[CANCER RESEARCH 45, 5625-5631, November 1985]

Effect of Low Level Direct Current on *in Vivo* Tumor Growth in Hamsters[1]

Sharon L. David, Darryl R. Absolom,[2] Charles R. Smith, John Gams, and Morley A. Herbert[3]

Department of Surgical Research, Research Institute [S. L. D., D. R. A., M. A. H.], and Department of Pathology [C. R. S.], Hospital for Sick Children, Toronto, Ontario M5G 1X8, and Medtronic, Inc., Mississauga, Ontario L5N 1W3 [J. G.], Canada

ABSTRACT

A preliminary study has been carried out on the effect of low level direct current on tumor growth using an experimental tumor model developed from an amelanotic melanoma (T1-4) in the hamster. An inoculum of 2×10^6 viable cells was injected s.c. on day 0; on day 7 the tumor-bearing animals were randomly divided into treatment and control groups. On days 7 through 11 inclusive, the treatment group was subjected to electrical current (direct current) at levels from 0.1 to 2.4 mA, for 1 h/day under general anesthesia. Control groups were subjected to the same procedures, with the exception that the electrodes were not connected to the current source. On day 14, the animals were killed and autopsied; their tumors were removed, weighed, and sectioned. Treated tumors decreased in mass (as a percentage of controls) from 89% at 0.1 mA to 2% at 2.4 mA. Increased necrosis of the treated tumors was noted macroscopically and microscopically. On histological examination, it was observed that a thin rim of viable cells remained around the periphery after treatment even at the highest current levels. Similar results were obtained with both stainless steel and platinum-30% iridium electrodes.

In separate experiments where the animals were allowed to survive after a treatment period (1 h/day for 5 days at 2.4 mA), the viable cells at the periphery developed into tumors whose mass at 28 days posttreatment averaged only 52% of that of the control tumors.

The mechanism of growth reduction is unknown but hyperthermia was shown not to be a factor.

INTRODUCTION

New cancer treatment modalities are in demand since many clinical cases do not respond to the conventional approaches of surgery, chemotherapy, and radiotherapy. Immunotherapy, hyperthermia, and magnetic microspheres are some of the newer techniques being investigated for their potential role in clinical therapy (4, 12, 17, 25, 27). We have begun to study the use of small electrical currents to destroy solid tumors in animals.

As early as 1776 it was suggested by Eason (22) that electricity might have a role in the treatment of tumors. He reported the case of a patient with a breast tumor who was struck on the shoulder by lightning and proceeded to have a remission of her tumor. Using the available electrolytic techniques, other investigators of that era reported positive results trying to treat tumors with electricity (22).

More recently necrosis and retardation of tumor growth were described in three solid tumor models [the mouse sarcoma 180 (9), hamster melanoma A-Mel-4 (6, 21), and rat Morris hepatoma (7)] when low-level DC[4] was passed through the tumors.

Exploration of this phenomenon holds great promise because both the direction and the spread of electric current can be controlled, thus limiting the effects to a defined area. It should also be possible to deliver the current to areas of the body inaccessible surgically. The work reported in this paper is an investigation of the effects of low-level direct current on a hamster melanoma model. Our work has confirmed the previously reported effects (21), while significantly extending the scope of the study.

MATERIALS AND METHODS

Hamsters. Seven- to 11-week-old male, Golden Syrian hamsters were obtained from the SPF colony of the Charles River Breeding Laboratories at Wilmington, MA.

Establishment of Cell Line Used to Produce Solid Tumors *in Vivo*. A transplantable hamster amelanotic melanoma (T1-4) was obtained from the tumor bank of the EG & G Mason Research Institute (Worcester, MA) as a cryopreserved fragment. The melanoma was spontaneous in origin and was frozen on July 16, 1969. When received, the tumor fragment was thawed and transplanted s.c. into hamsters in our laboratory. The resulting tumors were removed and established *in vitro* using a slight modification of the Snell technique (24).

The amelanotic melanoma cells were grown in culture in 95% α-minimal essential medium-5% fetal calf serum media with penicillin K salt and streptomycin sulfate at 100 μg/ml. Cells were harvested using 0.25% trypsin and were counted in suspension using an electronic particle counter (Model ZF, Coulter Electronics, Inc.). Viability was estimated using dye exclusion with trypan blue dye (5). Using conventional methods (16), the cell doubling time was found to be 14.3 h and the plating efficiency was 44 ± 4% (SE).

Establishment of Solid Tumor *in Vivo*. Under halothane-nitrous oxide anesthesia, hamsters were inoculated with 2.0×10^6 amelanotic melanoma cells placed s.c. over the right paralumbar fat pad. A palpable, single solid tumor was produced within 7 days. On day 7 postinoculation, the hamsters were randomly divided into two groups (treated and control). Hamsters with tumors smaller than 4.0 mm were excluded from the study.

