NASA Conference Publication 2051

Hyperthermia as an Antineoplastic Treatment Modality

Proceedings of a symposium
sponsored by Langley Research
Center, Hampton, Virginia, and
Eastern Virginia Medical School,
Norfolk, Virginia, January 28, 1978

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Hyperthermia as an Antineoplastic Treatment Modality

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PREFACE

A symposium entitled "Hyperthermia as an Antineoplastic Treatment Modality" was held at the Omni International Hotel, Norfolk, Virginia, on Saturday, January 28, 1978. The sponsors were the National Aeronautics and Space Administration, Langley Research Center (LaRC), Hampton, Virginia, and the Eastern Virginia Medical School (EVMS), Department of Radiation Oncology and Biophysics, Norfolk, Virginia.

Since October 1976 the Langley Research Center has been working in a collaborative biomedical application project with both the Eastern Virginia Medical School and the Medical College of Virginia (MCV), Richmond, Virginia, to develop improved methods of treating tumorous cancers with hyperthermia. The LaRC has fabricated radio-frequency heating equipment and also thermal measuring equipment. The MCV and EVMS are presently evaluating these systems in preclinical experiments. The LaRC is also developing (under contract to Microwave Associates, Inc., Burlington, Massachusetts) a noninvasive device that will provide microwave heating and simultaneous temperature monitoring of cancerous tissues. The MCV and EVMS plan to evaluate this device during the summer of 1978.

The purpose of this symposium was to provide an opportunity for the LaRC, EVMS, and MCV to discuss their progress to date and also to meet together with Microwave Associates, Inc., to discuss their future programs. Medical researchers from the National Cancer Institute, Veterans Administration, University of Virginia Medical School, and University of Maryland School of Medicine, who have also been investigating hyperthermia for cancer therapy, were also invited to participate.

The format of the symposium was as follows: two review papers, four scientific papers, one clinical paper, and four open-discussion sessions. The open-discussion sessions were entitled "Methods of Heating," "Thermal Measurements," "Preclinical Experiments," and "Clinical Trials," respectively. The questions and answers following each of the seven presented papers and also the four open-discussion sessions were recorded, transcribed, and edited and have been included in this publication.

May 1978

Sheila Ann T. Long
National Aeronautics
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HYPERTHERMIA AS AN ANTINEOPLASTIC TREATMENT MODALITY

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INTRODUCTORY REMARKS

I am very pleased to have the occasion to welcome you here for this Symposium convened to discuss the current status of hyperthermia in the treatment of malignant tumors. You may wonder why I, Professor and Chairman of the Department of Surgery at Eastern Virginia Medical School, has been asked to make these introductory comments, and the best reason that I can come up with is that I have been in "hot spots" at least once weekly for the last ten years. Actually, I am here representing both our Dean, Gerald Holman, and Dr. Donald Merchant, Professor and Chairman of the Department of Microbiology, who is Director of the Tidewater Regional Planning Cancer Center.

We have come a long way since the crude initial efforts involving Coley's toxin in the treatment of advanced malignancies. Just three days ago I performed an isolation perfusion of an extremity using hyperthermic perfusate as part of the treatment of an extremity sarcoma. Investigators in greater and greater numbers are attacking the conceptual and technical problems that relate to the utilization of hyperthermic techniques in tumor treatment.

I wish to thank particularly Drs. Anas El-Mahdi and James Shaeffer, as well as Mr. Jack Wakley for taking the responsibility of bringing all of you together. I look forward with interest and enthusiasm to the session today. I am confident that meetings such as this with the exchange of timely and pertinent information are one of the most effective ways to advance both the understanding and application of hyperthermia into the areas of human tumor treatment.

