provided information about possible confounding factors. A population-based case–control study in western Washington state found a relative risk of 1.5 (95% C.I. 1.0–2.2) [13]. The association was confined entirely to Catholic men, and the authors suggested that there might have been underreporting of vasectomy by Catholic controls. Another American case–control study was negative [14]. Jørgensen *et al.* (pp.1062–1064) suggest a mechanism by which vasectomy might possibly accelerate the growth of a testicular tumour, but there is no direct evidence to support this.

After reviewing all of the available biological and epidemiological evidence, the WHO group concluded that any causal relationship between vasectomy and the risk of cancer of the prostate or testis is unlikely. Because even a slight increase in risk would be of concern, the group made recommendations for further research. Nevertheless, it concluded that no changes in family planning policies concerning vasectomy are warranted at present.

D.C.G. Skegg
Department of Preventive and Social Medicine
University of Otago, Dunedin
New Zealand

1. Peterson HB, Huber DH, Belker AM. Vasectomy: an appraisal for the obstetrician-gynecologist. *Obstet Gynecol* 1990, 2, 568–572.
2. Alexander NJ, Wilson BJ, Patterson BD. Vasectomy: immunological effects on rhesus monkeys and men. *Fert Steril* 1974, 25, 149–156.
3. Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S. Vasectomy and the risk of prostate cancer. *Am J Epidemiol* 1990, **132**, 1051–1055.
4. Mettlin C, Natarajan N, Huben R. Vasectomy and prostate cancer risk. *Am J Epidemiol* 1990, **132**, 1056–1061.
5. Spitz MR, Fueger JJ, Babaian RJ, Newell GR. Re: "Vasectomy and the risk of prostate cancer" (letter). *Am J Epidemiol* 1991, **134**, 108–109.
6. Honda GD, Bernstein L, Ross RK, Greenland S, Gerkins V, Henderson BE. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *Br J Cancer* 1988, 57, 326–331.
7. Ross RK, Paganini-Hill A, Henderson BE. The etiology of prostate cancer: what does the epidemiology suggest? *Prostate* 1983, **4**, 333–344.
8. Sidney S. Vasectomy and the risk of prostatic cancer and benign prostatic hypertrophy. *J Urol* 1987, **138**, 795–797.
9. Sidney S, Quesenberry CP, Sadler MC, Guess HA, Lydick EG, Cattolica EV. Vasectomy and the risk of prostate cancer in a cohort of multiphasic health checkup examinees: second report. *Cancer Causes and Control* 1991, 2, 113–116.
10. Perlman JA, Spirtas R, Kelaghan J, Madans J, Cox C, Kleinman J. Re: "Vasectomy and the risk of prostate cancer" (letter). *Am J Epidemiol* 1991, **134**, 107–108.
11. Thornhill JA, Butler M, Fitzpatrick JM. Could vasectomy accelerate testicular cancer? The importance of pre-vasectomy examination. *Br J Urol* 1987, **59**, 367.
12. Cale ARJ, Farouk M, Prescott RJ, Wallace IWJ. Does vasectomy accelerate testicular tumour? Importance of testicular examinations before and after vasectomy. *Br Med J* 1990, **300**, 370.
13. Strader CH, Weiss NS, Daling JR. Vasectomy and the incidence of testicular cancer. *Am J Epidemiol* 1988, **128**, 56–63.
14. Moss AR, Osmond D, Bacchetti P, Torti FM, Gurgin V. Hormonal risk factors in testicular cancer. A case–control study. *Am J Epidemiol* 1986, **124**, 39–52.

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The Therapeutic Challenge of Gliomas

J. Gordon McVie

IN THEORY, a slow growing tumour which does not metastasise should not present a major therapeutic problem. In reality, malignant glioma answers this description and despite multidisciplinary attack remains an elusive problem. Is it over simplistic to say that it is a problem because it resides in a box? Has the fact that it occurs inside the skull got anything to do with the fact that it does not metastasise (or only very rarely)? Is there such a thing as the blood–brain barrier and is this really an acceptable excuse for the failure of chemotherapy and radiosensitisers? Whatever the answers to these questions, all would agree that a new drug which is active in this condition provides a welcome relief. One such drug is reported in the *European Journal of Cancer*, temozolomide. This short comment will review the state-of-the-art treatment of gliomas providing the back cloth against which temozolomide must be tested to assess its real value for the future.