Direct Current Treatment. The treatment current was provided by a battery powered constant current source. The current was continuously monitored by either a micro- or milliammeter placed in series with the electrodes. Six parallel electrode outputs (monitored individually) allowed up to six animals to be treated simultaneously.

The active electrode which was placed in the tumor was an 18-gauge stainless steel injection needle with the hub removed. It was insulated with tight fitting silicon tubing which covered the needle except at the bevel and hub end. The exposed bevel was 5.0 mm long, had a diameter of 1.3 mm, and a surface area of 0.2 cm^2. The ground electrode was an aluminum foil plate, 3.5 x 7.0 cm, covered with conducting paste, placed against the shaved skin of either the abdomen or left side of the hamster

[1] Supported in part by Medtronic, Inc., and by the National Cancer Institute of Canada.

[2] Supported in part by the Ontario Heart Foundation.

[3] To whom requests for reprints should be addressed, at Department of Surgical Research, The Hospital for Sick Children, 555 University Ave., Toronto, Ontario, M5G 1X8 Canada.

Received 9/23/82; revised 2/5/85; accepted 6/28/85.

[4] The abbreviation used is: DC, direct current.

On each treatment day the hamsters were subjected to halothane anesthesia induction in a bell jar, and then were maintained on a mask inhalation system with 1.0 to 1.5% halothane, 40% nitrous oxide, and 60% oxygen. The skin was shaved over the tumor area and the site of the ground plate. The animal was placed either in sternal or lateral recumbency on the ground electrode. The needle electrode was placed percutaneously through a small skin incision directly into the palpable tumor. The positive and negative electrodes were attached to the appropriate leads of the current source, and the treatment was carried out for 1 h/day on 5 consecutive days beginning on day 7 postinoculation of cells. After each treatment, the animals were allowed to awaken and were returned to their cages. Control animals underwent the same procedures but the electrodes were not connected to the current source. In the first series of experiments, the hamsters were killed 3 days after the last treatment (14 days postinoculation).

In another group of hamsters we tested the effects with both positive and negative electrodes simultaneously placed into the tumor. For this experiment 18-gauge stainless steel needles were used for both electrodes.

To study the effects attributable to electrode composition, platinum-iridium electrodes were also investigated. In two sets of experiments, the intratumor electrode was a 70% platinum-30% iridium wire, 0.01 in. in diameter, coated with Teflon except for 5 mm at each end (surface area approximately 0.04 cm^2). Experiments were carried out using currents of 0.6 and 1.0 mA.

Finally, the long term effect of treatment on tumor growth was assessed. Hamsters were treated for 1 h daily with a current of 2.4 mA on days 7 through 11 inclusive postinoculation. The animals were then allowed to live to day 28 without further treatment, at which time they were sacrificed.

Tumor Temperature Measurements. The tumor temperature was measured in hamsters undergoing treatment at 2.0 mA for 1 h daily on days 7 through 11 postinoculation using a stainless steel positive electrode. Calibrated needle thermistor tissue probes (YSI 514 series, Yellow Springs Instrument Co., Yellow Springs, OH) were inserted into the tumors and temperatures were recorded every 10 min. The temperature of the tumors in the anesthetized but untreated control group was also measured. In addition, rectal temperatures were recorded for both groups.

Collection of Experimental Data. The hamsters were killed by i.p. barbiturate overdose and autopsies were performed. The tumors were excised and weighed on an electronic balance (Precisa 200C-2000 D1, Precision AG, Zurich, Switzerland).

The tumors were then bisected along their greatest diameter. One-half was fixed in Baker's fixative and stained with hematoxylin and eosin for histological evaluation, while the other cut surface was examined and graded for necrosis using an arbitrary 6-point scale: Grade 0, no necrosis; Grade 1, minimal necrosis; Grade 2, less than half necrotic; Grade 3, half necrotic; Grade 4, greater than half necrotic; Grade 5, mostly necrotic with thin rim and/or small pockets of viable tissue; and Grade 6, completely necrotic.

RESULTS

Change in Mass of Treated Tumors. Table 1 summarizes the results from the first series of experiments with the positive electrode (stainless steel) inserted into the tumor and the ground plate placed under the animal. Current levels were tested between 0.1 and 2.4 mA. In all cases the tumors excised from the treated animals weighed substantially less than did their paired controls. At the lowest current level tested, 0.1 mA, there was a reduction in tumor mass by 11% which, although not statistically significant, represented the lowest measurable threshold effect. Tripling the current output to 0.3 mA had a marked effect on tumor size, reducing tumor mass by 43%. As the current increased there was a proportional decline in tumor mass until at 2.4 mA, the highest current tested, the tumor mass was reduced by 98%. In four of the six hamsters treated in this group, there was no visually identifiable tumor remaining, only a pitted scab with friable necrotic material underneath. All differences in tumor mass, with the exception of the 0.1 mA experiment, were statistically significant (*t* test).

