INT. J. HYPERTHERMIA, 1989, VOL. 5, NO. 6, 683–696

Cerebral blood flow response to the tissue temperature in tumour and brain tissues

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(Received 7 September 1988; revised version received 7 February 1989; accepted 10 February 1989)

The response of regional-cerebral blood flow (rCBF) to change in the tissue temperature was studied using normal and tumour-bearing monkeys. The local brain was selectively heated by the external microwave irradiation, while the body was kept hypothermic (30·1 ± 0·1 °C, mean ± standard error) by immersion in a cold water bath. The rCBF in brain and/or tumour tissues was sequentially measured by inhalation hydrogen clearance method. In the normal animal study ($n=7$), rCBF changed in response to the tissue temperatures over a range of 29·4–40·7 °C with a constant rate 15·2% per degree Celsius change. Similarly, rCBF in the tumour-bearing animals ($n=7$) changed proportionately with change in the tissue temperatures over a range of 28·4–42·5 °C in tumour and 27·6–41·8 °C in brain tissue. The rate in rCBF change per degree Celsius was 6·5% for tumour, which was significantly smaller than that for brain tissue (13·5%) ($P<0·01$). These results indicated that rCBF can be controlled by the defined application of selective heating with temperatures ranging from shallow hypothermia to modest hyperthermia. Vascular response to temperatures in the tumour and brain tissues may play a significant role in the application of heat to brain tumour treatment.

Key words: blood flow, brain, brain tumour, hyperthermia, hypothermia.

1. Introduction

The current therapy provides a median survival period of approximately 1 year for malignant gliomas (Wilson *et al.* 1982), or 5-year survival rates of 18–19·9% for anaplastic astrocytoma and 0–7·2% for glioblastoma multiforme, respectively (Sheline 1975, Committee of Brain Tumour Registry in Japan 1987). Because brain tumours are resistant to other treatments, thermotherapy can be a new addition to a multi-modality treatment for brain tumour.

With a simple hyperthermia for tumour control, elevation in temperature is limited to 42–43 °C or approximately a 5–6 °C temperature increase above baseline normothermia because of heat intolerance of normal brain tissue (Harris *et al.* 1962, Lyons *et al.* 1986). However, selective tumour heating applied with generalized hypothermia facilitates a large temperature difference between tumour and the surrounding normal tissues (Popovic and Masironi 1965, Nishimoto *et al.* 1978). This may enhance tumour response to heat, either alone or in conjunction with ionizing radiation and chemotherapeutic drugs. Additionally, hypothermically kept normal or pathological brain may be protected from a variety of insults such as anoxic damage (Dempsey *et al.* 1987), drug toxicity (Selker *et al.* 1979, Satoh *et al.* 1985), and radiation damage (Willett *et al.* 1987) via the decreased cerebral metabolism (Popovic and Popovic 1969).

The cerebral blood flow (CBF) plays an important role in heating the brain with regard to tissue metabolism (Smith and Wollman 1972) and tissue temperature distribution (Song

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1983, Emami and Song 1984). For the application of heat to brain tumour treatment, therefore, it is important to know the response of CBF in changing the tissue temperature. In the present study, regional-cerebral blood flow (rCBF) in normal and tumour-bearing monkeys was measured during selective brain heating under generalized hypothermia. The response of rCBF to the tissue temperature was determined within a specific tissue temperature range between shallow hypothermia and modest hyperthermia.

2. Materials and methods

2.1. *Animals*

Adult Japanese monkeys (*Macacae fuscatae fuscatae*), supplied by the Animal Center for Medical Research of Okayama University Medical School, were used for this study. For the normal animal study seven male animals weighing 9·0–12·0 kg, or 11·0±0·4 kg (mean ± standard error of mean, SE, $n=7$) were employed. Ages were uncertain but estimated to be between 10 and 14 years old based on their body weights (Kusama and Mabuchi 1970).

A brain tumour was induced in an animal by intracerebral inoculation of chick embryo fibroblasts (CEF) that were producing Schmidt-Ruppin strain (subgroup D) of Rous sarcoma virus (RSV) as described previously (Tabuchi *et al.* 1985, Satoh *et al.* 1986). Briefly, a small hole (2 mm in diameter) was made in the right frontal region of the skull under general anaesthesia with i.m. ketamine hydochloride (10 mg/kg). The RSV was infected to the 2nd–3rd cultures of CEF prepared from chick embryos in virus-free fertile eggs. Approximately 4×10^7 cells of RSV-producing CEF suspended in 0·3 ml volume of phosphate-buffered saline were inoculated 1 cm below the brain surface through the dura mater using a 21-gauge needle. Three to six weeks after inoculation a single tumour mass developed at the site of inoculation in more than half of the animals. One-third of tumour-bearing animals were killed by tumour progression. However, the remaining animals bearing relatively small brain tumours survived in the subsequent period with minimum enlargement in tumour size. Except for slight hemiparesis or occasional convulsive episodes, no abnormalities were noted in these animals. An induced tumour was detected in the frontal-white matter region by the computed tomography (figure 1).

For the tumour-bearing animal study, seven tumour-bearing monkeys surviving in the chronic course were employed. There were four females and three males, weighing 4·0–12·5 kg (7·5±1·0 kg, $n=7$). Ages of animals varied from 3 to 12 years (5·9±1·1 years old, $n=7$). Tumour ages in those animals, described as days after inoculation of RSV infected CEF, were 47–283 days (199·3±34·0 days, $n=7$). Size of tumours was small, with the maximum diameter 7–12 mm (9·2±0·9 mm, $n=7$). Each tumour (fibrosarcoma) appeared relatively homogeneous and well-demarcated from the surrounding cerebral parenchyma with minimal peritumoral oedema (figure 2).