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Inevitably, the major accent on research in the last few years has been refinement of local techniques of detection and destruction of the glioma. These have included physical treatments, immunotherapy and local instillation of cytotoxins and biological response modifiers via the carotid artery route. There is little doubt that stereotactic resection of tumours in the brain has proved a major technical advance [1]. The procedure is of particular benefit in reaching deep seated circumscript lesions but predictably unimpressive in treatment of infiltrating tumours or gliomas in essential areas of the brain. Using the same sort of stereotactic localisation, heat has been used either as a single therapeutic agent [2], or combined with interstitial brachytherapy [3]. Heat alone does produce short lived responses in localised tumours of the order of 20%. When ^{125}I seeds are implanted in addition to microwave heating, more toxicity is reported in the form of reversible seizures, increased neurological deficit and infection. 15 of 31 patients were "improved" in Sneed *et al's.* series, although the definition of improvement is not given. This is a problem area which relates to all reports of

treatment of gliomas and it is gratifying to see the present paper on temozolomide acknowledging it and proposing alternative methods of assessment of response and reporting results.

Physical disruption of the so-called blood–brain barrier which more correctly might be described as the blood–tumour barrier has been attempted by instillation of hyperosmolar mannitol in the area of a glioma immediately prior to treatment with conventional cytotoxic drugs such as methotrexate, cyclophosphamide and procarbazine [4]. Improved distribution of intra-arterially injected dyes can be achieved into the tumour area by this technique but response rates remain in the same arena as expected with conventional chemotherapy. No randomised trials are available to better define the contribution of the osmotic blood–tumour barrier interventions.

A recent review of the contribution of neutrons to the treatment of glioma [5] has concluded that there is no indication for adopting neutron treatment rather than conventional radiotherapy. Another physical approach, still in the experimental stages, is the use of lasers in combination with so-called phototherapy. Early results have been encouraging in animal experiments [6], particularly because the photosensitising drug, photofrin, is a particularly poor mixture of substances which hopefully will be out-moded by the development of new chemicals. Photofrin has been shown after intraperitoneal injection in rats to concentrate in brain tumour up to 96 h after installation, thus allowing subsequent intervention with steriotactic directed laser beams. Eventual toxicity of such treatment has yet to be mapped out, but there is reason to believe that because of the relative selectivity of retention of photosensitising agents within cancer cells and, in theory, the selective death of these cells after interaction of laser light this avenue of research deserves rapid clinical evaluation.

Locally directed immunotherapy has been reported using a number of different approaches [7], e.g. at the National Institute of Health, injected lymphokine-activated killer (LAK) cells and interleukin-2 have been instilled into human gliomas via a reservoir catheter system. All patients suffered increased neurological side-effects, perhaps due to cerebral oedema and only 1 out of 9 showed any shrinkage of tumour on computed tomography (CT) scan. An Italian group injected radiolabelled monoclonal antibody raised against tenascin which is expressed on stromal cells of malignant gliomas but not on normal brain tissue. In a phase I clinical trial [8], 10 patients were treated with mean radiation dose of 551.3 MBq of ^{131}I associated with around 2 mg of antibody. There was no noticeable toxicity in any patient and several patients were able to receive multiple injections. 2 patients enjoyed a partial remission as detected on CT or nuclear magnetic resonance scan; 1 patient had a complete remission which lasted several months. Intravenously administered radiolabelled antibodies would be much more practical and here too preliminary clinical evidence suggests that localisation at least of the antibody can be achieved in 18 of 27 patients [9]. The antibody labelled was against epidermal growth factor receptor or placental alkaline phosphatase and these antibodies were labelled with ^{123}I. Several patients were also treated with ^{131}I-labelled antibody delivered via the internal carotid artery and occasional clinical responses were reported. Importantly with the localised monoclonal antibody therapy, toxicity has been limited to that associated with the intervention, in marked contrast to the interleukin/ LAK cell studies [10]; sustained meaningful clinical remissions, however, have yet to be reported.