Table 1

Reduction in tumor mass with direct current using a stainless steel anode

Current (mA)	Tumor mass, *M* (g) Treated	(*N*)[a]	Control	(*N*)	% of $M_{treated}/M_{control}$	% of reduction	*P*
0.1	1.86 ± 0.82[b]	(5)	2.09 ± 0.56	(5)	89	11	NS
0.3	1.45 ± 0.57	(5)	2.56 ± 0.53	(5)	57	43	<0.05
0.7	0.90 ± 0.56	(5)	1.61 ± 0.34	(5)	56	44	<0.05
1.0	0.57 ± 0.17	(6)	1.65 ± 0.61	(6)	34	66	<0.005
1.7	0.42 ± 0.42	(4)	2.40 ± 1.11	(3)	17	83	<0.05
2.4	0.04 ± 0.06	(6)	1.67 ± 0.66	(5)	2	98	<0.001
1.0[c]	0.68 ± 0.22	(5)	2.07 ± 0.91	(6)	33	67	<0.05

[a] *N*, number of animals in group; NS, not significant.
[b] Mean ± SE.
[c] Tested with both positive and negative stainless steel electrodes in tumor, simultaneously.

The results of an experiment using 1.0 mA with both positive and negative stainless steel electrodes simultaneously placed directly in the tumor are also shown in Table 1. The measured difference in mass between the treated and untreated tumors is the same as that obtained in the experiment with the positive electrode in the tumor and the negative electrode as a ground plate.

In two further experiments, the polarity of the electrodes was reversed so that the needle electrode inserted into the tumor was negative. In the first experiment, an 18-gauge stainless steel needle was used as the cathode at 1.0 mA for 1 h on 5 consecutive days. When sacrificed on day 14, the tumor mass of treated animals was reduced to 27.8% of the controls, *i.e.*, a 72.2% reduction, which was slightly more than the 66% decrease measured at the same current level when the intratumor electrode was positive. When the platinum-iridium wire was used as the cathode in the tumor, a current of 0.9 mA for 5 days (1 h per day) reduced the tumor mass to 49.6% of control. In this case the decrease was less than that recorded for the same electrode biased positive.

Gross Appearance. At all current levels focal necrosis was visible on the surface of the tumor. At the higher current levels both the tumor and its overlying skin showed signs of destruction. With 2.4 mA no tumor material could be visually identified, with only a black, pitted scab present at the previous tumor site in four of six animals, and small tumor remnants in the other two animals.

When both the positive and negative electrodes were simultaneously in the tumor, the tumor around the electrodes showed significant necrosis.

Fig. 1 shows the results of treatment with a positive stainless steel electrode placed in the tumor. While both tumor groups show the expected variability in tumor size, significant reduction in the mass of the treated tumors is evident. The areas of necrosis on the surface are visible.

Upon gross visual examination the cut surface of the untreated tumors was dark red, with variable amounts of grey-white tissue

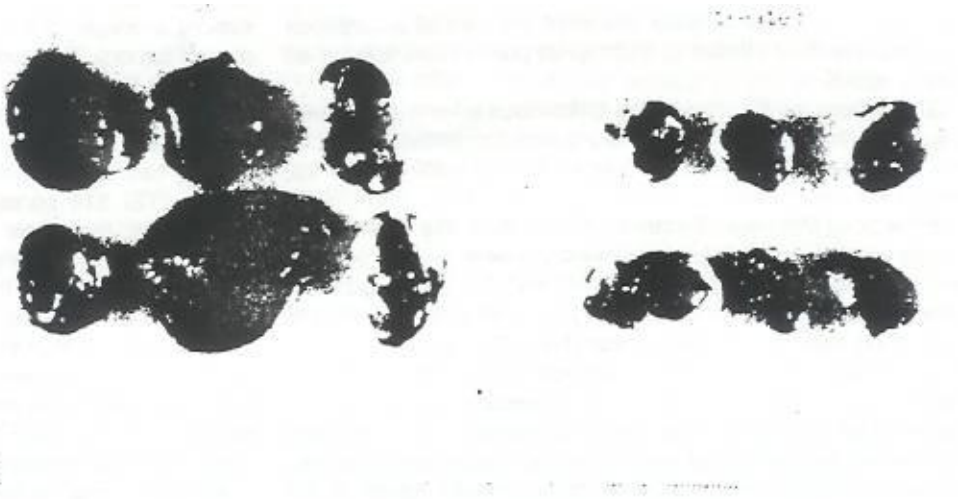

Fig. 1. Gross appearance of treated and control tumors after excision. Treated tumors were exposed to 1.0 mA from an 18-gauge stainless steel needle insulated with silicon tubing except for 5 mm at its tip. Treatment was for 1 h/day on days 7 through 11. The treated tumors are smaller and show blackened necrotic areas.

