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Comments and Critique

Meningiomas and Sex Hormones

MENINGIOMAS ARE benign tumours arising from the dura mater of the cranium and spinal column and occasionally from the ventricles. Until recently these tumours remained very much the preserve of the neurosurgeon and surgery is effective in two-thirds of cases. Meningiomas occur more commonly in women and may grow rapidly in pregnancy [1], have an epidemiological link with breast cancer [2], and are associated with the central form of von Recklinghausen's disease. It is difficult to estimate mortality from meningiomas but it is not unreasonable to suggest that at least 1000 patients a year die from this disease in Western Europe. Dying from a benign intracranial tumour is slow and is often associated with repeated surgery and increasing neurological deficits over months and sometimes years. Meningiomas tend to grow slowly and in the very elderly may be found at necropsy. These postmenopausal tumours do not seem to induce the usually associated central nervous system oedema. As far as treatment is concerned, much is known about surgical treatment; where tumours are not resectable, because they are within or near the base of skull or in an intimate relation with the brainstem or cranial nerves, then subtotal excision undoubtedly has a place. Neurological deficits after such surgery are not uncommon and generally radiotherapy is offered, although there is no evidence that external beam radiotherapy, even when stereotactically focused, will slow tumour growth rate.

As regards histological typing, there are four types of tumour. The three benign varieties, transitional, angiomatous and psammomatous, have been studied in depth. There is little correlation between histological tumour appearance and prognosis, although the angiomatous type is more likely to be associated with incomplete surgical excision. The very rare malignant variety behaves as a malignant tumour and has an extremely poor prognosis.

Over the past decade, research into hormonal aspects of meningiomas has revealed some interesting new ideas. Initially, in the early 1980s, contradictory findings were reported with clearly faulty attempts at correlation between sex steroid hormone binding and meningiomas. It has now become established that meningiomas are the only tumours in which there is nearly always a progesterone binding affinity [3, 4]. The use of hormones to treat meningiomas is being investigated, but unfortunately there remains a lack of understanding of sex steroid hormone binding affinity and receptors and the hormonal milieu in relation to benign tumour behaviour. There are, however, many interesting findings from this research that may not only help in the future in the treatment of meningiomas but also in other hormone associated malignant tumours, such as breast cancer, diseases of the genital tract (i.e. endometriosis) and pituitary tumours; and, indeed, illuminate the function of sex steroid hormones and the normal brain [5]. There are also genetic implications such as the relation between meningiomas and breast cancer, and between meningiomas and neurofibromatosis (with suspected abnormalities on chromosome 22).

It is difficult to define exactly what a sex steroid hormone receptor is and what it does [6]. The lesson from tamoxifen and oestrogen receptors in breast cancer, where prognosis is not well related to oestrogen receptor status, has not been lost on investigators into progesterone receptors and meningiomas. The highest levels of progesterone receptors in meningiomas are in perimenopausal women with sphenoidal tumours prone to recurrence [7]. Progesterone binding analysis, whether by cytosolic (dextran-coated charcoal), immunocytostaining or nuclear analysis, is difficult and often open to misinterpretation.

At present there is no meningioma cell line since these tumours tend to become fibroblastic in culture after 30 days. Tumour culture experiments have to be done over long periods, with cell doubling time of 5 days; each experiment must thus be continued for 4 weeks. In addition, until recently [8], there has been no successful animal model of meningioma which, like other benign tumours, does not grow well outside the human body. There has been considerable speculation about whether progesterone agonists or antagonists may be useful in the treatment of inoperable meningiomas [9]. Here the neuro-oncologist has an advantage: it is easy to measure accurately tumour growth rate with meningiomas which are uniformally enhancing and well delineated on computed tomography. There are several drugs available with agonistic and antagonistic progesterone activity. Many of these drugs have few side-effects and, most ill-advisedly, progesterone agonists have been used in man. This is foolish because progesterone levels are known to rise during pregnancy and this is the one time clinically when it is known that meningiomas can grow more rapidly. Others have chosen one of the most potent and controversial progesterone antagonists, mifepristone, for laboratory and clinical trials. This drug, in common with many of the other synthetic antiprogesterone agents, has been developed for gynaecological disease and in particular for the procurement of abortion. There has been considerable pressure on the manufacturer by the anti-abortion lobby not to release this drug and in addition mifepristone has potent antiglucocorticoid activity which makes the compound unsuitable for meningiomas in which cerebral oedema may be controlled with dexamethasone.

More understanding of progesterone receptors and the genetic aspects of sex steroid hormone receptors and tumour heterogenity is required, and much of this work could be complementary

to research in breast cancer [10] and other hormone associated tumours. This work will not be fruitful until there is more cooperation between steroid biochemists, endocrinologists, oncologists and neurosurgeons. At present, for practical purposes, gestrinone [11], a potent antiprogesterone drug without antiglucocorticoid effects, is the best choice in treating men and postmenopausal women with inoperable meningiomas. I have four patients in whom such tumours have not grown for up to 3 years, but have also not shrunk. Gestrinone has few side-effects and can be used long-term; however, it is not the final answer. If meningiomas prove to be homogeneous in progesterone binding activity then a radiolabelled antiprogesterone drug may be the answer, but such speculation is premature until a more scientific basis for treatment is established.