Intra-arterial injection of cytotoxics is not an easy matter and must be regarded as very experimental because the complications associated with the catheterisation of the internal carotid artery and its branches are aggravated by the direct toxicity of some of the agents instilled. Cisplatin is a prime example [11], where optic neuropathy is a common side-effect. It is not clear that carboplatin is any safer, nor are the nitrosoureas to be recommended. A randomised trial of intra-arterial vs. intravenous 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) with or without intravenous 5-fluorouracil in gliomas was recently reported by Shapiro [12]. This is one of the rare examples of a phase III trial addressing a pharmacological question and 505 patients were randomised in it. Survival for the intravenous and intra-arterial BCNU patients were identical and indeed for anaplastic astrocytoma patients the intra-arterial patients did worse. Neuropathology reports indicated that the intra-arterial BCNU had produced necrosis of white matter and the authors recommended discontinuing the use of this drug given in this fashion [10]. A short report of intra-arterial tumour necrosis factor alpha from Japan has reported safety in this technique in 10 patients. Some patients showed improvement of neurological symptoms even when CT scans showed no improvement [13].

The failure of various drug regimes and radiation, indeed, even when delivered on to the doormat of the brain tumour has stimulated scientific interest in the basis of this resistance. One of the reasons that temozolomide may work in glioma is the variation of alkyltransferase repair capacity of glioma cells. This has also been recognised by Levin and Prados [14], who tried to manipulate existing cytotoxics such as fluorouracil, hydroxyurea timed after lomustine, thioguanine, dibromodulcitol and procarbazine which were calculated to reduce alkyltransferase repair. This empirical combination therapy has provided some interesting preliminary results with 60% of patients with glioblastoma multiforme achieving either a partial response or stable disease for 8 or 9 months. This does involve, however, the use of six drugs with all the pragmatic complications involved with that and clearly a simpler solution would be more valuable. Dolan has shown at least *in vitro* and nude mice experiments that human gliomas can be made more sensitive to nitrosourea by administration of O^6-benzylguanine [15]. This could be important for selection of patients who would eventually respond to temozolomide plus or minus drugs which lower alkyltransferase such as O^6-benzylguanine, because Mineura *et al.* have shown [16] in a study of 17 gliomas from humans that 10 patients had low levels of O^6-alkylguanine DNA alkyltransferase (less than 100 fmol/mg/h) and that there was a significant difference between activity of the enzyme between gliomas and non-glial tumours.

Turning briefly to radio resistance it is worth reporting that a new approach to oxygenation of brain tumours has been reported using fluosol. This is a small study of patients treated for brain tumours and further evaluation is awaited with interest [17], particularly if vascular manipulation could be achieved with a substance such as nicotinamide.

State-of-the-art treatment of patients presenting with an inoperable glioma is clearly radiation and as none of the leads discussed earlier to enhance local therapy show any clear advantage, the question is should the radiotherapy be followed by adjuvant treatment? A large study from the Brain Tumour Cooperative Study Group randomised 603 patients to receive conventional radiotherapy or hyperfractionated radiotherapy (twice a day) with addition of BCNU, streptozocin and/or misonidazole. There were no differences in the overall survival for the various groups, therefore, the conclusion was that conventional radiotherapy and a nitrosourea is an appropriate

state-of-the-art treatment [18]. There was no arm with radiotherapy alone. Shapiro then reported a large trial which also adopted BCNU after radiation therapy as standard treatment and compared that to addition of procarbazine or hydroxyurea with the standard therapy. No advance was gained by the addition of the extra chemotherapy. A second randomisation to whole brain radiotherapy vs. coned-down therapy showed that the coned-down option was as effective as full whole brain radiation therapy [19].

