Hormonal manipulation of meningiomas in vitro

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Speculation that meningiomas are subject to endocrine influence is supported by their higher incidence in women, reports of exacerbation of symptoms during pregnancy, and the discovery that these tumors harbor progesterone- and estrogen-binding proteins. To evaluate if these properties could be exploited therapeutically, specimens from three convexity meningiomas were used for estrogen- and progesterone-binding protein assays and establishment of tissue cultures. Each tumor (designated A, B, and C, respectively) was grown in experimental media containing $7.5 \times 10^{-5}$ to $10^{-12}$ M $17\beta$-estradiol, $2.5 \times 10^{-4}$ to $10^{-12}$ M progesterone, $10^{-7}$ to $10^{-9}$ M tamoxifen (an estrogen antagonist), and $10^{-6}$ to $10^{-10}$ M RU486 (a progesterone antagonist). After incubation, cell growth was compared to control preparations by counting the meningioma cells present in each medium.

Tumors A, B, and C contained estrogen-binding proteins of 8.45, 13.6, and 26.9 fmol/mg cytosol protein and progesterone-binding proteins of 210, 130, and 126 fmol/mg cytosol protein, respectively. The media containing $17\beta$-estradiol and progesterone caused 21% to 36% growth stimulation in Tumors A and B. In Tumor A, the addition of tamoxifen stimulated growth by 35%, while it caused only transient stimulation in Tumor B and had no effect on Tumor C. RU486, the progesterone antagonist, caused inhibition of cell growth in all three tumors, ranging from 18% to 36%.

These data suggest that selected meningiomas are subject to hormonal influence in vitro. The inhibition of meningioma growth in vitro by the antiprogesterone, RU486, has not been previously reported, and serves to encourage further development of alternative modes of therapy for recurrent and unresectable meningiomas.

KEY WORDS · meningioma · estrogen · progesterone · cell culture · tamoxifen

It has been suggested that meningiomas are subject to endocrine influence. This conjecture is based on epidemiological and clinical factors, such as the predominance of these tumors in women, and case reports of exacerbation of meningioma symptoms associated with pregnancy. Investigations resulting from these observations have led to the discovery of estrogen- and progesterone-binding proteins, as well as other steroid hormone-binding proteins in meningiomas.

Surgical resection of meningiomas is the treatment of choice; however, not all such lesions are amenable to this approach. The discovery of hormone-binding proteins in these tumors led to the proposal that endocrinological manipulation may prove to be an alternative mode of therapy, especially in cases with unresectable or recurrent tumors.

In order to evaluate this as a therapeutic option, we have studied the effects of $\beta$-estradiol, progesterone, and their pharmacological antagonists on meningiomas in tissue culture.

Materials and Methods

Clinical Material

Specimens were taken from three convexity meningiomas at the time of resection, which will be referred to as Tumors A, B, and C, respectively. Each specimen was divided into three portions for histological studies, estrogen- and progesterone-binding protein assays, and establishment of cell cultures.

Histopathological Preparation

Light microscopic examination was performed on
specimens after formalin fixation, paraffin embedding, and staining with hematoxylin and eosin.

**Estrogen Receptor and Progesterone-Binding Protein Assay**

Tissue obtained at operation (250 to 500 mg) was immediately frozen in liquid nitrogen and stored in the vapor phase of liquid nitrogen until assayed. The tissue was thawed on ice, weighed, homogenized with a Brinkman polytron in 0.01 M Tris buffer (pH 8), and centrifuged for 15 minutes at 1800 G in a Beckman J-6 centrifuge.* The supernatant was removed and centrifuged for 1 hour at 105,000 G and the cytosol obtained was used for estrogen and progesterone receptor determinations. An aliquot of cytosol was also used for determination of protein concentration.**

For estrogen receptor determinations, cytosol was incubated with 1 nM hydrogen-3(3H)-labeled estradiol (101 Ci/mM) and increasing concentrations of unlabeled estradiol (0 to 500 pg/tube) at 4°C for 18 hours. Bound and free hormones were separated by the addition of 10% dextran-coated charcoal, and radioactivity was determined in a Hewlett-Packard liquid scintillation counter.†

Progesterone receptor determinations were made by incubation of cytosol with 1 nM 3H progesterone (Promeestone, 87 Ci/mM) and increasing concentrations of unlabeled progesterone (0 to 1000 pg/tube) at 4°C for 4 hours. Receptor concentration and binding affinity were determined by Scatchard analysis.‡ Receptor concentration was expressed as fmol/mg of cytosol protein.