2.2. *Measurement of regional-cerebral blood flow (rCBF)*

The rCBF was repeatedly measured at the same tissue site in brain by means of inhalation hydrogen clearance method (Doyle *et al.* 1975). After 3–5 min inhalation of 7–10% hydrogen gas, micro-current produced in an electrode (0·15 mm o.d.) was polarographically amplified (PHG-203, Unique Medical Co., Tokyo, Japan) and was recorded on a polygraph. A clearance curve was manually plotted on semi-logarithmic chart with respect to time. The rCBF (ml/100 g per min) was then calculated by the following equation:

$$\mathrm{rCBF}=\lambda\ 0\cdot693/T_{1/2}\times100$$

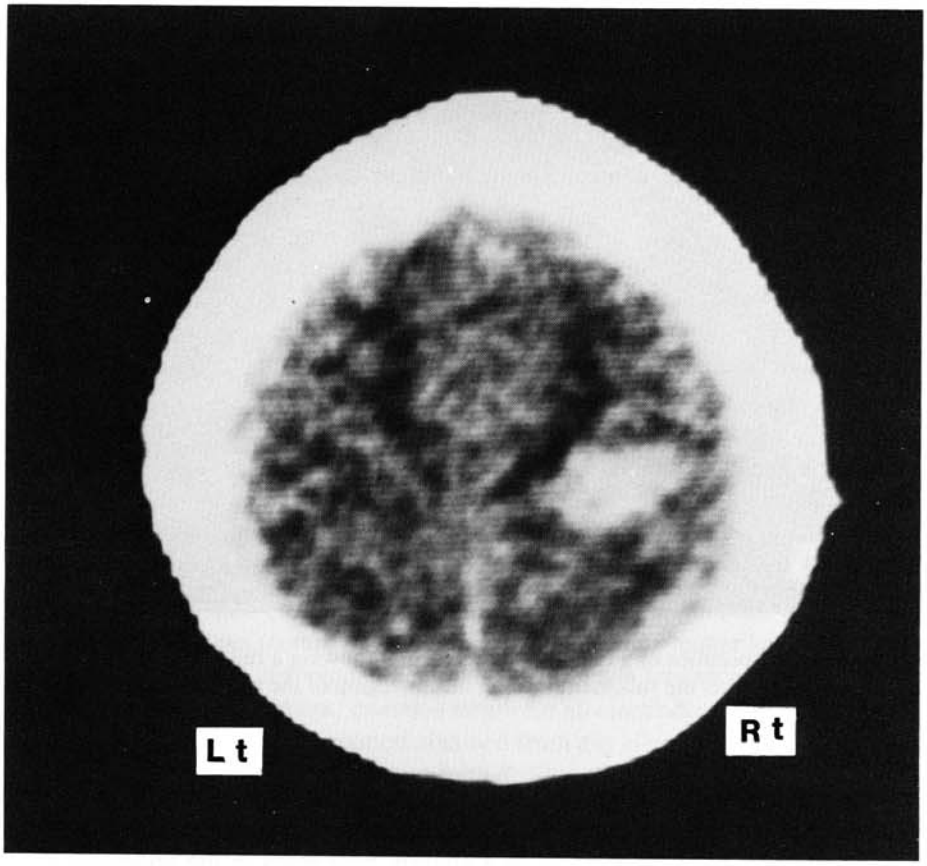

Figure 1. Contrast-enhanced CT image of a tumour-bearing animal 220 days after inoculation of Rous sarcoma virus-infected chick embryo fibroblasts in brain. Tumour mass is demonstrated as a well-demarcated high-density area in the right frontal–white matter region. Note the minimal peritumoral oedema without shifted midline.

where λ is the blood–brain partition coefficient for hydrogen gas ($\lambda=1$), $T_{1/2}$ is the time in minutes required for the clearance curve to diminish one-half, and 100 is for normalizing of blood flow to 100 g tissue weight.

2.3. *General experimental procedures*

Each animal was premedicated with i.m. atropine sulphate (0·015 mg/kg) and was anaesthetized with i.m. ketamine hydrochloride (20 mg/kg) and pancuronium bromide (0·4 mg/kg). Respiration was artificially controlled by a respirator to maintain arterial carbon dioxide concentration throughout the experiment. Arterial blood gases including PaO_2, $PaCO_2$ and pH were periodically measured by a pH/blood gas system (Model 165/2, Corning Co., Conneticut, U.S.A.). Blood pressure was continuously monitored in the abdominal aorta by a pressure transducer. Continuous infusion of Ringer's solution (1–2 ml/kg per hour) was used to maintain the body fluid.

Each animal's head was positioned on the head-holder instrument. Before heating the brain, generalized hypothermia (hypothermic baseline) with the oesophageal temperature of $30\cdot1 \pm 0\cdot1$°C (mean ± SE, $n=14$) was induced by immersion of the whole body, except head and neck, into a cold (4–20°C) water bath for 1·5–2 h (figure 3). The scalp was shaved and incised, and then fronto-temporo-parietal craniectomy (approximately 3×4 cm

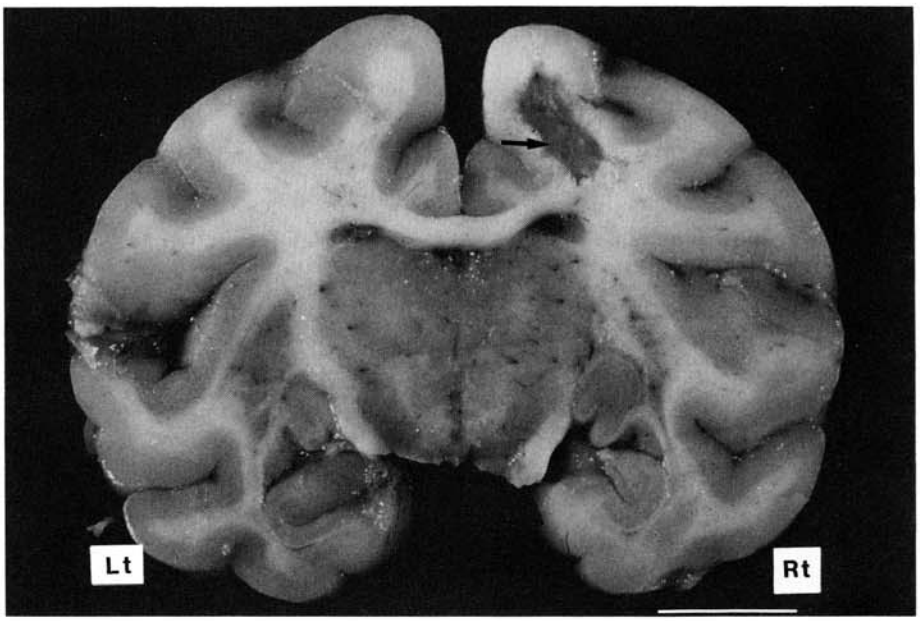

Figure 2. Autopsy specimen of a tumour-bearing animal showing a relatively small brain tumour (arrow) localized in the subcortical–white matter region of the right frontal lobe. Bar shows 1 cm.

in size) was performed on both sides of the skull. The dura mater was extensively incised and was turned over. In case of a tumour-bearing animal, the tumour was not observed at the brain surface, but was palpable as a slightly hard mass in the underlining brain.