HYPERTHERMIA IN THE TREATMENT OF CANCER

A REVIEW OF THE RADIOBIOLOGICAL BASIS

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SUMMARY

Temperatures in the range 41.5°C to 43.5°C tend to be more damaging to malignant than nonmalignant cells. Where local hyperthermia (41.5°C to 43.5°C) is combined with ionizing radiation, a significant therapeutic ratio may be realized. Total body hyperthermia, alone or combined with other therapeutic modalities, can provide palliation for some systemic malignancies but may not be as effective as local hyperthermia for treating local disease. The influence of hyperthermia on immune mechanisms and the risk of metastatic spread of potential tumor growth stimulation need further investigation. Among other questions needing elucidation before hyperthermia can be considered a standard treatment modality are the time-dose (for heating) relationships to produce an optimal therapeutic ratio and whether the late sequela of combined heat and ionizing radiation may result in an unacceptable risk of patient morbidity.

INTRODUCTION

Radiation therapy may fail to achieve local control of a cancer either because of geographic miss or because of insufficient total dose or time-dose, or both. In the latter case, it may not be possible to deliver a dose of radiation large enough to sterilize all the clonogenic cells because some critical organ in the treated volume, e.g., spinal cord, will receive an intolerable dose. Another possible reason for local failure is the presence of hypoxic foci of tumor cells whose low radiosensitivity results in a significant number of surviving cells when the tolerance dose has been delivered. Another contributing factor could be the inherent capacity of cells from tumors of certain histologies to repair a large proportion of radiation injury following each daily fraction. A number of schemes have therefore been evolved either to increase the radiation sensitivity of the tumor cells or to decrease the sensitivity of the normal tissues in the irradiated volume. Hyperthermia is a technique which has potential for increasing the therapeutic ratio by increasing the radiosensitivity of tumor cells.

Hippocrates described at length the beneficial effects of heat and hot baths in maintaining good health and as a therapeutic regimen for many diseases. It is interesting to speculate whether in Japan, for example, where many people take daily hot baths, there is a connection between this practice and the fact that the national incidence of breast, penile, testicular, and skin cancers is among the lowest in the world. The temperature of these baths ranges from 42°C to 48°C and results in rectal temperatures of approximately 39°C. (See ref. 1.) In Finland, where sauna bathing is practiced, the incidence of testicular and mammary cancer is lower than in neighboring countries where the sauna is not used. (See ref. 2.)

For many years there have been clinical reports indicating that heat has a selectively destructive effect on cancer cells *in vivo* in comparison with surrounding normal tissues.

Some early clinical reports reviewed by Selawry, *et al* (ref. 3) and Cavaliere *et al* (ref. 4) include an 1866 account describing histologically proven sarcoma of the face which regressed after high fever associated with syphilis. The reviewers also mentioned a discussion by Coley *et al* (ref. 5) of 38 patients with advanced carcinoma who had an association with accidental or deliberate infections. In this series there was complete disappearance of the tumors in 12 cases, and a significant regression in 19 cases. A detailed review of this study was done by Nauts *et al* (ref. 6).

In Vitro Studies

When population of cells are exposed to a series of graded doses of X-rays and the percentage of surviving cells counted, the plot of surviving fraction (S) on a log scale against dose on a linear scale yields a dose-effect relationship characterized by an initial shoulder region at low doses and an exponential region at higher doses.

The parameters of this relationship, D_o, D_q, and n, can be used to define the radiosensitivity of the cells as an estimate of their capacity to repair radiation injury. (See fig. 1.)

If cell populations are incubated at elevated temperatures for different periods of time, the proportion of cells surviving the hyperthermia may be described by using a notation similar to that used for survival after X-radiation.

Figure 2, taken from report by Henle and Leeper (ref. 7), illustrates the response of cells either to X-ray or hyperthermia. The similarities in shape of the dose-response relationships do not imply common mechanism of action, and care must be exercised not to draw unwarranted conclusions by giving the survival characteristics the same interpretation for hyperthermia as for X-ray.

An example of the potentiating effect of hyperthermia on the radiation response of CHO cells is shown in figure 3 taken from a report by Gerner (ref. 8). On the right side of the figure is shown the effect of incubating the cells at temperatures up to 43°C for 1 hour before the X-radiation. The solid circles (upper curve) show the response to radiation at a normal physiological temperature, 37°C. Note that increasing the incubation temperature up to 43%C, a temperature which by itself decreased cell survival to 20 per cent, causes a dramatic increase in radiosensitivity, i.e., by a factor of 2.