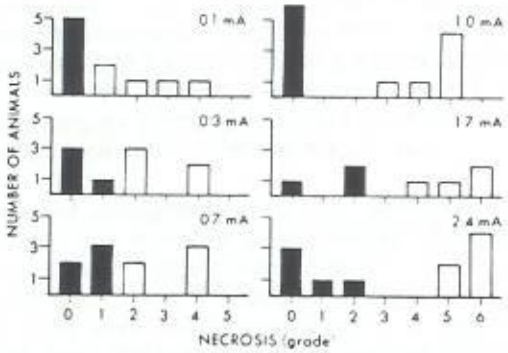

Chart 1. Necrosis score for control (■) and treated (□) tumors at each current level.

found most often in the periphery. The tumors ranged from oval to round, and occasionally were slightly lobulated. Some control tumors had small areas of central necrosis evidenced by a tan color, but were never scored higher than 2 (less than one-half necrotic). In contrast the treated tumors had significant amounts of necrotic black or tan areas on their cut surfaces. The histograms in Chart 1 indicate the extent of tumor necrosis with increasing current levels. In all cases the control tumors scored macroscopic necrosis grades of 0 (no necrosis) or 1 (minimal necrosis), with only the occasional value of 2 (less than one-half necrotic). Treated tumors never scored below 1 even at the lowest current group, while at 2.4 mA most were scored the maximum 6 (completely necrotic).

Tumors exposed to currents when the intratumor electrode was negatively biased showed gross pathology very similar to those with the positive electrode in the tumor. Some skin and muscle necrosis was present in one-half of the animals, although no quantitative measurements could be made. Microscopically the tumors were indistinguishable from those treated with the positive electrode.

Postmortem examination of the side in contact with the ground electrode showed superficial skin scabs at pressure contact points with the plate electrode. Internally, muscle directly below the tumor in the path of the "active" electrode sustained mild to severe injury; the extent was current dependent.

Tumor treatment carried out with two needles placed into the tumor resulted in the same amount of tumor destruction as with the corresponding current level experiment using one needle in the tumor and a large surface area negative electrode. However, in this experiment there was no observable change in the surrounding muscle tissue, since no current path existed outside the tumor.

Histological Appearance. Microscopic examination of the histological sections showed some foci of hemorrhage and necrosis running through the control tumors (Fig. 2*A*). These areas varied in amount and tended to be centrally located within the lobules of the tumor. Clumps of normal appearing tumor cells could still be found scattered throughout these central areas of necrosis. Histological sections of the tumors from the treated animals, when compared to the control group, demonstrated three prominent features: (*a*) the overall size of the treated tumors was significantly smaller, suggesting a slower growth rate. This conclusion is supported by the presence of an increased amount of residual adipose tissue as compared to the control group; in the treated tumors, the fat has not undergone pressure atrophy, as occurs in control tumors. (*b*) A disproportionate amount of the treated tumor mass was necrotic, which could not be accounted for by its size or through comparison with weighted controls. The prominent areas of necrosis were centrally located within the tumor mass. These areas were characterized by a mass of amorphous material, at the edge of which were seen outlines of necrotic appearing cells. In the treated tumors no viable appearing cells were observed in those areas of necrosis, unlike tumors from control animals where clumps of viable cells were visible in all areas of necrosis. The necrotic material in the treated tumors was surrounded by a thin rim of chronic inflammatory cells composed of lymphocytes, plasma cells, and macrophages. Outside this area was a margin of granulation in which proliferating fibroblasts and endothelial-lined vascular channels were seen. Adjacent to the area of inflammation, often at the periphery, were lobules of viable tumor appearing the same microscopically as the control tumor cells. Even at 2.4 mA, the peripheral areas contained some viable cells. (*c*) There was

evidence of electrical injury to the tissue; fibrillar areas from collagen breakdown were found near regions of tumor necrosis. Fig. 2*B* illustrates the typical appearance of a tumor treated with 1.0 mA (1 h/day for 5 days). Some of the central amorphous material has lifted off during histological preparation, leaving an empty space.

There were no life threatening deleterious effects of stimulation. All hamsters recovered mobility quickly posttreatment. They ate immediately and appeared fully recovered within 3 h of the end of the anesthesia.

Effects of Different Electrode Material. In the two experiments carried out using platinum-iridium wire as the positive electrodes (with current levels of 0.6 and 1.0 mA), significant reductions of treated tumor mass by 54% ($P < 0.02$) and 71% ($P < 0.01$), respectively, were seen (Table 2). Fig. 3 is a photograph showing the tumors removed from treated hamsters who received 1.0 mA for 1 h on each of 5 consecutive days, and their corresponding controls. The overall difference in size between the treated and untreated tumors is readily apparent. Changes in tumor mass following treatment corresponded closely to the results with stainless steel electrodes (Chart 2).

