried out (Fig. 7). The animals were significantly better on Days 2, 3, and 4 (p < 0.05) than on Day 1. The effect was transient, however, and by Day 6 they became significantly worse than on Day 1.

Survival

The median survival time for all of the animals is noted in Table 1. Cyclophosphamide, whether delivered when the animals were at Grade 4 or Grade 6 weakness, significantly prolonged survival, although it was much more effective when given earlier. Radiation therapy, likewise, prolonged survival when either of the two fractionated dose schedules was used. Other treatment modalities had no significant effect on the survival of the animals.

Discussion

This animal model provides new data in several areas, some of which may be of clinical relevance. First is the effect of dexamethasone. We have previously demonstrated that dexamethasone given at Grade 4 spinal-cord compression in this model both decreases the water content of the edematous spinal cord overlying the tumor and improves the clinical symptoms.14 We suggested that dexamethasone improved clinical symptoms by decreasing spinal cord edema, but an alternative possibility is that dexamethasone has a direct effect on the tumor, decreasing its bulk.14 The evidence from these present experiments supports the former interpretation. The rapid resolution of clinical symptoms with dexamethasone strongly argues that it is resolution of edema that produces the salutary effect, since a much more effective chemotherapeutic agent, cyclophosphamide, does not produce clinical improvement for several days. Even the most rapid irradiation course (1000 rads in a single dose) failed to produce clinical improvement for several days. If the mechanism of action of dexamethasone were shrinkage of tumor, one would expect that, like cyclophosphamide and radiation therapy, the effect would not be seen immediately but several days later.

Although dexamethasone is exceedingly effective in causing rapid resolution of symptomatology, the effect is transient. Whether the drug is discontinued after 3 days or continued for the life of the animal, weakness of the hind limbs recurs and the animals rapidly become paraplegic. The development of paraplegia is slightly more rapid if the dexamethasone is discontinued on Day 4, but both groups of animals become unable to walk again by the fourth day after treatment was begun. These findings also argue against dexamethasone having its primary effect as a chemotherapeutic agent upon the tumor, since one might have expected that if the tumor had shrunk enough to allow the animals to walk within 1 day, tumor recurrence would not produce Grade 4 weakness within 3 to 5 days and paraplegia within 8 to 10 days.

Dexamethasone was only effective if used before the animals became paraplegic. None of the nine animals treated when they became paraplegic regained useful motor function in the hind limbs.

Another finding of interest in this study relates to the effectiveness of cyclophosphamide on the tumor model. The Walker 256 carcinoma is known to be highly sensitive to cyclophosphamide,17 and therefore it is not surprising that the tumor could be cured with that drug. Two findings were of interest, however. One is the long delay between the time cyclophosphamide was given and the improvement in the animals' function. There was no significant change in the Grade 4 animals until the seventh day after therapy was begun. Second was that all Grade 4 animals walked by the 18th day. The long delay in improvement and the final outcome suggest that the cord can be compressed for a long period of time at levels producing significant weakness, and yet if decompression is effective, animals can return virtually to normal. Histological and physiological studies done after cyclophosphamide therapy should yield data concerning the degree of damage that the spinal cord suffers under these circumstances. Somewhat less striking, but of equal interest, were the effects of cyclophosphamide given to animals who had already become paraplegic. Five of the seven
animals which survived the first several days after treatment recovered sufficient motor function to walk, and three became essentially normal. Thus, even though animals were paraplegic for up to 24 hours before the use of cyclophosphamide, and even though they remained paraplegic for 4 to 5 days after cyclophosphamide was given, the ultimate return of motor strength was good. The tumor, however, was not cured by this dose of cyclophosphamide and four of the seven animals eventually redeveloped paraplegia, and died of recurrent tumor. Thus, the development of total paraplegia does not obviate eventual return of motor function if appropriate treatment can be administered. We have no data on the length of time the animals can be paraplegic before treatment is undertaken.