As in many new investigative procedures, researchers have adopted a technical jargon. One such expression is the thermal enhancement ratio or TER. This is generally the ratio of a dose of X-ray or drug required to elicit a given effect, compared with the dose of the same agent required to

give the identical effect when combined with hyperthermia.

The term can also be used to indicate the ratio of the slopes of the exponential portions of the dose-response curves when the relationships are determined with and without hyperthermia. It can be considered as analogous to the expressions "dose-modifying factors (DMF)" or OER commonly used in radiation biology.

In the example just stated, the thermal enhancement ratio would be indicated as $TER_{43/1\ hr.} = \frac{140}{65} = 2.2$.

In this system, the post-irradiation heating did not result in a TER significantly different from that found with pre-irradiation hyperthermia.

At temperatures between 41.5°C and 43°C, a number of systems show tumor cells to be more sensitive to thermal injury than are the normal cells of the same origin. Figure 4, taken from a report by Giovanella et al. (ref. 9) is representative of a large body of information indicating this differential thermal sensitivity. The optimum therapeutic advantage probably will be obtained with hyperthermia in the range of 41.5°C to 43°C and that the differential effect between tumor and normal cells may diminish at higher temperatures.

Thermodynamics considerations suggest the possibility that temperatures slightly in excess of 37°C might prove stimulatory to tumor cell growth. Some in vitro studies tend to support this condition (refs. 10, 11, and 12). Above 41.5°C a consistent inhibitory effect can be demonstrated. In applications of hyperthermia to clinical oncology (table 1), temperatures between 41.5°C and 43.0°C are thought to be optimal for differentially sensitizing tumor cells to damage by ionizing radiation.

In some systems the effects of combined X-ray and hyperthermia on cell survival are influenced by the sequence in which the treatments are applied. Gerner et al. (ref. 13) found a slightly increased thermal enhancement of radiation damage of CHO cells heated (one hour at 43°C) immediately after irradiation, but noted an opposite response for HeLa cells. Van der Schueren 1975 (ref. 14), using a cell line derived from ureteral tissue, found a greater thermal enhancement of cell kill by heating near the end of, or immediately following, exposure to X-radiation.

Sapareta et al. 1976 (ref. 15) compared the effect of heating (42.5°C or 45.5°C) CHO cells during and up to 120 minutes before or after a 500 rad dose of X-radiation. The data clearly showed that the potentiating effect of heat on cell death was greatest when the radiation was delivered early during the heating interval. There was a rapid loss of thermal effect if the radiation was given after the heating. Using radiation damage to mouse skin as the criteria of response, Field et al. (ref. 16) found that heating (42°C or 43°C for 1 hour) at intervals up to 2 hours before X-radiation yielded a significant thermal enhancement. The thermal enhancement was lost rapidly if the heat was given after the irradiation.

Gillette and Thrall in 1975 (ref. 17) found thermal potentiation of X-ray

damage to mouse mammary carcinoma to be highest when the heat was applied immediately after irradiation. Based on extensive clinical experience, Holt (ref. 18) concluded that the TER is maximum when the hyperthermia was delivered before the irradiation. Overgaard and Overgaard (ref. 19) using a solid tumor in mice find that the potentiating effect of hyperthermia on the response of the tumor to X-radiation was independent of the sequence in which the treatment were applied up to an interval of 24 hours.

It seems reasonable to assume that the maximum potentiation of radiation damage by hyperthermia would occur when the interval between treatments was short. In the application of hyperthermia to clinical radiation oncology, the sequence will probably be determined by the treatment logistics of the department at least until the basis of selecting one sequence over another is more clearly evident. The expression of thermal damage is not limited to the potentiation of X-ray responses. Figure 5 (ref. 19) shows the interaction of hyperthermia and drugs when temperatures of 42°C produce very large decreases in cell survival. Figure 6 (ref. 20) shows the response of population of tumor cells which were treated in vivo but assayed in vitro. These data indicate that both in vivo and in vitro hyperthermia enhances the effectiveness of these cytotoxic agents.

There are no data available at this time showing the effect of multidrug chemotherapy and hyperthermia. Such studies might yield valuable information.