Adjuvant studies employing other drugs such as dibromodulcitol, dianhydrogalactitol, procarbazine, teniposide, dacarbazine (DTIC) and cisplatin are inconclusive [20]. A number of variations on the cocktail theme have been tested in phase II and very rarely in phase III trials, none springing out as a clear state-of-the-art adjuvant therapy. Lately, however, the Northern Cooperative Oncology Group have reported on the mature results of a trial comparing BCNU in an adjuvant situation with *N*-(2-chloroethyl)-*N*^{1}-cyclohexyl-*N*-nitrosourea (CCNU), procarbazine and vincristine [21]. There are two comments about this; firstly, the choice of standard arm was again BCNU which has never been adequately established by any single trial or any meta-analysis as adding more than a few weeks at best to survival. The second point is that there was a slight advantage for the combination of the three drugs over BCNU alone and this is threatening to become the standard state-of-the-art adjuvant treatment for adult glioma in North America. There remains some healthy scepticism in Europe, however, and it is likely to be acceptable that a new drug such as temozolomide might be added to radiotherapy and compared to radiotherapy alone in a large randomised trial.

Reports of other new active agents exist only in the form of phase II studies. The problems about these reports is that they almost always forget to take account of prognostic factors which are generally agreed in this as in many other solid tumours to influence the outcome of a trial by selection bias. Young age, history of epileptic fits, high performance status and successful removal of the majority of tumour by surgery have been reported by the Medical Research Council (MRC) as predicting for better survival. These factors are generally borne out by other large series [22]. The MRC now propose a prognostic index which should split patients into groups according to their prognosis with 2-year survival rates varying between 1 and 32%. This is important not only for phase II trials, but for eventual stratification in phase III trials. Of the new agents that have been reported most have been disappointing, such as spirogermanium and vindesine [23], ranomustine [24], liposomal platinum [25], homoharringtonine [26] and intra-arterial HECNU and ACNU [27, 28]. Lonidamine may have some activity and is going on to phase III trial [29] and a re-evaluation of procarbazine has been recently reported with "response + stabilisation rate" (whatever that is) of 27% for patients with glioblastoma multiforme, and 28% for anaplastic gliomas [30].

Mention has been made above about the heterogeneity of reporting of response. A variety of proposals have been made recently ranging from strict application of usual measurement criteria based on CT or magnetic resonance imaging (MRI) interpreted in the light of steroid use and neurological findings [31] through volumetric measurement on CT-scanning [32, 33] to NMR spectroscopy [34] and single photon emission CT (SPECT) scanning with dual-isotopes (201) thallium and (99 m) technetium-HMPAO [35].

Temozolomide has now survived phase I [36] and the first responses against patients with high grade glioma and a couple of case reports of mycosis fungoides and melanoma have been published [37]. The first phase II evaluation confirms the activity against glioma which is remarkable in terms of the high activity in patients who have failed conventional therapy including surgery, radiation therapy and often chemotherapy. The description of responses is clear in this paper and raises the dilemmas of assignment of a patient who has a complete neurological response, but no alteration on CT scan. The assessment of temozolomide in glioma must surely be by randomised phase II or phase III trial and the preference would be to compare this in addition to radiation therapy, with radiation therapy alone. It is possible that North American trials may compare radiation and temozolomide with radiation and BCNU or radiation and CCNU vincristine and procarbazine. Of the single agents tested in the last 10 years temozolomide clearly stands out as the most promising and its further progress is watched with interest.

J.G. McVie
Scientific Department
Cancer Research Campaign
Cambridge House
6–10 Cambridge Terrace
Regents Park
London NW1 4JL
U.K.