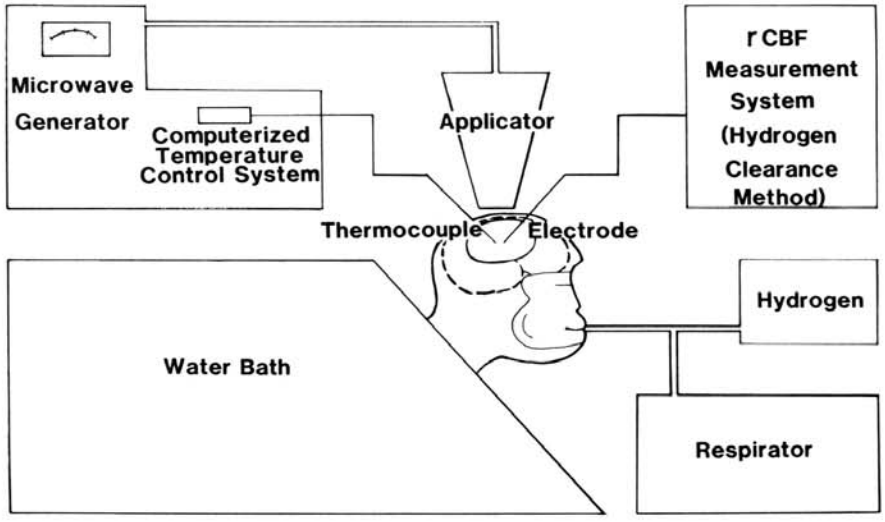

Figure 3. Schema showing experimental set-up for selective brain heating under generalized hypothermia. A unilateral hemisphere is heated by means of external microwave irradiation, while the whole body was kept hypothermic by immersion in a cold water bath. Thermocouple temperature sensing probes are used for controlling generator power and for monitoring tissue temperatures. The electrodes are used for rCBF measurement by the inhalation hydrogen clearance method.

2.4. *Selective brain heating under generalized hypothermia*

The unilateral hemisphere of each hypothermic normal or tumour-bearing animal was locally heated from the surface (figures 3 and 4), by means of 2450 MHz microwave heating system (HMS-010, Aloka Co., Tokyo, Japan). A single external helical-type microwave applicator (HTA-2450, Aloka Co., Tokyo, Japan), 16×30 cm in size, was placed 4–8 cm above the brain surface to obtain the optimal match between the generator/applicator and tissue loads. A Teflon-coated 0·7 mm, single copper-constantan thermocouple probe (Type T, Omega Engineering Inc., U.S.A.) was used for measuring the tissue temperature. The generator power (150 W maximum) was computer-controlled by feedback of the tissue temperature at 30 s intervals. All time and temperature information was automatically recorded by an eight-channel digital thermometric unit.

Two or three electrodes for rCBF measurement were directly implanted approximately 1 cm deep in the centre of the tumour mass (tumour) and/or in the white matter of the ipsilateral brain tissue (brain). Thermocouple probes were implanted in the immediate vicinity ($r \leq 0 \cdot 5$ cm) of each electrode to obtain the tissue temperature. The rCBF and tissue temperature were measured at several different times during the course of heating, including hypothermic baseline, mid-heating, heated peak, mid-cooling, and terminal hypothermia. An aluminium-foil screen was employed for shielding microwave irradiation to the contralateral side (figure 4). The rCBF and temperature of the contralateral hypothermic hemispheres (control) were measured in the white matter approximately 1 cm below the surface at the corresponding times during each treatment.

At the end of each experiment, insertion length for all electrodes and temperature probes was carefully re-measured. Information obtained from any electrode or probe moved more than 1 mm from implanted length was omitted.

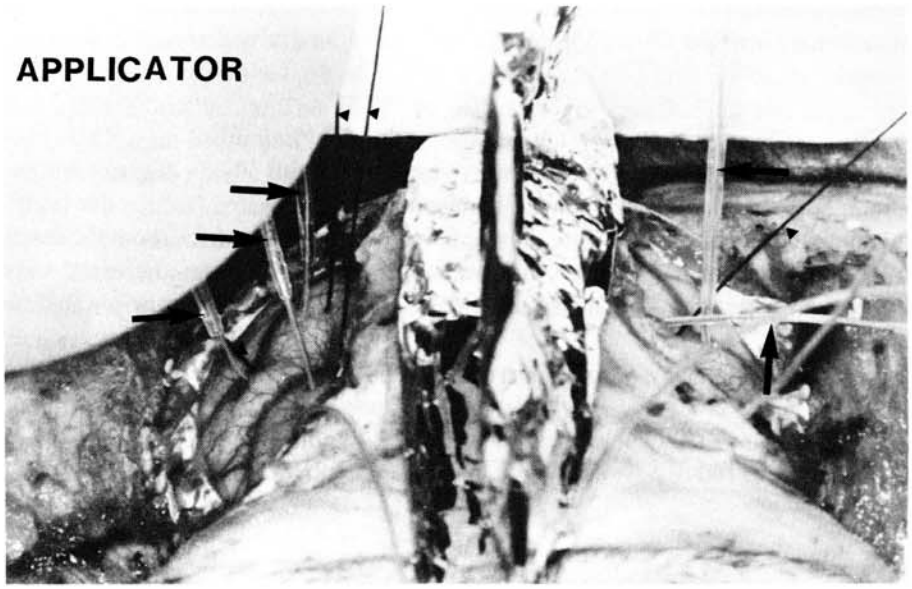

Figure 4. Close-up, showing cerebral hemispheres after extensive bilateral craniectomy. The unilateral (viewer's left) hemisphere is heated by an external microwave applicator (upper corner). An aluminium-foil screen placed on the mid-line of the skull is used to prevent heating in the contralateral (viewer's right) hemisphere. Temperature-sensing probes for measuring the tissue temperature (arrows) and electrodes for measuring rCBF (arrowheads) are shown.