Long Term Effects. In one group, treatment of 2.4 mA was terminated on day 11 post inoculation and the hamsters were allowed to survive until day 28 without further treatment. After the final treatment in the series (day 11) no palpable tumor was present, although there was mild swelling and some skin ulceration. By day 28 tumors had partially regrown but were now divided by a taut puckered scar into 2 or 3 lobes. This pattern of regrowth suggests that parts of the tumor, probably the peripheral areas, were not destroyed completely by the treatment. During the 28 days the control tumors had grown to an average mass of 18.9 ± 1.9 g, while the electrically treated tumors averaged 9.1 ± 3.4 g, only 48% of the mass of the control tumors. This reduction of 52% in mass was statistically significant ($P < 0.01$).

Table 2

Reduction in tumor mass with direct current using a platinum-iridium anode

Current (mA)	Tumor mass, *M* (g)				% of $M_{treated}/M_{control}$	% of reduction	*P*
	Treated	(*N*)[a]	Control	(*N*)			
0.6	1.07 ± 0.27[b]	(6)	2.30 ± 0.87	(6)	46	54	<0.02
1.0	0.59 ± 0.26	(6)	2.00 ± 0.89	(6)	29	71	<0.02

[a] *N*, number of animals per group.
[b] Mean ± SE.

Tumor Temperatures. To assess whether the reduction in tumor mass with treatment was due to thermal effects from heating caused by passage of the currents, thermistor tissue probes (YSI 514 series) were placed adjacent to the active electrode in the tumor. Measurements were made of tumor temperatures in tumors treated with 2.0 mA and in control tumors. The results of the experiments are shown in Chart 3.

During the 1-h course of treatment no change was seen in the temperature of either the treated or control tumors. The tumor temperature during treatment was not measurably higher than that measured 5 min before the start, nor did it drop after the cessation of treatment. No statistical difference was found between the mean temperatures at any time during the experiment.

Although rectal temperatures for both treated and control hamsters tended to fall to the same extent with time under anesthesia, both control and treated tumor temperatures were relatively stable at 30.2 ± 0.8 and 31.0 ± 1.6°C, respectively.

Control tumors, although hypothermic, grew as expected whereas treated tumors (also hypothermic) weighed only 7.6% that of the controls. Thus hypothermia alone does not account for tumor reduction.

Electrode Voltage. The potential difference between electrodes tended to fall over the 1-h treatment at 2.0 mA, initially measuring 3.0 ± 0.4 V, and declining after 1 h to 2.7 ± 0.7 V.

Specificity. To assess whether the effects of the treatment were restricted to tumor tissue or were more generalized, a series of tumor-free animals were treated with 1 mA. For these experiments the positive electrode (either stainless steel or platinum-iridium) was placed into the lumbar fat pad with the ground electrode as previously described. Six animals were used in each group and treatment was 1 h/day for 5 days. Upon postmortem, the treated area was swollen and ulcerated, while underneath

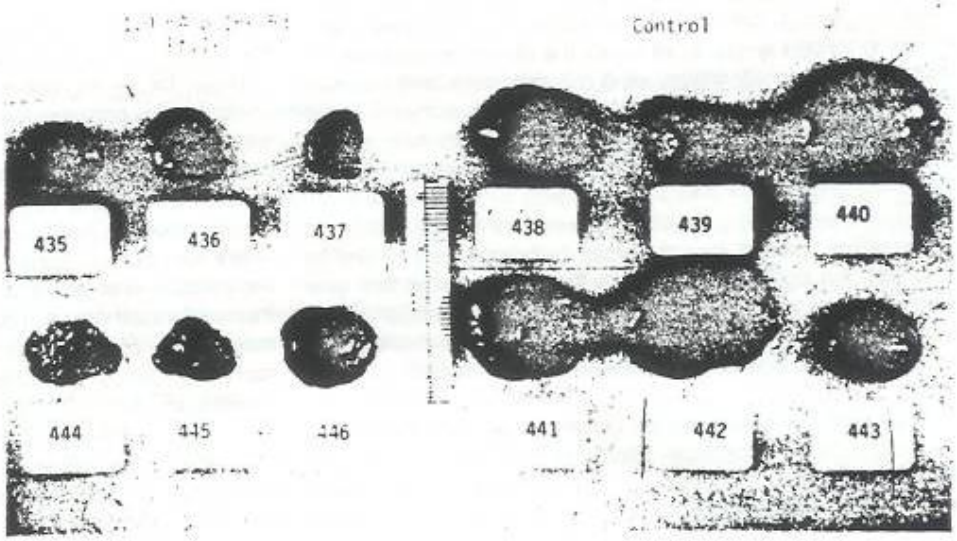

Fig. 3. Gross appearance of treated and control tumors following excision. Current at 1.0 mA was delivered to treated tumors from a 0.01-in. platinum-iridium (30%) wire exposed only 5 mm at its tip. Treatment was for 1 h/day on days 7 through 11. The treated tumors show large blackened areas.