Before the potentiating action of hyperthermia can be exploited as part of a therapeutic regimen, it is necessary to establish whether a significant therapeutic ratio can be achieved.

The therapeutic ratio is essentially a cost-benefit assessment. Figure 7 illustrates this relationship. It is determined by estimating the damage done to the tumor, i.e., regression in size or palliation of symptoms compared with the damage done to the normal tissues in the irradiated volume.

Table 2, based on the work of Robinson in Baltimore (ref. 21) shows that although both the TER for tumor and normal tissues increase with temperature, the TER for tumors increases faster than that for normal tissue (skin). This observation indicates that a significant therapeutic ratio can be achieved. There are data indicating that the differential sensitivity of normal and tumor cells is absent at higher temperatures.

Radiation and the Oxygen Effect

One of the problems confounding the radiotherapist is the fact that hypoxic cells have a reduced radiosensitivity. If the radiosensitivity of cells made severely hypoxic during irradiation is compared with those fully oxygenated, the sensitivities characteristically differ by a factor of between 2 and 3. This ratio is designated as the oxygen enhancement ratio or the OER. In a number of systems, hypoxic cells have been shown to be more sensitive to thermal injury than are toxic cells. In many systems, therefore, it is possible to demonstrate a significant reduction in OER by hyperthermia. This fact is potentially of very great significance, since it may increase the chance of control or provide palliation of bulky local disease

which would otherwise be impossible. This is demonstrated by table 3 taken from a report by Robinson (ref. 21). Other investigators (ref. 22) have also observed an enhanced TER for hypoxic polls.

Whole Body Hyperthermia

About 1913, A. A. Strauss used surgery and hyperthermia to treat carcinoma of the rectum and colon, with excellent results (ref. 23). By 1956 he had treated 250 such patients, and long-term follow-up indicated results comparable with, or superior to, any therapy then available (ref. 24).

Pettigrew et al. (refs. 25 and 26) treated a number of terminal-stage cancer patients with total-body hyperthermia (41°C to 42°C) and occasionally combined this treatment with chemotherapy. In all cases the patients were no longer treatable by conventional therapeutic modalities. For those treated, hyperthermia alone produced a significant regression in sarcomas and in tumors of the gastro-intestinal tract. Breast and genito-urinary tumors responded poorly. All patients with pain or bleeding experienced palliation of these symptoms. Figure 8 taken from a report by Stolwijk (ref. 27) shows the probably range of temperatures that might be tolerated for whole body hyperthermia. It is unlikely that a temperature in excess of 43°C could be tolerated for more than a few minutes without significant risk of severe damage. Most clinical series have therefore attempted to achieve a core temperature in the range of 40°C to 42.5°C.

As with any therapy whose mechanism of action is not well understood there are many questions that remain to be resolved. It seems likely that temperatures only slightly above the normal physiological range may stimulate tumor growth rather than inhibit it. There are some experimental data which support this possibility (ref. 28). There is some indirect evidence from animal studies that whole body hyperthermia (to 40°C temperature elevation) may temporarily suppress immune mechanisms and perhaps potentiate metastatic spread. Figures 9 and 10 taken from a report by Dickson (ref. 12) illustrate this concern. Animals studies (refs. 29 and 30) indicate an increased risk of metastatic spread with whole body hyperthermia. Evidence for an increased risk from local hyperthermia has not been clearly demonstrated. The effectiveness of local compared with total body hyperthermia is illustrated by figure 11 taken from a report by Dickson and Muckle (ref. 30). This may not be critical consideration in palliative therapy for systemic disease.

Regional Hyperthermia by Perfusion

A number of investigators have used hyperthermic perfusion of extremities to treat disease when local spread was suspected. The data in table 4 from a report by Stehlin et al. (ref. 31) show the results of hyperthermia perfusion on melanoma lesions of the extremities. The data shows hyperthermia resulted in an increased incidence in regional control and palliation of disease.