2.5. *Data analysis*

In the comparison of rCBF for several tissue temperature conditions the difference in mean rCBF values was tested for significance using Student's *t*-test or paired *t*-test (two-tailed). In order to reduce the influences of inhomogeneity in the brain tissue temperature and variation in rCBF between tissue sites and animals, results were further analyzed as the relative quantification of rCBF change (rCBF rate, %) with respect to the temperature difference from hypothermic baseline (ΔT, °C) in the identical tissue site. The rCBF rate was calculated from the following equation:

$$\text{rCBF rate } (\%) = \text{rCBF}(\Delta T)/\text{rCBF}_{(\text{Baseline})} \times 100$$

where rCBF (ΔT) is rCBF at temperature with ΔT, $\text{rCBF}_{(\text{Baseline})}$ is rCBF at a hypothermic baseline, and 100 is for normalizing to percentage. Tests for correlation between rCBF rate and ΔT for each different tissue category were made using a linear regression analysis applied to the following relationships:

$$Y = AX + B$$

where Y is rCBF rate (%); and X is ΔT (°C); A and B are best-fit coefficients. The linear regression coefficients (A) for each tissue category were further tested for significance of the slope in each treatment groups (Zar 1974).

3. Results

3.1. *Physiological parameters in hypothermic baseline*

Mean values for the oesophageal temperature, arterial blood pressure, pH, and blood gas parameters in hypothermic baseline for 14 animals are given in table 1. Each animal showed an arterial blood pressure of 94 mmHg or higher, a PaO_2 above 89.4 torr, and a $PaCO_2$ between 31·4 and 40·9 torr for generalized hypothermia with an oesophageal temperature of 30·1 ± 0·1°C ($n = 14$). Arterial carbon dioxide concentration varied between animals, but a variation of ≤ 15% for the individual animals in repeated samples was maintained.

3.2. *rCBF response to the tissue temperature in normal animals*

By means of externally applied microwave irradiation with 30–80 W generator power, temperature in the irradiated (heated) hemisphere was elevated, while the body and contralateral brain temperatures generally remained hypothermic throughout the treatment (table 2). It was difficult, however, to obtain uniform heating over the entire exposed hemisphere by microwave irradiation. There were 2–3°C temperature variations in different

Table 1. Temperatures, blood pressure, and blood gas data at hypothermic baseline in normal and tumour-bearing animals.

	Normal animals		Tumour-bearing animals	
No. of animals	7		7	
Parameters	Mean	SE	Mean	SE
Oesophageal temperature (°C)	30·0	0·3	30·3	0·1
Arterial pressure (mmHg)	116·9	5·2	124·9	6·7
Blood pH	7·419	0·026	7·411	0·017
PaO_2 (torr)	136·7	6·0	102·9	6·0
$PaCO_2$ (torr)	34·8	1·4	33·3	0·3

SE = Standard error of mean.
Blood gases and pH were measured after correction at a temperature of 37°C.

Table 2. Tissue temperature and corresponding rCBF measured in normal animals during selective brain heating under generalized hypothermia.

Time course	Normal brains				Controls			
	No.	Min.	Max.	Mean ± SE	No.	Min.	Max.	Mean ± SE
Hypothermic baseline								
Temp.	11	29·7	31·0	30·3 ±0·1	6	29·1	31·0	30·1 ±0·3
rCBF	11	8·06	23·90	15·64 ± 1·43	6	7·97	32·23	21·64 ± 4·44
Mid-heating								
Temp.	7	33·5	35·9	34·9 ±0·4†	4	29·7	32·3	31·2 ±0·6*
rCBF	7	16·90	34·65	26·26 ± 3·51†	4	11·75	38·50	20·06 ± 6·31*
Heated peak								
Temp.	11	36·6	40·7	38·1 ±0·5‡	6	30·6	32·7	31·7 ±0·4‡
rCBF	11	14·29	46·29	34·52 ± 2·89‡	6	9·43	34·30	21·96 ± 4·38*
Terminal hypothermia								
Temp.	11	29·4	32·3	30·9 ±0·4*	6	29·6	31·0	30·4 ±0·2*
rCBF	11	8·38	25·48	17·78 ± 2·04*	6	8·56	34·65	22·20 ± 4·75*

Normal brains: heated hemispheres of the normal animals; Controls: contralateral hypothermic hemispheres of the normal animals; Temp: temperature of the brain tissue (°C); rCBF: regional cerebral blood flow (ml/100 g per min); No.: number of sites for measurement; Min.: minimum value obtained in each time course; Max.: maximum value obtained in each time course.

*No significant difference from baseline for paired *t*-test ($P > 0·1$).

Significantly different from baseline for paired *t*-test ($P < 0·01$†, $P < 0·001$‡).

parts of the brain in each animal. Because of the influence of electromagnetic field on a metal electrode, the polarogram for each hydrogen clearance curve showed minor electrical noise. The above phenomenon was unchanged with constant power for each rCBF measurement, so that it was possible to identify the clearance curve on the polarogram.

The tissue temperature and rCBF were measured 9·7 ± 0·3 mm (mean ± SE, $n = 17$) and 10·7 ± 0·5 mm below the brain surface, respectively. With hypothermic baseline, rCBF for brain showed 15·64 ± 1·43 ml/100 g per min ($n = 11$) at the tissue temperature of 30·3 ± 0·1°C (table 2). The rCBF increased to 26·26 ± 3·5 ml/100 g per min at 34·9 ± 0·4°C (mid-heating, $P < 0·003$), and to 34·52 ± 2·89 ml/100 g per min at 38·1 ± 0·5°C (heated peak, $P < 0·001$). After cooling down to terminal hypothermia, rCBF (17·78 ± 2·04 ml/100 g per min) was not different from hypothermic baseline ($P > 0·1$). Because of an insufficient shielding of microwave irradiation, the tissue temperature in the contralateral hypothermic hemisphere (control) fluctuated between 30·1 and 31·7°C. The rCBF in the control, however, showed similar value to hypothermic baseline throughout the experiment ($P > 0·1$).

Scatter plots of 29 repeated measurements in 11 different tissue sites of heated brains demonstrated a general positive correlation between rCBF rate and ΔT (figure 5). The results of linear regression testing of the correlations between rCBF rate (Y) and ΔT (X) revealed a regression line of $Y = 15·2X + 101·7$ ($R = 0·925$, $P < 0·001$) within a ΔT range of −0·8 to 10·6°C.