C. Davis
Royal Preston Hospital
P.O. Box 66
Preston, Lancs PR2 4HT, U.K.

1. Bickerstaff ER, Small FY, Guest JA. The relapsing course of certain meningiomas in relation to pregnancy and menstruation. *J Neurol Neurosurg Psychiat* 1968, **21**, 84–91.
2. Schoenberg BS, Christine BW, Whishart JP. Nervous system neoplasms and primary malignancies of other sites: The unique association between meningiomas and breast cancer. *Neurology* 1975, **25**, 705–712.
3. Markwalder T, Markwalder RV, Zara DT. Estrogen and progesterone receptors in meningiomas: Clinicopathological correlations. *Clin Neuropharmacol* 1984, **7**, 368–374.
4. Martuza RL, Millder DC, MacLaughton DT. Estrogen and progesterone binding by cytotoxic and nuclear fractions of human meningiomas. *J Neurosurg* 1985, **62**, 750–756.
5. Kloet ER. Function of steroid receptor systems in the central nervous system. *Clin Neuropharmacol* 1984, **7**, 272–280.
6. King RB. Enlightenment aqnd confusion over steroid hormone receptors. *Nature* 1984, **312**, 701–702.
7. Davis C, Jones J, Yoshino E, *et al.* Steroid sex hormones in non-pituitary brain tumours. In: *Brain Oncology*. Leider, Martinus Nyhoff, 1987, 165–167.
8. Medkhour A, Van Rooy U, Sobel RA, Fingert MJ, Lee J, Martuza RL. Implantation of human meningiomas into the subrenal capsule of the nude mouse. A model for studies of tumour growth. *J Neurosurg* 1989, **71**, 545–550.
9. Jääskelainen J, Laasonen E, Kärkkäinen J, Haltia M. Troup H. Hormone treatment of meningiomas: Lack of response of medroxyprogesterone acetate (MPA) *Acta Neurochirurgica* 1986, **80**, 35–41.
10. Fantl V, Richards MA, Smith R *et al.* Gene amplification on chromosome band 11q13 and oestrogen receptor status in breast cancer. *Eur J Cancer* 1990, **26**, 423–428.
11. Robyn C, Delogue-Deinoeck J, Bourdoux P, Copunschi G. *Endocrine Effects of Gestrinone*. New York, Raven Press, 1989, 207–221.

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Is the Outlook Changing for Patients with Renal Cell Cancer?

THERE HAVE been radical changes in the treatment of renal cell cancer that have led clinicians to reassess their management policies for this condition. Before the mid-1980s the main treatments for metastatic renal cell cancer were hormonal and chemotherapeutic, with surgery as an option for those rare patients with solitary metastases [1]. Hormonal therapies developed from the empirical observations of the effects of orchiectomy upon renal cell cancer in hamsters. However, the initial observation that medroxyprogesterone acetate produced regression of metastatic disease in approximately 30% of patients [2] was not confirmed and the true response rate is less than 5% [3–5]. Other hormonal agents, including flutamide and tamoxifen, have been used with response rates of between 5 and 10% [6, 7]. Hormonal therapies are attractive because of their relative lack of toxicity compared with chemotherapy. Vinblastine and lomustine are probably the most effective of the agents used but the true order of response is low at less than 10%. Combinations increase toxicity but not efficacy [8–10]. Newer cytotoxic drugs have almost as little effect on the course of disease as more established therapies [11–13].

This comparative lack of response to conventional therapies has resulted in a continued search for new treatments and in this context the role of immunotherapy has been investigated with enthusiasm. The first report of the effects of the interferons in renal cell carcinoma came in 1983. Human leucocyte interferon was used to treat 19 patients, 5 of whom had partial responses [14]. Similar response rates have been seen with lymphoblastoid and recombinant interferon alpha [15, 16]. An overview of 1532 patients treated with alpha interferon showed complete response in 32 (2%) and partial response in 219 (14%) [17]. The median duration of complete response was 8 months. Several different treatment schedules have been investigated but there is no advantage with high doses of interferon and a considerable disadvantage in terms of toxicity. Beta interferon has been used in 18 patients and 2 partial responses were reported [18]. Gamma interferon has greater *in vitro* antitumour activity than alpha or beta interferon and clinical trials with this agent started optimistically. However, only 1 complete and 10 partial responses were seen in 121 patients, showing no advantage with gamma compared with alpha or beta interferon [17]. Interferons combined with chemotherapy are not synergistic [19, 20].

At the United States National Cancer Institute, a new form of treatment with interleukin 2 and lymphokine activated killer