**Establishment of Cell Culture**

Under a laminar flow hood, the tumor specimens were immersed in Ham's F-12 media supplemented with 20% heat-inactivated fetal bovine serum (FBS) and penicillin (0.02% ethylenediaminetetra-acetic acid (EDTA) for 10 minutes at 37°C. A suspension of these cells was thawed on ice, weighed, homogenized with a Brinkman polytron in 0.01 M Tris buffer (pH 8), and centrifuged for 1 hour at 105,000 G and the cytosol obtained was used for estrogen and progesterone receptor determinations. An aliquot of cytosol was also used for determination of protein concentration.**

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To study the effect of the hormones in question, cells were harvested from the 75-sq cm flasks by the method described above and distributed among 25-sq cm tissue culture flasks at a density of 2.5 × 10⁴ cells per flask. These cells were allowed to attach over a period of 48 to 72 hours in maintenance medium. This medium was then replaced by experimental medium after the cells were washed with protein-buffered saline. The control medium contained 20% heat-inactivated FBS, which had also been treated with dextran-coated charcoal to remove unbound steroids, according to the method described by Eckert and Katzenellenbogen.** The PSG combination was also added to this medium. The appropriate amount of steroid hormone in question was then added to the control medium in order to form the other experimental media. The steroid hormone had previously been dissolved in 95% alcohol, and the total alcohol content in the resultant medium did not exceed 0.01%. The 17β-estradiol solutions were formulated in 7.5 × 10⁻⁵, 2.5 × 10⁻⁶, 10⁻⁸, 10⁻¹⁰, and 10⁻¹² M concentrations. Progesterone was formulated in solutions of 2.5 × 10⁻⁴, 2.5 × 10⁻⁶, 10⁻⁸, 10⁻¹⁰, and 10⁻¹² M concentrations. Tamoxifen was tested at 10⁻⁷ and 10⁻⁹ M concentrations. A synthetic steroid and progesterone antagonist, RU486 supplied by Roussel-Uclaf Co., Paris, France.†‡ was tested at 10⁻⁴, 10⁻⁶, and 10⁻¹² M concentrations.

After the experimental medium was placed on the cells in triplicate or quadruplicate, the flasks were returned to the environment described above and the medium was changed weekly. Because of persistent cell detachment, the groups of flasks containing 2.5 × 10⁻⁴ and 2.5 × 10⁻⁶ M progesterone and 7.5 × 10⁻² and 2.5 × 10⁻⁶ M estradiol were harvested after 14 days and counted with a hemocytometer. The cells in 10⁻⁸, 10⁻¹⁰, and 10⁻¹² M estradiol and progesterone were incubated for 28 days, harvested, and counted in a Coulter counter† standardized to counts obtained in a hemocytometer.

The various concentrations of tamoxifen and RU486 were studied with similar numbers of cells and incubated in a similar manner. Some of the flask were harvested and counted in a Coulter counter on the day of preparation of the experimental media and weekly thereafter for 4 weeks. The results were analyzed using

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† Liquid scintillation counter, Model 4530, manufactured by Hewlett-Packard Co., Palo Alto, California.

‡ RU486 supplied by Roussel-Uclaf Co., Paris, France.