3.3. *rCBF response to the tissue temperature in tumour-bearing animals*

The tissue temperatures were measured 7·2 ± 0·7 mm ($n = 10$) and 8·3 ± 0·9 mm ($n = 6$) below the surface for the tumour and heated brain, respectively. The tumour blood flow was measured at 8·4 ± 0·9 mm from the brain surface, and rCBF was measured at 8·4 ± 0·8 mm (table 3). There were certain differences in rCBF measured in hypothermic baseline between the tumour (24·65 ± 2·41 ml/100 g per min) and brain

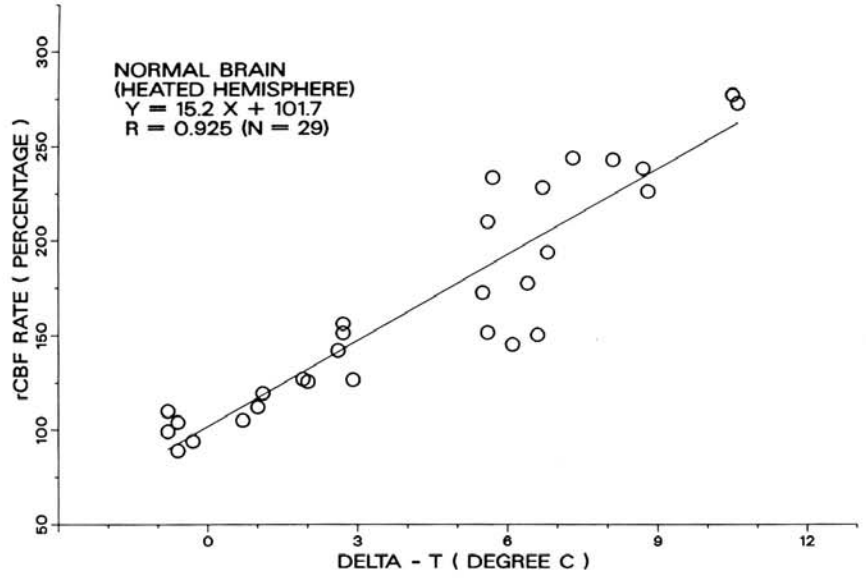

Figure 5. Scatter plot of the relative rCBF change (rCBF rate, % of hypothermic baseline) vs. temperature difference from hypothermic baseline (ΔT, °C) for all data points ($n=29$) measured in 11 different tissue sites of heated brains in seven normal monkeys. The solid line ($Y=15{\cdot}2X+101{\cdot}7$) is the linear regression fit, showing a high correlation coefficient ($R=0{\cdot}925$, $P<0{\cdot}001$) with a ΔT ranging from $-0{\cdot}8$ to $10{\cdot}6$°C.

($16{\cdot}21\pm3{\cdot}75$ ml/100 g per min) ($P=0{\cdot}025$), and the tumour and control ($15{\cdot}80\pm2{\cdot}76$) ($P=0{\cdot}035$).

The rCBF generally changed in relation to changes in the tissue temperatures (table 3, figure 6). As compared to rCBF obtained in hypothermic baseline ($24{\cdot}65\pm2{\cdot}41$ ml/100 g per min), blood flow in tumour increased significantly in mid-heating ($30{\cdot}38\pm2{\cdot}81$ ml/100 g per min, $P<0{\cdot}001$), in heated peak ($37{\cdot}12\pm3{\cdot}20$ ml/100 g per min, $P<0{\cdot}001$), and in mid-cooling ($30{\cdot}57\pm3{\cdot}72$ ml/100 g per min, $P=0{\cdot}008$). At the terminal hypothermia with temperatures of $30{\cdot}2\pm0{\cdot}5$°C, blood flow showed larger value than hypothermic baseline, but the difference was not significant ($P>0{\cdot}1$). Similar change in rCBF in response to the tissue temperature was observed in heated hemisphere (brain); rCBF increased with the increase in temperature and decreased with the decrease in temperature. The rCBF in the contralateral hypothermic brain (control) generally did not change throughout the experiment.

Scatter plots for tumour and brain are shown in figure 7 (a) and (b). Linear regression testings for tumour revealed a high correlation ($R=0{\cdot}834$, $n=37$, $P<0{\cdot}001$) with a ΔT range between $-1{\cdot}8$°C and $10{\cdot}6$°C. Correlation was similarly observed for heated brain showing a correlation coefficient of $0{\cdot}920$ ($n=25$, $P<0{\cdot}001$) with ΔT ranging from $-2{\cdot}0$°C to $12{\cdot}2$°C. The slope of the regression line for the brain ($13{\cdot}5$) was significantly ($P<0{\cdot}01$) higher than that for the tumour ($6{\cdot}5$), but was not different ($P>0{\cdot}5$) from the value obtained for normal brain described in the previous section.

4. Discussion

The blood flow in experimental brain tumours is reported variable in individual tumours as well as different tumour models (Blasberg *et al.* 1981, Hossmann *et al.* 1982, Groothuis *et al.* 1983). In the present study, rCBF in the monkey brain tumour model was measured by the hydrogen clearance method. The rCBF at the hypothermia, with an oesophageal

Table 3. Tissue temperature and corresponding rCBF measured in tumour-bearing animals during selective brain heating under generalized hypothermia.

Time course	Tumours				Brains				Controls			
	No.	Min.	Max.	Mean ± SE	No.	Min.	Max.	Mean ± SE	No.	Min.	Max.	Mean ± SE
Hypothermic baseline												
Temp.	10	29·3	31·6	30·3 ±0·3	6	29·1	31·5	30·2 ±0·4	5	29·3	31·3	30·2 ±0·3
rCBF	10	14·59	38·50	24·65 ± 2·41	6	11·18	25·91	16·21 ± 3·75	5	11·01	27·89	15·80 ± 2·76
Mid-heating												
Temp.	11	31·4	34·4	33·6 ±0·5‡	7	32·4	34·2	33·7 ±0·7†	6	29·2	31·5	30·6 ±0·4*
rCBF	11	17·17	47·74	30·38 ± 2·81‡	7	13·30	42·01	25·39 ± 3·75§	6	11·45	27·90	16·04 ± 2·67*
Heated peak												
Temp.	10	34·6	42·5	37·9 ±0·7‡	6	35·7	41·8	38·4 ±1·1‡	5	30·5	32·4	31·6 ±0·3†
rCBF	10	19·47	51·71	37·12 ± 3·20‡	6	23·70	51·56	39·95 ± 4·64‡	5	12·28	34·86	19·13 ± 4·14*
Mid-cooling												
Temp.	6	33·2	37·1	35·0 ±0·5‡	6	33·4	37·8	35·4 ±0·8‡	3	29·7	32·0	31·2 ±0·7*
rCBF	6	18·48	43·26	30·57 ± 3·72†	6	18·22	41·50	30·17 ± 4·07†	3	14·45	30·96	21·64 ± 4·88¶
Terminal hypothermia												
Temp.	10	28·4	32·4	30·2 ±0·5*	6	27·6	32·3	30·1 ±0·7*	5	27·8	31·5	29·9 ±0·6*
rCBF	10	13·57	40·91	25·53 ± 3·10*	6	9·83	33·40	18·01 ± 3·93*	5	11·27	25·66	16·38 ± 2·55*

Tumours: heated tumours of the tumour-bearing animals; Brains: ipsilateral heated hemispheres of the tumour-bearing animals; Controls: contralateral hypothermic hemispheres of the tumour-bearing animals; Temp: temperature of the brain tissue (°C); rCBF: regional cerebral blood flow (ml/100 g per min); No.: Number of sites for measurement; Min.: minimum value obtained in each time course; Max.: maximum value obtained in each time course.