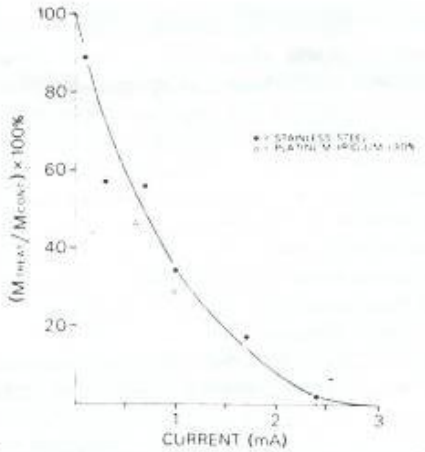

Chart 2. Change in treated tumor mass with current (stainless steel and platinum-iridium electrodes shown).

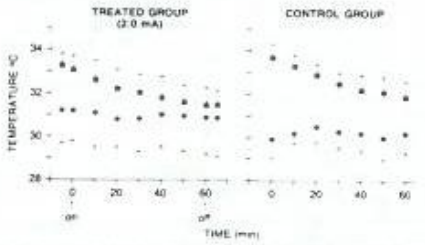

Chart 3. Control and treated tumor temperatures (●) during treatment at 2.0 mA for 1 h. Rectal temperature (■) was also measured. *Bars*, SE.

both fat and muscle were friably necrotic and were surrounded by a hyperemic line of demarcation. The extent of overt necrosis was comparable to that found when stainless steel was used to treat tumors. However, when the platinum iridium electrode was used, the observed damage was less severe.

DISCUSSION

The work reported here suggests that even with short treatment periods, quite dramatic destruction of tumors can occur. The amount of destruction is current dependent, approaching nearly total destruction (on the gross level) with a current of only 2.4 mA. In this preliminary work total eradication of all viable tumor cells was not achieved using only one electrode in the tumor. A multiple electrode array may improve significantly the amount of tumor destruction, while minimizing any trauma to underlying tissue.

Several possible mechanisms may account for the tumor destruction observed in this work. Temperature (both hyperthermic and hypothermic) effects can be ruled out by the temperature measurements reported. Theoretical considerations would also suggest that temperature effects are minimal. Assuming cylindrical electrode geometry and that maximum heating effects would occur at the electrode surface, the temperature change can be estimated from the following equation (23):

$$T_{max} = T_o + \frac{P \ln(Ro/Re)}{2\,kL}$$

In the case of the stainless steel electrode the radius (Re) is 0.65 mm, the exposed length (L) = 5 mm and the input power (P) 6.7 mW for 2.4 mA. If it is assumed that the temperature has returned to T_o (37°C) at a distance of Ro (5 mm) and the conductivity of the tumor is similar to that of water and brain tissue ($K = 6.5 \times 10^{-3}$ $W\ cm^{-1}$) (15), then for a maximum current of 2.4 mA the maximum value of $T_{max} = 39.1$°C. This represents a temperature increase of only 2.1°C at the surface of the electrode, with normal temperatures reached 5 mm distant. The calculated rise is within the range of normal values seen *in vivo*. Similar calculations using the 0.01-in.-diameter platinum wire produce a 3.8°C temperature rise at 2.4 mA and 1.6°C rise at 1 mA. Since the experimental results show that the treatment effects with both stainless steel and platinum-iridium electrodes are similar, it is unlikely that this theoretical difference in temperature rise is important. Samuelsson and Jonsson (19) have reported that with currents up to 30 mA, no increase in temperature could be measured at the electrode in pig lung tissue.

The temperature measurements confirmed that the necrotizing effects and growth retardation produced by the current used in these experiments are not caused by thermal factors. It is noted that under our experimental conditions, both control and treated tumor temperatures were below normal during treatment because of anesthesia hypothermia and did not fall concomitantly with rectal temperature. While it is possible to postulate that the current was preventing the tumor temperature from falling, it should be remembered that the control animals also showed similar tumor temperature stability. It is more likely that environmental factors such as the operating room lamps were responsible for moderating tumor temperature. Even if the treatment protocol produced some heat, the small temperature rises should be well within accepted biological limits.

Another possible mechanism is changes in pH arising from alteration in the H^+ ion concentration. At a current of 2.4 mA, the total number of electrons injected into the solution during the 1-h treatment could produce a maximum of 9×10^{-5} mol of $[H^+]$ excess during each day of treatment. If localized within the average tumor volume of 3 ml, the pH could theoretically drop to as low as pH 2 (ignoring any buffering effects). In experiments passing 10 mA for 2 h through saline soaked pads, pH values have been measured as low as pH 2.9 within 5 mm of the anode (in this case platinum) (20). Whether this same change occurs *in vivo* is yet unknown. The fraction of the current that actually goes into chemical reaction, diffusion of ions away from the site, and buffering reactions are all unknown.