† Counter manufactured by Coulter Electronics, Hialeah, Florida.
TABLE 1
Meningioma estrogen- and progesterone-binding protein levels and binding affinity (Kd) values

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Estrogen Binding</th>
<th>Progesterone Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Protein Levels*</td>
<td>Kd Values†</td>
</tr>
<tr>
<td>A</td>
<td>8.45</td>
<td>$0.57 \times 10^{-9}$</td>
</tr>
<tr>
<td>B</td>
<td>13.6</td>
<td>$0.78 \times 10^{-9}$</td>
</tr>
<tr>
<td>C</td>
<td>26.9</td>
<td>$0.24 \times 10^{-9}$</td>
</tr>
</tbody>
</table>

* Expressed in fmol/mg tumor protein.
† Dissociation constant of labeled steroid from binding protein, measured in moles.

Student’s t-test for unpaired data, with p < 0.05 being the criterion for significance.

Results

Histopathology

Light microscopy revealed that all three tumors were composed of cells that were predominantly meningothelial in character. At the external convexity of Tumor C, there were some fibrous characteristics, but the tissue for receptor assay and cell culture was not taken from that location.

Estrogen Receptor and Progesterone-Binding Protein Assay

Assays of Tumors A, B, and C revealed detectable levels of both estrogen- and progesterone-binding proteins (Table 1). The estrogen-binding protein levels are relatively low. Analysis of the binding data revealed linear Scatchard plots which are indicative of high affinity binding to a single class of receptors of uniform binding affinity.

Cell Culture

By phase contrast microscopy, the cells assumed numerous irregular shapes with long spindle-like cytoplasmic processes. As the cell population density increased, the processes overlapped. Electron microscopic evaluation of transverse and *en face* sections revealed numerous regions of overlapping cytoplasmic processes and irregular nuclear borders with cytoplasmic invaginations.

Cell population doubling times were 7.5, 4, and 6 days for Tumors A, B, and C, respectively (Fig. 1). These data indicated that a long incubation period was necessary for evaluation of the hormone effects.

Cell Culture Studies

Incubation of all three tumors in the two highest concentrations of estradiol and progesterone resulted in little or no cell multiplication, and in most cases progressive cell death and detachment was evident. Because of this apparent toxicity, incubation of this culture was terminated after 14 days.

Tumor A showed no response to incubation in $10^{-8}$ M estradiol and progesterone. However, at this concentration Tumor B showed a significant increase in growth in estradiol. Tumor C was inhibited to a significant degree in both hormones. At $10^{-10}$ M concentrations, Tumor A was significantly stimulated in estradiol, Tumor B in both progesterone and estradiol, and Tumor C was not significantly affected (Fig. 2). Incubation in $10^{-12}$ M progesterone and estradiol resulted in no significant change from control in any tumor.

Addition of tamoxifen to the control medium for Tumor A resulted in significant stimulation of growth in the $10^{-7}$ M solution and a trend toward stimulation in the $10^{-9}$ M solution after 4 weeks. Prior to this, growth in the control and two experimental media was not significantly different. Tumor B showed transient significant stimulation in $10^{-7}$ M tamoxifen after 21 days, but by 28 days there was no significant difference (Fig. 3). At no time was the growth of Tumor C noted to be significantly changed by these concentrations of tamoxifen.

The exposure to RU486 resulted in significant inhi-
TUMOR B

TUMOR C

FIG. 2. Bar graphs of tumor cell counts after 28 days in media containing filtered 20% fetal bovine serum in Ham's F12 medium (control, filtered 20% FBS/F12), progesterone, or β-estradiol. Only those cases where cell counts were significantly different from the control are demonstrated here. Note the stimulation of Tumor B by $10^{-8}$ M β-estradiol ($p < 0.05$, upper left), inhibition of Tumor C by $10^{-8}$ M progesterone and β-estradiol ($p < 0.01$ and $p < 0.001$, respectively, upper right), stimulation of Tumor A by $10^{-10}$ M β-estradiol ($p < 0.01$, lower left), and stimulation of Tumor B by $10^{-10}$ M progesterone and β-estradiol ($p < 0.05$, lower right). Values represent the mean cell count per milliliter ± standard error.