Significantly different from baseline for paired *t*-test ($P<0·05$§ $P<0·01$†, $P<0·001$‡).

No significant difference from baseline for paired *t*-test ($P>0·05$¶, $P>0·1$*).

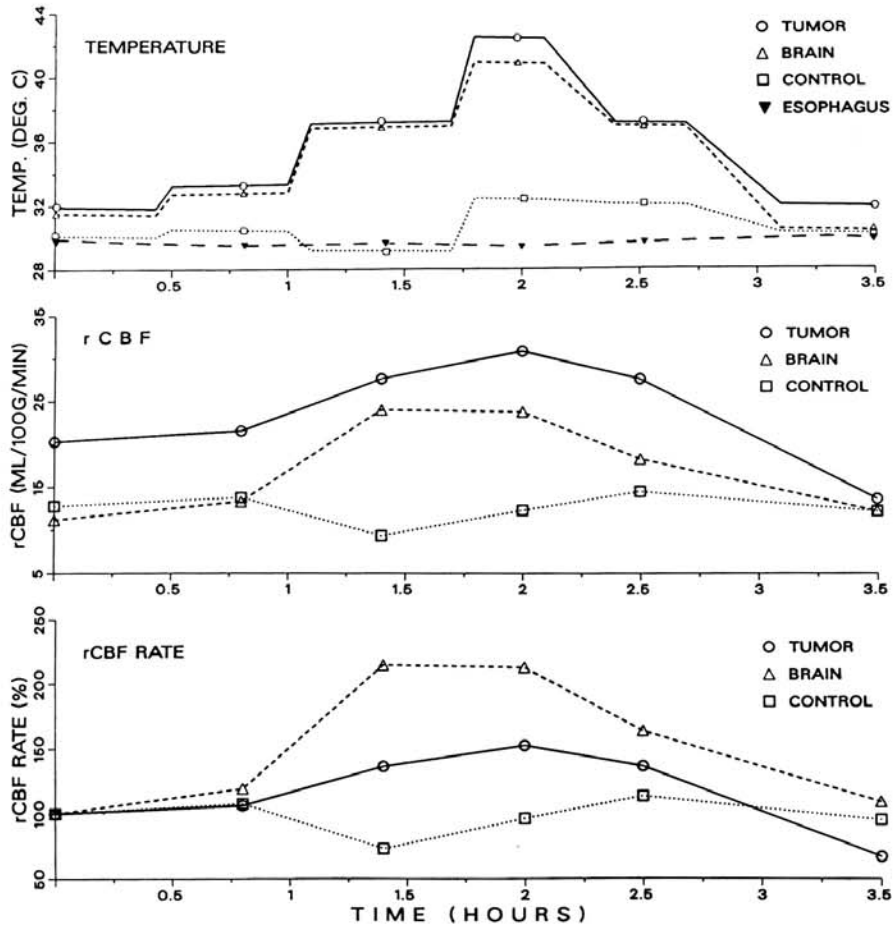

Figure 6. Relationship of temperatures (°C) in tissues and oesophagus, rCBF (ml/100 g per min), and rCBF rate (% of hypothermic baseline) with respect to time course (hours) in one tumour-bearing animal. Note remarkable change in temperature of the heated tumour tissue (tumour) and ipsilateral heated hemisphere (brain), with the relatively constant hypothermic temperatures in the contralateral hemisphere (control) and the body (oesophagus). The rCBF in tumour and brain increased with the increase in the tissue temperature and decreased with the decrease in temperature.

temperature of 30·3°C, showed slightly higher value in tumours than those in the corresponding white matter of the ipsilateral and contralateral hemispheres. Groothuis *et al.* (1983) reported that the mean blood flow in rat brain tumours was not significantly different from that of the same anatomic, tumour-free brain region of the contralateral hemisphere. The tumour blood flow, moreover, did not correlate with histological classification, tumour size, central versus peripheral tumour regions, intraparenchymal tumour location, or cell density in tumour.

The influences of the change from hypothermic to hyperthermic temperatures on the blood flow of the normal and tumour tissues have not been extensively studied. Willett *et al.* (1987) studied the change in tumour blood flow over a temperature range of 18–46°C using transplanted fibrosarcoma in mice. Maximum blood flow was observed at 35°C, which was twice as much as that at 24°C and at 39°C. Using transplanted mammary carcinomas in rats, Gullino *et al.*(1978) noted that cooling of tumours (27·4–33·5°C) which were initially at physiological temperature (34·2–35·9°C) consistently reduced blood