Two of the three radiation schedules (1000 rads in 1 day, 1500 rads in 5 days) are essentially biologically equivalent. Biological equivalence is based on cell kill in vitro and in vivo. Despite the fact that these doses were biologically equal, there were significant differences in the response of the animals' weakness. The single dose of 1000 rads improved the animals more rapidly than the slower course of radiation, as might have been expected, but it failed to maintain improvement for as long as the 1500 rads given over 5 days, although the 1500-rads course produced improvement somewhat more slowly than the 1000 rads. The 8-day course produced improvement much more slowly than the 1000 rads. The 8-day course produced improvement much more slowly — so much so that some animals died or became paraplegic by the time the radiation was finished. If the 200 rads daily dose had been carried to biological equivalence with the other schedules (about 15 days), many animals would have probably died, and it is doubtful that more improvement would have occurred. For those animals that survived the course of irradiation, however, improvement lasted at least as long as the 1500 rads in a 5-day course. These data suggest that one must compromise between giving the entire irradiation dose as rapidly as possible in order to prevent irreversible spinal cord damage and fractionating the dose in order to prolong the period of clinical improvement. In the only other experimental model of spinal cord compression treated by radiation therapy, Rubin, et al. (using a Murphy-Sturm lymphoma), produced cord compression by implanting tumor into the nape of the neck of Sprague-Dawley rats. They used the model to study the effects of radiation therapy. The results with two doses, 500 rads daily for 3 days and 100 rads daily for 10 days, were studied. The tumor was exceedingly sensitive to radiation therapy and he was able to cure most animals using either dose schedule. However, the higher dose was more efficacious in reversing spinal cord symptoms. Moreover, the higher dose produced no deleterious effects such as increased weakness, a finding which the present study confirms. Walker 256 carcinoma is less sensitive to radiation therapy than the Murphy-Sturm lymphoma and thus did not respond as rapidly or as completely to irradiation. However, even at a single dose of 1000 rads, twice Rubin's dose, there was no evidence of a deleterious effect of radiation therapy such as might occur if the high doses produced spinal cord edema or swelling of the tumor to further compress the cord. High doses thus appear to be safe, although not as efficacious as the more protracted doses.

When steroids are combined with the high-dose protracted course of radiation therapy (1500 rads in 5 days), improvement was immediate as a result of steroid therapy and protracted as a result of radiation therapy. Next to the use of cyclophosphamide, this appeared to be the most effective modality of treatment for spinal cord compression in this model.

Laminectomy was performed carefully under a microscope. It failed, however, to improve the animals significantly, being much less effective than steroids, chemotherapy, or radiation therapy. When laminectomy was combined with steroid therapy, it was somewhat more effective, but no more effective than steroids alone. In all instances the tumor regrew rapidly, and animals progressed to paraplegia. Laminectomy itself had no deleterious effects since the animals did not become more rapidly paraplegic than the control animals nor, when laminectomy was performed in normal animals, were any abnormal clinical findings apparent.

Dimethyl sulfoxide, a drug that has been reported to be of therapeutic efficacy in paraplegia from spinal cord trauma, and that has recently been reported to relieve symptoms of chronic spinal cord compression caused by an implanted plastic mass, failed to produce any effect in this model.
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McCallum and Bennett$^4$ noted that improvement occurred within 90 minutes after a single dose, and the animals deteriorated again over the subsequent 3 hours. The effect, however, was repeatable. We might have missed such a transient effect in this model, but certainly, even giving dimethyl sulfoxide twice daily, there was no discernible improvement in animals.

Thus, in the experimental model, the treatment of choice appears to be chemotherapy with a drug to which this particular tumor is highly sensitive. If the tumor is not highly sensitive to chemotherapy, the combination of steroids and irradiation by a high dose but fractionated course appears to be the treatment of choice.

How can the animal data here be extrapolated to the human problem? Several immediate problems with extrapolation arise. First of all, rats are not humans, and what applies to the experimental animal cannot be assumed to apply exactly to the human being. Secondly, the Walker 256 carcinoma is not a human cancer, and although its relative radioresistance resembles that of carcinomas of the breast, lung, and prostate which frequently produce spinal cord compression, its extreme chemosensitivity is much more similar to Hodgkin's disease. Thirdly, laminectomies performed on a rat are not equivalent to laminectomies performed on the larger human being. Finally, the experimental model produces cord compression without collapse of vertebral bodies, while in man there are often vertebral metastases, and the vertebral body is destroyed, leading to instability of the spine. In some patients, it is difficult to be certain whether it is only collapse or tumor causing the cord compression. In our model, instability of the spine is not a problem, but the failure of the vertebral body to be destroyed in this model is an advantage since we are able to study the effects of tumor independent of the instability of the spine.