According to Harguindey (8), tumor hyperacidification might activate cytolytic mechanisms via increased activity of lysosomes, resulting in destruction of tumor tissues. Low pH also inhibits glycolysis and protein synthesis, upon which malignant tissues are dependent. Some authors (8) have suggested that hyperchloremic metabolic acidosis is responsible for the clinical remission of bladder carcinomas seen after some urinary diversion procedures. It would appear that lowering tumor pH may have therapeutic value. Further experiments are currently underway to clarify these points and to see whether these effects play a role in the system described in this report.

The dissolution of metal may also be an important factor. A positive potential on metal electrodes leads to corrosion of the metal with the release of metal ions from the electrode and possible resultant necrosis due to metal toxicity. At the anode the stainless steel electrode is corroded with the ferrous ions going into solution.

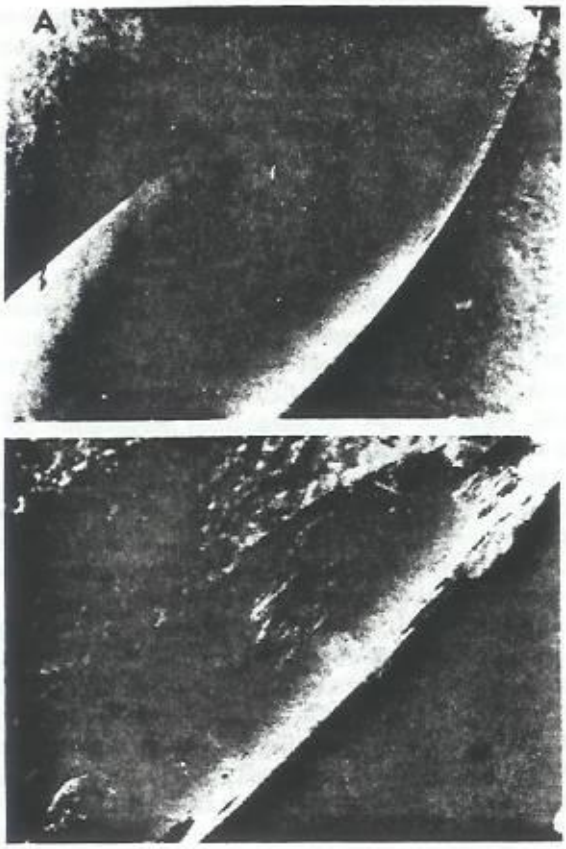

Fig. 4. *A*, normal appearance of tip of stainless steel electrode. Unused 18-gauge needle. × 80. *B*, corrosion damage to tip of stainless steel electrode. Needle after 1 mA for a total of 2 h. × 80.

In saline, other important anodal reactions (3) include: electrolysis of water, oxidation of saline, and oxidation of inorganics (*e.g.*, Equation A):

$$C_6H_{12}O_6 + 6H_2O \rightarrow 6\ CO_2 + 24\ H^+ + 24\ e^- \qquad (A)$$

These reactions can produce gas, pH changes, kinetically active oxidizers (ClO^-, ClO_4^-) and possibly toxic, local concentrations of metal ions.

Most of the work done on metal dissolution with electrodes has been done using pulsed wave forms (3, 13, 14, 26). While there is no question that the metal dissolves under DC conditions, the charge transfer limits are not understood. The charge injection at 2.4 mA is 2.4 mC/s or 12 mC/s/cm^2, well above the studied ranges for pulse systems. The current levels used in our work did produce significant corrosion of the stainless steel electrode. Fig. 4 shows an unused needle (*A*) magnified ×80 by scanning electron microscopy; (*B*) is the same type of needle after it was used to deliver a treatment of 1 mA for 1 h on 2 consecutive days.

It has been shown previously that dissolved platinum in solution can affect cellular growth in the region (18). Platinum compounds are now used as a treatment against various tumors, although toxicity problems arise from large systemic doses (1, 2, 28). The use of DC current with a platinum electrode system polarized positively provides the possibility of supplying platinum ions to the desired area without subjecting the rest of the body to large doses. Large ion concentrations could be produced in the tumor with negligible whole body loadings. Similar possibilities exist for other metals now finding use in treatment (10, 11).

In the experiments with the negative electrode in the tumor, the tumor destruction was similar to that observed with the positive electrode placed in the tumor. This suggests three possible conclusions: (*a*) the polarity sensitive reactions are not the primary source of the observed results; (*b*) there may be different mechanisms depending on the polarity of the electrode in the tumor; or (*c*) there is a direct effect of the electrical current on cells and their growth. We are carrying out *in vitro* studies to assess those possibilities.

The use of DC current for tumor destruction is a novel concept. Further studies of the mechanisms of action are under way.