TUMOR A

TUMOR B

FIG. 3. Bar graphs of tumor cell counts in media containing tamoxifen. Only those cases where cell counts were significantly different from the control filtered 20% fetal bovine serum in Ham's F12 medium (filtered 20% FBS/F12) are demonstrated here. Note the stimulation of growth in Tumor A after 28 days in $10^{-7}$ M (p < 0.05), and a trend toward stimulation in the $10^{-9}$ M tamoxifen (p < 0.1). In Tumor B, stimulation of cell counts in $10^{-7}$ M tamoxifen was evident after 21 days (p < 0.01). At 28 days, although stimulation still appeared to be present in the $10^{-7}$ M tamoxifen, it was not statistically significant (p < 0.1). Values represent the mean cell count per flask ± standard error.

Discussion

Clinical observations and the epidemiological features regarding meningiomas have intrigued those who have dealt with them. Meningiomas, which account for 13% to 18% of all intracranial neoplasms,26 have been noted to occur predominantly in females,18,44,70 who account for two-thirds of all cases70 and almost four-fifths of the cases in patients between 30 and 50 years of age.64 The presence of meningioma in prepubertal or elderly patients is very uncommon,89 and in these age ranges the male:female case ratio is equal.42 In intracranial meningiomas, estimates of the female: male ratio range from 2:1 to 2.5:1.17,20,42,68 The preponderance of females with intraspinal meningiomas is estimated to be even higher, ranging from 4:11,57 to 9:1.42

Further epidemiological evidence is also worthy of note. The incidence of simultaneous meningioma and breast cancer in the same patient is well above that expected from random occurrence in the general population.44,75 These patients also have an increased incidence of risk factors normally associated with breast cancer; for example, associated gynecological tumors and abnormal lactation during pregnancy.61,73 Similarly, the incidence of obesity in females with meningiomas is greater than predicted.53 Other tumors accepted as hormonally sensitive, including breast and endometrial carcinoma, are also associated with an increased incidence of obesity.31

The most convincing clinical observation supporting a relationship between sex steroids and these tumors is that, in women harboring a previously occult meningioma, a rapid onset of symptoms may occur during pregnancy.2,13,17,23,41,43,57,67,69,83,84 This is seen especially in the last 4 months of gestation5,58 and in cases where...
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Fig. 4. Bar graphs of tumor cell counts in media containing the antiprogesterone RU486. There was significant inhibition of cell counts compared to the control medium of filtered 20% fetal bovine serum in Ham's F12 medium (filtered 20% FBS/F12) in Tumor A with $10^{-10}$ and $10^{-10}$ M RU486 ($p < 0.05$), in Tumor B with $10^{-8}$ and $10^{-10}$ M RU486 ($p < 0.01$), and in Tumor C with $10^{-6}$, $10^{-8}$, and $10^{-10}$ M solutions ($p < 0.01$, $p < 0.05$, and $p < 0.01$, respectively). The values represent the mean cell count per flask ± standard error. The standard error of Tumor C in $10^{-10}$ M RU486 solution is below the resolution of this graph at ± 154 cells/flask.

cranial nerves and vessels at the base of the skull are involved. The symptoms have been reported to resolve completely in some cases, only to recur with the next pregnancy. Less common are cases in which symptoms increase during the luteal phase of the menstrual cycle. This correlates well with the presentation in pregnancy, in that symptoms are manifested when circulating progesterone levels are relatively high.

The discovery of estrogen- and later progesterone-receptors in malignant breast tumors led to studies of the hormonal responsiveness of breast carcinoma in vitro. These studies demonstrated stimulation of growth with physiological concentrations of estradiol and inhibition by the antiestrogen, tamoxifen. Extension of these findings to the clinical realm led to correlation of estrogen- and progesterone-receptor levels with a prediction of the efficacy of hormonal treatment in a patient with a given breast carcinoma.

Further investigation of steroid hormone receptors of other normal and abnormal tissues demonstrated that meningiomas also contain estrogen- and progesterone-binding proteins. Since then, several studies have confirmed the presence of these estrogen- and progesterone-binding proteins in meningiomas. In nearly all instances where both progesterone binding and estrogen binding have been assayed, the occurrence of progesterone-binding protein has been more frequent, of a larger quantity, and of a higher affinity than that of estrogen. In our tumors, the quantity of progesterone-binding protein was greater than estrogen-binding protein, but the binding affinity (reflected by the binding coefficient (Kd) values) was quite similar (Table 1). The presence of estrogen- and progesterone-binding proteins in meningioma is not unexpected in view of the findings of these moieties in normal leptomeninges and dura.