Despite these problems, some of our findings in experimental animals can be related to those in man. The first is that steroids are helpful in ameliorating clinical symptoms, probably by decreasing the amount of edema in the spinal cord. There are no clinical studies in the literature identifying dexamethasone as an effective agent for the treatment of cord compression since most physicians who give dexamethasone for this condition proceed immediately to more definitive therapy. There are a few reports suggesting that corticosteroids are efficacious.$^4$ Our experiments demonstrate that dexamethasone is an exceedingly effective drug for the treatment of spinal cord compression, although its effect is transient and even if continued symptoms will recur and eventually progress to paraplegia. The dose of dexamethasone that we use in experimental animals is high and translates to a dose of about 100 to 150 mg/70 kg in man.$^8$ We have not tried either higher or lower doses in our experimental animals, but as a result of these experiments we believe that dexamethasone should be used in the treatment of epidural spinal cord compression in humans, probably at high doses. The effectiveness of radiation therapy that we found in ameliorating symptoms of spinal cord compression can also be extrapolated to man. We had previously reported our clinical experience that radiation therapy is as efficacious in the treatment of spinal cord compression as is decompression laminectomy.$^{11}$ The experiments in animals confirm this and furthermore suggest that a fractionated dose rather than a single high dose of radiation therapy is probably the treatment of choice. The use of a single dose of 1000 rads in humans was suggested by Millburn, et al.,$^6$ on the basis of the successful treatment of a single patient with an epidural metastasis from prostate carcinoma. Because of the findings in our experimental model, we now treat human spinal cord compression with 500 rads of cobalt radiation daily for 3 days to achieve rapid amelioration of symptoms and then, after a 4-day rest, 200 rads a day for eight doses in an attempt to get protracted relief of symptoms.

The fact that even high doses of radiation therapy do not affect the cord deleteriously, at least acutely, may also be applied to man. The problem of swelling in the spinal cord after radiation therapy has been raised as a relative contraindication to the use of that modality, but the experimental evidence indicates that this is not a problem.

Finally, the data suggest that when tumors are highly sensitive to chemotherapy, as is the Walker 256 carcinoma, chemotherapy might be as efficacious as radiation therapy. Silverberg and Jacobs$^{14}$ report three cases of spinal-cord compression caused by Hodgkin's
disease in which dramatic improvement of spinal dysfunction was achieved initially by chemotherapy with nitrogen mustard or cyclophosphamide. Despite these findings, we still prefer radiation therapy for the treatment of even Hodgkin's disease since our clinical results with that modality have been excellent and local radiation therapy does not cause as much bone-marrow depression as does high-dose chemotherapy.

Less clearly related, but potentially applicable to human beings, is the problem of laminectomy. The data in the experimental animals indicate that radiation therapy alone is better than laminectomy alone, although we might expect that laminectomy combined with radiation therapy would be the equal of radiation therapy. We have found the same thing in a retrospective non-controlled study in humans. However, the differences mentioned above between rats and humans preclude extrapolating these data directly.

Also potentially applicable to man are the data in animals that even paraplegia does not preclude improvement if effective treatment is undertaken. In our previous study, only two of 21 patients who were paraplegic at the onset of treatment walked again, and some physicians do not aggressively treat patients already paraplegic. The data in animals suggest that if the patient has recently become paraplegic, aggressive treatment should be undertaken because the potentiality for improvement remains. It also seems likely that further studies in animals with fractionation schedules for radiation therapy might be applicable to humans.

References

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This work was supported in part by Grants CA-15792 and CA-08747 from the National Cancer Institute, U.S. Public Health Service.

Address reprint requests to: Jerome B. Posner, M.D., 1275 York Avenue, New York, New York 10021.