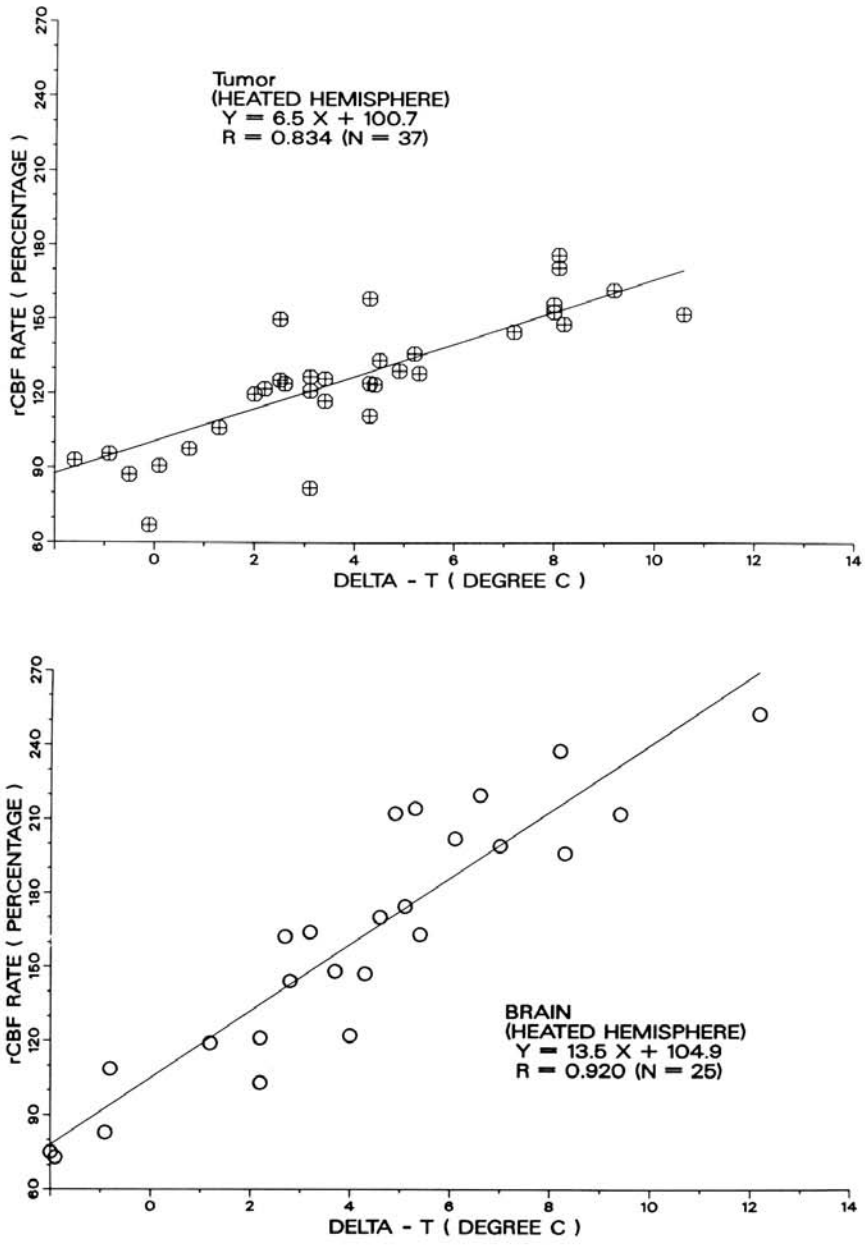

Figure 7. Scatter plots of the relative rCBF change (rCBF rate, % of baseline hypothermia) vs. temperature difference from hypothermic baseline (ΔT, °C) for data obtained in tumours (**a**) and brains (**b**) in seven brain tumour-bearing animals. Solid lines represent linear regression fit. Note linear regression coefficient in tumour (6·5) is significantly ($P<0·01$) less than that obtained in heated brain (13·5).

flow. It is interesting that warming of initially normothermic tumours to 38·7–42·6°C failed to produce any consistent change in blood flow, whereas warming of initially hypothermic tumours to 32·5–39·6°C increased blood flow.

The present study demonstrated that rCBF in the normal brain, with initially a hypothermic temperature, changed with change in the tissue temperature, ranging from

shallow hypothermia (29·4°C) to modest hyperthermia (40·7°C). The rCBF in a specific volume in brain is suggested to be controllable by the defined application of heating. This further implies that selective heating in combination with generalized hypothermia may create a large contrast in circulatory conditions between treated and non-treated tissues. Vascular response to the tissue temperature in normal brain is considered important because tissue adjacent to or in the field of heat treatment is forced to increase in blood flow, which may result in increase in local brain metabolism as described by others (Ikeda *et al.* 1982, Lilley *et al.* 1984).

The rCBF measured in the tumour-bearing animals, kept in generalized hypothermia, changed proportionately with change in the tissue temperatures over a range of 28·4–42·5°C in tumour and 27·6–41·8°C in brain tissue, respectively. The rate of change in blood flow in tumour (6·5%) was significantly ($P<0·001$) smaller than that in brain tissue (13·5%). These vascular responses may play a significant role in the application of heat to brain tumour treatment, especially when used in conjunction with chemotherapeutic drugs. It is reported that under the generalized hypothermic condition, a relatively high concentration of drugs was maintained in cold blood for a long time, due to delay of drug degradation (half-life time) or to the diminished drug excretion from kidneys (Popovic and Popovic 1969, Selker *et al.* 1979, Satoh *et al.* 1985). Systemic toxicity of the drugs can be reduced by reduced uptake and utilization of the drugs in the cold tissues with the depressed metabolism. On the contrary, increased blood flow in the heated tissue may increase drug delivery; this is especially critical for lipid-soluble drugs such as nitrosoureas (Levin and Kabra 1974). Increased drug delivery to the tissue, accompanied by biological drug–cell interactions at elevated temperatuers (Hahn 1979, Dewey 1984) may enhance the tumour response to chemotherapeutic drugs. However, it should be taken into consideration that increase in rCBF could be higher in normal tissue than that in tumour tissue, as demonstrated in the present study, when the brain surrounding tumour might be simultaneously heated at the same temperature. It may be required to deliver well-defined heating in a tumour mass to create selective change in circulatory as well as metabolic conditions in the tumour tissue.

In conclusion, rCBF in a specific volume in brain can be controlled by selective brain heating applied with a generalized hypothermia over a temperature range between shallow hypothermia and modest hyperthermia. Vascular response to tissue temperature in normal and tumour tissues may play a significant role in the application of heat to brain tumour treatment, either when used alone or in conjunction with ionizing radiation and chemotherapeutic drugs.

Acknowledgements

The authors thank Dr Chang W. Song, University of Minnesota, for reviewing this manuscript, and Mr Hideki Wakimoto for preparing photographs. Supported in part by Grant-in-Aid for Cancer Research (58010032, 59010030, 59480304) and Grant-in-Aid for Scientific Research (58870074) awarded from the Ministry of Education, Science and Culture of Japan.

References

BLASBERG, R. G., GROOTHUIS, D. R., and MOLONAR, P., 1981, The application of quantitative autoradiographic measurements in experiemental brain tumors. *Seminars in Neurology*, **1**, 203–221.

COMMITTEE OF BRAIN TUMOR REGISTRY IN JAPAN, 1987, *Brain tumor registry in Japan*, vol. 6 (Tokyo, National Cancer Center), pp. 101–175.

DEMPSEY, R. J., COMBS, D. J., MALEY, M. E., COWEN, D. E., ROY, M. W., and DONALDSON,

D. L. 1987, Moderate hypothermia reduces postischemic edema development and leukotriene production, *Neurosurgery*, **21**, 177–181.