1. Camacho A, Kelly PJ. Volumetric stereotactic resection of superficial and deep seated intraaxial brain lesion. *Acta Neurochir Suppl Wien* 1992, **54**, 83–88.
2. Kida Y, Mori Y, Hattori T, Kobayashi T. Interstitial hyperthermia of malignant gliomas with implant heating system. *No Shinkei Geka* 1990, **18**, 1007–1014.
3. Sneed PK, Gutin PH, Phillips TL, *et al.* Interstitial brachytherapy and hyperthermia for recurrent malignant brain tumours (meeting abstracts). Thirty-eighth Annual Meeting of the Radiation Research Society and Tenth Annual Meeting of the North American Hyperthermia Group. 7–12 April 1990, LA, New Orleans, p.7.
4. Gumerlock MK, Belshe BD, Madsen R, Watts C. Osmotic blood–brain barrier disruption and chemotherapy in the treatment of high grade malignant glioma: Patient series and literature review. *J Neuro Oncol* 1992, **12**, 33–46.
5. Griffin BR, Berger MS, Laramore GE, *et al.* Neutron radiotherapy for malignant gliomas. *Am J Clin Oncol* 1989, **12**, 311–315.
6. Ji Y, Walstad DL, Brown JT, Powers SK. Relation between polyporphyrin distribution and blood brain barrier changes in the rat glioma model. *Lasers Surg Med* 1992, **12**, 174–179.
7. Barba D, Saris SC, Holder C, Rosenberg SA, Oldfield EH. Intratumoral LAK cell and interleukin-2 therapy of human gliomas. *J Neurosurg* 1989, **70**, 175–182.
8. Riva P, Arista A, Sturiale C, *et al.* Treatment of intracranial human glioblastoma by direct intratumoral administration of (131) I-labelled anti-tenascin monoclonal antibody BC-2. *Int J Cancer* 1992, **51**, 7–13.
9. Kalofonos HP, Pawlikowska TR, Hemingway A, *et al.* Antibody guided diagnosis and therapy of brain gliomas using radiolabelled monoclonal antibodies against epidermal growth factor receptor and placental alkaline phosphatase. *J Nucl Med* 1989, **30**, 1636–1645.
10. Merchant RE, Ellison MD, Young HF. Immunotherapy for malignant glioma using human recombinant interleukin-2 and activated autologous lymphocytes: A review of pre-clinical and clinical investigations. *J Neurooncol* 1990, **8**, 173–188.
11. Dropcho EJ, Rosenfeld SS, Morawetz RB, *et al.* Preradiation intracarotid cisplatin treatment of newly diagnosed anaplastic gliomas. *J Clin Oncol* 1992, **10**, 452–458.
12. Shapiro WR, Green SB, Burger PC, *et al.* A randomized comparison of intra-arterial versus intravenous BCNU, with or without intravenous 5-fluorouracil, for newly diagnosed paitents with malignant glioma. *J Neurosurg* 1992, **76**, 772–781.
13. Yoshida J, Wakabayashi T, Mizuno M, *et al.* Clinical effect of