REFERENCES

1. Aggarwal, S. K., Broomhead, J. A., Fairlie, D. P., and Whitehouse, M. W. Platinum drugs: combined anti-lymphoproliferative and nephrotoxicity assay in rats. Cancer Chemother. Pharmacol., *4:* 249–258, 1980.
2. Alsabti, E. A. K., Ghalib, O. N., and Salem, M. H. Effect of platinum compounds on murine lymphocyte mitogenesis. Jpn. J. Med. Sci. Biol., *32:* 53–65, 1979.
3. Brummer, S. B., and Turner, M. J. Electrochemical considerations for safe electrical stimulation of the nervous system with platinum electrodes. IEEE Trans. Biomed. Eng., *24:* 59–63, 1977.
4. Emami, B., Nussbaum, G. H., Hahn, N., Piro, A. J., Dritschilo, A., and Quimby F. Histopathological study on the effect of hyperthermia on microvasculature Int. J. Radiat. Oncol. Biol. Phys., *7:* 343–348, 1981.
5. Freshney, R. I. Culture of Animal Cells. A Manual of Basic Technique, p. 208. New York: Alan R. Liss, Inc., 1983.
6. Habal, M. B., and Schauble, M. K. Clinical device note: an implantable DC power unit for control of experimental tumor growth in hamsters. Med. Instrum. (Arlington), *7:* 305–306, 1973.
7. Habal, M. B. Effect of applied DC currents on experimental tumor growth in rats. J. Biomed. Mater. Res., *14:* 789–801, 1980.
8. Harguindey, S. Hydrogen ion dynamics and cancer: an appraisal. Med. Pediatr. Oncol., *10:* 217–236, 1982.
9. Humphrey, C. E., and Seal, E. H. Biophysical approach toward tumor regression in mice. Science (Wash. DC), *130:* 388–390, 1959.
10. Kopf-Maier, P., and Kopf, H. Tumor inhibition by titanocene dichloride. First clues to the mechanism of action. Naturwissenschaften, *67:* 415–416, 1980.
11. Kopf-Maier, P., Wagner, W., Hesse, B., and Kopf, H. Tumor inhibition by metallocenes: Activity against leukemias and detection of the systemic effect. Eur. J. Cancer, *17:* 665–669, 1981.
12. Lindholm, C. E., Kjellen, E., Landberg, T., Nilsson, P., and Persson, B. Microwave induced hyperthermia and ionizing radiation. Preliminary clinical results. Acta Radiol. Oncol., *21:* 241–254, 1982.
13. Loucks, R. B., Weinberg, H., and Smith, M. The erosion of electrodes by small currents. Electroencephalogr. Clin. Neurophysiol., *11:* 823–826, 1959.
14. McFadden, J. Metallurgical principles in neurosurgery. J. Neurosurg., *31:* 373–385, 1969.
15. Pond, J. B. The role of heat in the production of ultrasonic focal lesions. J. Acoust. Soc. Am., *47:* 1607–1611, 1970.
16. Paul, J. Cell and Tissue Culture. London: Churchill-Livingstone, Ltd., 1975.
17. Rand, R. W., Snow, H. D., and Brown W. J. Thermomagnetic surgery for cancer. J. Surg. Res., *33:* 177–183, 1982.
18. Rosenberg, B., Van Camp, L., and Krigas, T. Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. Nature (Lond.), *205:* 698–699, 1965.
19. Samuelsson, L., and Jonsson, L. Electrolytic destruction of tissue in the normal lung of the pig. Acta Radiol. Diagn., *22:* 9–14, 1981.
20. Sances, A., Jr., and Larson, S. J. Analysis of saline soaked electrodes. *In:* A. Sances, Jr. and S. J. Larson (eds), Electroanesthesia: Biomedical and Biophysical Studies. Clinical Engineering Series, pp. 16–21. New York: Academic Press, Inc., 1975.
21. Schauble, M. K., Habal, M. B., and Gullick, H. D. Inhibition of experimental tumor growth in hamsters by small direct current. Arch. Pathol. Lab. Med. *101:* 294–297, 1977.
22. Schechter, D. C. Flashbacks: containment of tumors through electricity. PACE, *2:* 100–114, 1979.
23. Schenck, H. Heat Transfer Engineering. Englewood Cliffs, NJ: Prentice-Hall, Inc., 1961.
24. Snell, G. D. A cytosieve permitting sterile preparation of suspensions of tumor cells for transplantation. J. Natl. Cancer Inst., *13:* 1511–1515, 1953.
25. Urano, M., Rice, L., Epstein, R., Suit, H. D., and Chu, A. M. Effect of whole body hyperthermia on cell survival, metastasis frequency, and host immunity in moderately and weakly immunogenic murine tumors. Cancer Res., *43:* 1039–1043, 1983.
26. Wetzel, M. C., Howell, L. G., and Bearie, K. J. Experimental performance of steel and platinum electrodes with chronic monophasic stimulation of the brain. J. Neurosurg., *31:* 658–669, 1969.
27. Widder, K. J., Senyei, A. E., and Seas, B. Experimental methods in cancer therapeutics. J. Pharm. Sci., *71:* 379–387, 1982.
28. Williams, C. J., and Whitehouse, J. M. A. Cis-platinum: a new anticancer agent. Br. Med. J., *6179:* 1689–1691, 1979.