### TABLE 2

<table>
<thead>
<tr>
<th>Tumor &amp; Medium</th>
<th>Concentration</th>
<th>Effect</th>
<th>% Change From Control</th>
<th>Significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-estradiol</td>
<td>$10^{-10}$ M</td>
<td>stimulation</td>
<td>36%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>tamoxifen</td>
<td>$10^{-7}$ M</td>
<td>stimulation</td>
<td>35%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>RU486</td>
<td>$10^{-4}$ M</td>
<td>inhibition</td>
<td>24%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>RU486</td>
<td>$10^{-6}$ M</td>
<td>inhibition</td>
<td>18%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Tumor B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-estradiol</td>
<td>$10^{-8}$ M</td>
<td>stimulation</td>
<td>21%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>β-estradiol</td>
<td>$10^{-10}$ M</td>
<td>stimulation</td>
<td>23%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>progesterone</td>
<td>$10^{-8}$ M</td>
<td>stimulation</td>
<td>25%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>tamoxifen</td>
<td>$10^{-7}$ M</td>
<td>stimulation*</td>
<td>19%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>RU486</td>
<td>$10^{-4}$ M</td>
<td>inhibition</td>
<td>31%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>RU486</td>
<td>$10^{-10}$ M</td>
<td>inhibition</td>
<td>32%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Tumor C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-estradiol</td>
<td>$10^{-8}$ M</td>
<td>inhibition</td>
<td>30%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>progesterone</td>
<td>$10^{-8}$ M</td>
<td>inhibition</td>
<td>36%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RU486</td>
<td>$10^{-4}$ M</td>
<td>inhibition</td>
<td>36%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>RU486</td>
<td>$10^{-10}$ M</td>
<td>inhibition</td>
<td>28%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>RU486</td>
<td>$10^{-10}$ M</td>
<td>inhibition</td>
<td>21%</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

* Significant stimulation was transient, present only at 21 days and not at 28 days.

In spite of disagreement about the exact biochemical nature of hormonal effects on meningiomas, numerous recommendations have been made that study be devoted to determination of the clinical usefulness of endocrine manipulation in their management.
Researchers have long been able to study meningioma in tissue culture. Prior work on ultrastructural morphology, karyotypes, viral inclusions, and cellular metabolism are but a few examples. Despite this, only two previous studies have examined the influence of hormones on meningioma in vitro. Zava, et al., showed transient stimulation of meningioma growth in vitro with dihydrotestosterone and hydrocortisone. Over the short period of their study, no significant effect of estradiol, progesterone, or tamoxifen was noted. Jay, et al., demonstrated stimulation of meningiomas in the presence of physiologically relevant concentrations of estrogen, progesterone, and tamoxifen in vitro. In a clinical study of eight patients with recurrent or unresectable meningioma, Markwalder, et al., showed that tamoxifen therapy did not change the size of the tumor or lead to clinical improvement.

Our results indicated that meningiomas are sensitive to hormonal manipulation in vitro, although not uniformly so. In two of the three tumors tested, stimulation of growth occurred with progesterone and estrogen over a relatively narrow range. No specific correlation was noted between estrogen and progesterone-binding levels and the tumor response. In fact, Tumor A, which had the lowest estrogen-binding protein level, showed significant stimulation in the presence of 10^{-10} M β-estradiol. This response to the presence of estradiol and progesterone correlates with clinical and epidemiological expectations for such sensitivity.

As noted in the Results section, concentrations in the range of 10^{-4} to 10^{-6} M of β-estradiol and progesterone were not stimulatory, and in some cases resulted in rapid cell death. This is in keeping with the observation made in breast carcinoma, where cytotoxicity is seen in concentrations greater than 10^{-7} M estradiol. The inhibition of growth of Tumor C at 10^{-8} M β-estradiol and progesterone may be explained on the basis that this concentration is at the high end of the physiological spectrum, and that this tumor was more sensitive to these compounds.