intra-arterial tumor necrosis factor-alpha for malignant glioma. *J Neurosurg* 1992, **77**, 78–83.
14. Levin VA, Prados MD. Treatment of recurrent gliomas and metastatic brain tumors with a polydrug protocol designed to combat nitrosourea resistance. *J Clin Oncol* 1993, **10**, 766–771.
15. Dolan ME, Stine L, Mitchell RB, Moschel RC, Pegg AE. Modulation of mammalian O (6)-alkylguanine-DNA alkyltransferase *in vivo* by 0 (6)-benzylguanine and its effect on the sensitivity of a human glioma tumor to 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea. *Cancer Commun* 1990, **2**, 371–377.
16. Mineura K, Isumi I, Watanable K, Kowada M. 0(6)-alkylguanine-DNA alkyltransferase activity in human brain tumors. *Tohoku J Exp Med* 1991, **165**, 223–228.
17. Evans RG, Kimler BF, Morantz RA, *et al.* A phase I/II study of the use of Fluosol registered as an adjuvant to radiation therapy in the treatment of primary high-grade brain tumours. *Int J Radiat Oncol Biol Phys* 1990, **19**, 415–420.
18. Deutsch M, Green SB, Strike TA, *et al.* Results of a randomized trial comparing BCNU plus radiotherapy in the postoperative treatment of malignant glioma. *Int J Radiat Oncol Biol Phys* 1989, **16**, 1389–1396.
19. Shapiro WR, Green SB, Burger PC, *et al.* Randomized trial of three chemotherapy regimens and two radiotherapy regimens in postoperative treatment of malignant glioma. *J Neurosurg* 1989, **71**, 1–9.
20. Stewart DJ. The role of chemotherapy in the treatment of gliomas in adults. *Cancer Treat Rev* 1989, **16**, 129–160.
21. Levin VA, Silver P, Hannigan, Wara WM, Gutin PH, Davis RL, Wilson CB. Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. *Int J Radiat Oncol Biol Phys* 1990, **18**, 321–324.
22. Anonymous. Prognostic factors for high-grade malignant glioma: Development of a prognostic index. A report of the Medical Research Council brain tumour working party. *J Neurooncol* 1990, **9**, 47–55.
23. Alavi JB, Schoenfeld D, Skeel RT, Kirkwood R, Tsung L, Marsh JC. Phase II trial of spirogermanium and vindesine in malignant glioma. *Am J Clin Oncol* 1989, **12**, 8–10.
24. Tonn JC, Schonmayr R, Kraemer HP. Sensitivity of human malignant intracranial tumours against MCNU in vitro in comparison to ACNU and BCNU. *J Neurooncol* 1990, **8**, 41–45.
25. Shibata S, Ochi A, Mori K. Liposomes as carriers of cisplatin into the central nervous system: Experiments with 91 gliomas in rats. *Neurol Med Chir Tokyo* 1990, **30**, 242–245.
26. Feun LG, Savaraj N, Landy H, Levin H, Lampidis T. Phase II study of homoharringtonine in patients with recurrent primary malignant central nervous system tumours. *J Neurooncol* 1990, **9**, 159–163.
27. Poisson M, Chiras J, Fauchon F, Debussche C, Delattre JY. Treatment of malignant recurrent glioma by intra-arterial infra-ophthalmic infusion of HECNU 1-(2-chloreothy)-1-nitroso-3-(2-hydroxyethyl) urea: A phase II study. *J Neurooncol*, 1990, **8**, 255–262
28. Piana C, Pasquini U, De Nicole M, *et al.* Intraarterial chemotherapy with ACNU (nimustine) in the treatment of gliomas. *Riv Neuroradiologia* 1990, **3/2**, 153–163.
29. Carapella CM, Paggi MG, Cattani F, *et al.* The potential role of lonidamine (LND) in the treatment of malignant glioma. Phase II study. *J Neurooncol* 1989, **7**, 103–108.
30. Rodrigues LA, Prados M, Silver P, Levin VA. Reevaluation of procarbazine for the treatment of recurrent malignant central nervous system tumours. *Cancer* 1989, **64**, 2420–2423.
31. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990, **8**, 1277–1280.
32. Chisholm RA, Stenning S, Hawkins TD. The accuracy of volumetric measurement of high-grade gliomas. *Clin Radiol* 1989, **40**, 17–21.
33. Riding MD, Gerig LH, Girard A, Stewart D. Multivolumetric analysis of CT-scans on patients with glioma. *Acta Radiol Suppl Stockh* 1986, **369**, 216–219.
34. Glickson JD. Clinical NMR spectroscopy of tumors. Current status and future directions. *Invest Radiol* 1989, **24**, 1011–1016.
35. Schwartz RB, Carvalho PA, Alexander E III, Loeffler JS, Folkerth R, Holman BL. Radiation necrosis vs high-grade recurrent glioma: differentiation by using dual-isotope SPECT with (201)Tl and (99 m)Tc-HMPAO. *Am J Roentgenol* 1992, **158**, 399–404.
36. Newlands ES, Blackledge GRP, Slack JA, *et al.* Phase I trial of temozolomide (CCRG 81045: M and B 39831: NSC 362856). *Br J Cancer* 1992, **65**, 287–291.
37. O'Reilly SM, Newlands ES, Stevens MF, Brampton MH, Slack JA, Rustin GJ. Temozolomide (CCRG 81045, M and B 39831, NSC 362856): a new oral cytotoxic agent with activity against melanoma, mycosis fungoides and high-grade glioma (meeting abstract). *Proc Am Assoc Cancer Res* 1992, **33**, A1267.