Cavaliere et al. (ref. 4) reported tumor regression in 15 of 22 patients treated with heated perfused blood for sarcomas and melanomas of the extremities. In the Proceedings of the International Symposium on Cancer

Therapy by Hyperthermia and Radiation, Cavaliere et al. (ref. 32) reviewed their experience in using hyperthermic perfusion to treat 111 patients with advanced tumors of the extremities: 5, squamous-cell carcinoma; 27, osteogenic sarcoma; 28, other sarcomas; and 51, melanoma. In some instances, chemotherapeutic agents were incorporated into the perfusate. Most of these patients subsequently underwent amputation of the affected limb. Although there was a variety of temperatures, durations, and other conditions, there was no doubt that initial tumor response and NED survival for comparable stages of clinical disease treated without hyperthermia (historical controls) were consistently improved by the use of hyperthermia.

Hall et al. (ref. 33) perfused the bladders of 32 patients suffering from carcinomas of the urinary bladder with solutions at temperatures between 41.5°C and 45°C. There was substantial tumor regression in 26 of the patients and complete tumor regression in 4.

Cockett et al. (ref. 34) reported a reduction in tumor size following local hyperthermia and regional radiotherapy in 7 elderly patients with incurable carcinomas of the bladder. In contrast, Lunglmayr et al (ref. 35) reported that local hyperthermia combined with chemotherapy failed to offer any substantial gain in the treatment of low stage vesicle papillomas because of a high rate of complications which followed this treatment.

Local Hyperthermia

Selawry et al. (ref. 3) made reference to more than 30 published clinical series in which a wide spectrum of tumors were treated by various combinations of X-ray and hyperthermia. All these reports noted the potentiating effect of hyperthermia on radiation response of the tumor, although uncertainties in radiation dosimetry and temperatures measurements made more precise comparisons of response impractical.

Holt (ref. 18) treated patients by means of a device consisting of 12 RF generators operating at 433.92 MHz and placed in a circular configuration, with the patient sitting or standing in the center of the cylindrical array. For most patients the RF irradiation was combined with X-ray therapy or chemotherapy. The report indicated that 363 patients with advanced disease were treated. The author gave no details concerning tissue temperatures, duration of the radiofrequency treatments, or intervals between RF and X-ray treatments (H + Rx). He concluded that RF radiation produced significant enhancement of therapeutic ratio for patients receiving X-ray therapy. Hornback et al. (ref. 36) using a similar technique reported a significant enhancement of radiation response for patients with a wide range of malignancies.

Brenner (ref. 37) combined hot air jets and microwave (2450 mc/sec) to induce local hyperthermia which they used with orthovoltage radiation to achieve impressive tumor regression in 6 patients. LeVeen (ref. 38) reported a series of 21 patients treated by inducing local hyperthermia in tumors through use of a radio frequency generator operated at 13.56 MHz. In all cases there was significant tumor regression.

Johnson (ref. 39) reported results of a pilot clinical trial to assess the therapeutic ratio when X-radiation was combined with local hyperthermia to treat patients with multiple superficial lesions, i.e., up to 2 cm. in depth. The lesions were heated to 41°C to 42.5°C with 915 MHz microwaves for periods of 1½ to 2 hours. Heating alone produced no damage to the normal skin. The thermal enhancement ratio (TER) for irradiated normal skin was 1.2 to 1.3. Heating during and immediately after irradiation produced the maximum response of tumor and normal tissues. The data are not yet sufficiently complete to make possible an estimate of the therapeutic ratio.

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TABLE 1.

37.0 - 38° 0°C	39.0° - 41° 0°C	41.5 - 43.0°C	43.5 - 46.0°C
Normal Temperature	Potential Stimulation	Differential Thermal damage to tumor cells	Loss of differential for thermal damage to tumor cells

Table - 1 shows the probable useful range of temperatures for tumor sensitization in therapeutic oncology.

TABLE 2.

TEMP. (°C)	SKIN RESPONSE T.E.D.$_{50\%}$ (rads)	SKIN RESPONSE T.E.R.*	TUMOR RESPONSE T.C.D.$_{50\%}$ (rads)	TUMOR RESPONSE T.E.R.*	TUMOR T.E.R. SKIN T.E.R.
37.5	2522	1.00	5250	1.00	1.00
41.0	2122	1.18	3800	1.38	1.17
42.5	1506	1.67	1910	2.74	1.64
43.0	1223	2.06	1230	4.27	2.06

A comparison of the thermally induced increase in radiation sensitivity of C3H mammary tumors and normal mouse skin. T.E.R. (Thermal Enhancement Ratio) is defined here as the ratio of the dose required to produce 50 percent response at 37.5°C to the dose required to elicit the same response at a specified elevated temperature.