The stimulation of growth of meningioma cells in vitro with progesterone and estradiol similar to that in Tumors A and B was seen by Jay, et al., at 10^{-7} and 10^{-9} M estradiol and progesterone. At no point did they record inhibition of cell growth with these hormones. On the other hand, Zava, et al., exposed meningiomas to 10^{-8} M estradiol and 10^{-7} M progesterone in vitro and saw no significant effect. The incubation period in experimental medium was 4 days in the study of Jay, et al., and 10 days in the investigation by Zava, et al., this was significantly shorter than that in our study. We believe that it is important to perform growth studies over at least two cell cycles.

Tamoxifen is known to impede growth of breast carcinoma in vitro. The application of this antiestrogen to tumors known to have high-affinity estrogen binding was hypothesized to result in growth inhibition.
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Progesterone-binding protein and significant presence of nuclear binding protein for progesterone has led to the consensus that progesterone binding is more important in meningiomas than estrogen binding. The continued presence of progesterone binding in primary tissue culture likewise supports its probable greater physiological importance. It follows that an agent with antiprogesterone activity would be more likely to have an effect on meningioma cell growth. Blankenstein, et al., have noted that, in meningiomas, RU486 has the same affinity for progesterone-binding protein as does R5020, a known progesterone analogue and binder of the progesterone receptor. We propose that, in a similar manner, RU486 competes with progesterone for the progesterone-binding protein site in meningioma that is grown in vitro. This may be part of the mechanism by which the inhibition of cell growth occurred in the three tumors in this study. A clear dose-response effect was seen only in Tumor C indicating that competitive inhibition may not be solely responsible for this result. Again, ongoing studies are aimed at defining the mechanism of this inhibition and whether it might be blocked by progesterone or possibly a glucocorticoid.

Besides the work done on estrogen receptors and progesterone receptors and their potential effects, further study is needed on the potential effects of other steroid hormone receptors on meningiomas. Androgen receptors have been mentioned previously, and glucocorticoid receptors and mineralocorticoid receptors have also been detected. Zava, et al., showed transient growth stimulation with hydrocortisone exposure. In reviewing these data and the technique used to obtain them, as with all in vitro studies, caution must be used in extrapolating results to the in vivo situation. The media in which the cells are incubated are certainly important. The removal of free steroid molecules with dextran-coated charcoal from the FBS may well destroy other factors important to growth. In vitro, the cells themselves are likely to change physiologically, resulting in responses to hormonal manipulation different from those of the original tumor. Indicative of this are the data of Zava, et al., which showed loss of measurable estrogen receptor from the tumor specimen to the primary culture, and revealed that there was no correlation between the tumor and culture progesterone receptor values.

The rate at which these tumors grow in our laboratory is slow compared to lung neoplasms, breast tumors, and melanomas. The time over which they are exposed to the experimental media should encompass at least one and preferably more doubling times in order to adequately evaluate the effect of media variation. The container in which they are grown should be large enough and the cell density low enough to avoid possible contact inhibition following increases in cell population.

After three to four passages, meningioma cells undergo senescence visible both by light microscopy and electron microscopy. As emphasized by others, cells subjected to more than four passages are no longer morphologically similar to those in primary cultures, let alone to the original tumor. We concur with previous suggestions that meningioma cells beyond four passages are probably unreliable for experimentation.

In agreement with Schwartz, et al., and later with Jay, et al., we believe that these assays only measure binding protein levels and, although highly specific, do not indicate whether or not that protein functions as a receptor. However, even allowing for that uncertainty, the possibility of hormonal manipulation in the treatment of meningioma remains.

In conclusion, the meningiomas described herein are sensitive to hormonal manipulation in vitro under the conditions specified. The inhibitory effects of the synthetic antiprogesterone, RU486, are encouraging. This suggests the need for further investigation of these effects in vitro and in vivo, hopefully as a guide to developing alternative therapy for humans with recurrent or unresectable meningiomas.

Acknowledgments

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References


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