DEWEY, W. C., 1984, Interaction of heat with radiation and chemotherapy. *Cancer Research (Suppl.)* **44**, 4714s–4720s.

DOYLE, T. F., MARTINS, A. N., and KOBRINE, A. I., 1975, Estimating total cerebral blood flow from the initial slope of hydrogen washout curves, *Stroke*, **6**, 149–152.

EMAMI, B., and SONG, C. W., 1984, Physiological mechanisms in hyperthermia: A review, *International Journal of Radiation Oncology, Biology and Physics*, **10**, 289–295.

GROOTHUIS, D., BLASBERG, R. G., MOLONAR, P., BIGNER, D., and FENSTERMACHER, J. D., 1983, Regional blood flow in avian sarcoma virus (ASV)-induced brain tumors. *Neurology (Cleveland)*, **33**, 686–696.

GULLINO, P. M., YI, P-N., and GRANTHAM, F. H., 1978, Relationship between temperature and blood supply or consumption of oxygen and glucose by rat mammary carcinomas. *Journal of the National Cancer Institute*, **60**, 835–847.

HAHN, G. M., 1979, Potential for therapy of drugs and hyperthermia. *Cancer Research*, **39**, 2264–2268.

HARRIS, A. B., ERICKSON, L., KENDIG, J. H., MINGRIN, S., and GOLDRING, S., 1962, Observation on selective brain heating in dogs. *Journal of Neurosurgery*, **19**, 514–521.

HOSSMAN, K. A., NIEBUHR, I., and TAMURA, M., 1982, Local cerebral blood flow and glucose consumption of rats with experimental gliomas. *Journal of Cerebral Blood Flow and Metabolism*, **2**, 25–32.

IKEDA, K., TABUCHI, K., KATAGI, Y., YOKOYAMA, Y., HARADA, Y., and NISHIMOTO, A., 1982, Influence of differential hypothermia treatment on the cerebral metabolism. *No To Shinkei (Tokyo)*, **34**, 165–171 (in Japanese).

KUSAMA, T., and MABUCHI, M., 1970, *Stereotaxic Atlas of the Brain of Macaca fuscata* (Tokyo: University of Tokyo Press), pp. 9–12.

LEVIN, V. A. and KABRA, P., 1974, Effectiveness of the nitrosourea as a function of their lipid solubility in the chemotherapy of experimental rat brain tumors. *Cancer Chemotherapy Reports, Part 1*, **58**, 787–792.

LILLY, M. B., NG, T. C., EVANOCHKO, W. T., KATHOLI, C. R., KUMAR, N. G., ELGAVISH, G. A., DURANT, J. R., HIRAMOTO, R., GHANTA, V., and GLICKSON, J. D., 1984, Loss of high-energy phosphate following hyperthermia demonstrated by in vivo ^{31}P-nuclear magnetic resonance spectroscopy. *Cancer Research*, **44**, 633–638.

LYONS, B. E., OBANA, W. G., BORCICH, J. K., KLEINMAN, R., SINGH, D., and BRITT, R. H., 1986, Chronic histological effects of ultrasonic hyperthermia on normal feline brain tissue. *Radiation Research*, **106**, 234 –251.

NISHIMOTO, A., TABUCHI, K., ARIMORI, M., SUGA, K., YAMADA, S., and KATAGI, R., 1978, Treatment of malignant brain tumors: experimental and clinical studies. *Seara Medica Neurocirurgica (Sao Paulo)*, **7**, 211–229.

POPOVIC, P., and POPOVIC, V. P., 1969, Protective effects of differential hypothermia, *Depressed Metabolism*, edited by MUSACCHI and SANDERS (New York: American Elsevier), pp. 499–524.

POPOVIC, V. P., and MASIRONI, R., 1965, Disappearance of euthermic tumors after 10-hour generalized hypothermia. *Life Science*, **4**, 533–543.

SATOH, T., MORIYAMA, E., TAMIYA, Y., NAKASONE, S., MATUMOTO, K., FURUTA, T., MORIYA, Y., and NISHIMOTO, A., 1985, Pharmacokinetics of ACNU in differential hypothermia. *Progress in Hyperthermic Oncology*, edited by S. Egawa, (Tokyo: Shinohara), pp. 128–129.

SATOH, T., NAKASONE, S., MATUMOTO, K., NISHIMOTO, A., OGURA, H., FUJIWARA, T., and TABUCHI, K., 1986, Computed tomography of monkey brain tumors. *Journal of Computer Assisted Tomography*, **10**, 827–830.

SELKER, R. G., BOVA, E., KRISTOFIK, M., JONES, E., IANNUZZI, D., LANDAY, A., and TAYLOR, F., 1979, Effect of total body temperature on toxicity of 1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU). *Neurosurgery*, **4**, 157–161.

SHELINE, G. E., 1975, Conventional radiation therapy of gliomas. *Recent Results of Cancer Research*, **51**, 125–134.

SMITH, A. L., and WOLLMAN, H., 1972, Cerebral blood flow and metabolism: Effects of anesthetic drugs and techniques. *Anesthesiology*, **36**, 378–400.

SONG, C. W., 1983, Blood flow in tumors and normal tissues in hyperthermia (Chapter 8) *Hyperthermia in Cancer Therapy*, edited by F. K. Storm (Boston; G. K. Hall), pp. 187–206.

TABUCHI, K., NISHIMOTO, A., MATUMOTO, K., SATOH, T., NAKASONE, S., FUJIWARA, T., and

OGURA, H., 1985, Establishment of a brain-tumor model in adult monkey. *Journal of Neurosurgery*, **63**, 912–916.

WILLETT, C. G., URANO, M., SUIT, H. D., STRAUSS, H. W., KAHN, J., and OKUNIEFF, P. G., 1987, Effect of temperature on blood flow and hypoxic fraction in a murine fibrosarcoma. *International Journal of Radiation Oncology, Biology and Physics*, **13**, 1309–1312.

WILSON, C. B., LEVIN, V. A, and HOSHINO, T., 1982, Chemotherapy of brain tumors (Chapter 96). *Neurological Surgery*, Vol. 5, edited by J. R. Youmans (Philadelphia: W. B. Saunders), pp. 3065–3095.

ZAR, J. H., 1974, *Biostatistical Analysis* (Englewood Clifts, NJ: Prentice-Hall), pp. 228–251.