TABLE 3.

TEMP (°C)	ANOXIC	OXYGENATED	O.E.R.
37.5	0.385 ± .022	0.947 ± .046	2.46 ± .18
41.0	0.406 ± .017	1.16 ± .09	2.86 ± .25
42.0	0.68 ± .06	1.86 ± .017	2.72 ± .35
42.5	1.07 ± .06	1.81 ± .18	1.69 ± .14
43.0	1.93 ± .09	2.66 ± .12	1.38 ± .09
43.5	2.24 ± .17	2.09 ± .33	0.87 ± .16

The differential effect of hyperthermia on anoxic and oxygenated mouse bone marrow cells. The main body of the table gives slopes of both anoxic and well-oxygenated cells in units of 10^{-2}/rad. Treatment times were for one hour except for the highest treatment temperature, 43.5°C. for which a shorter time of 20 minutes was used. The O.E.R. values were calculated from the ratio of survival curve slopes.

TABLE 4.

COMPARATIVE DATA ON STAGE IIIA METASTATIC MELANOMA OF THE EXTREMITIES

	No Heat (*1951–65*)	*Heat* (*1967–74*)
Number of patients	27	30
Female	13	24
Male	14	6
Extremity involved		
Upper	7	2
Lower	20	28
Regional nodes proved negative microscopically	22/27, 81%	17/30, 56%
Patients with more than one recurrent (metastatic) nodule	21, 78%	23, 77%
Radical amputation	8/27, 30%	0
Patients perfused	21/27, 78%	30/30, 100%
Perfusion drug	Alkeran	Alkeran
Average dose Lower extremity	1.2–1.6 mgm./kgm.	0.9 mgm./kgm.
Perfusion time	45–120 mins.	45–120 mins.
Skin temperature	86–90°F.	102–105°F.
Muscle temperature	92–95°F.	102–104°F.
Five year survival rate		
Males and females	22.2%*	76.7%†
Females only	13, 30.7%*	24, 88.7%†

*Crude.
†Berkson-Gage.

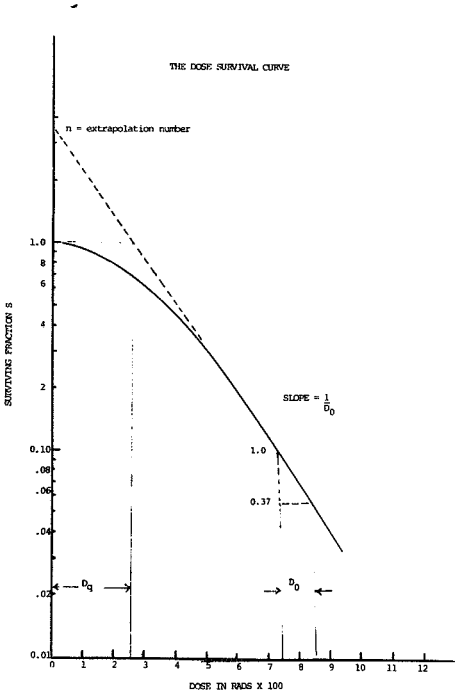
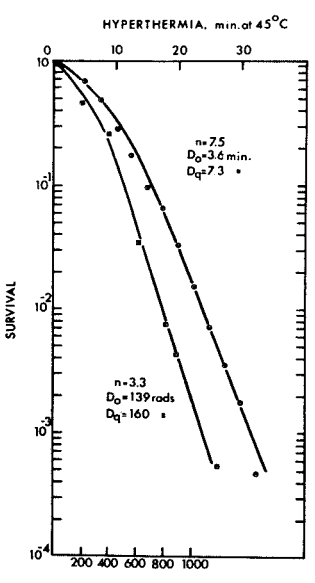
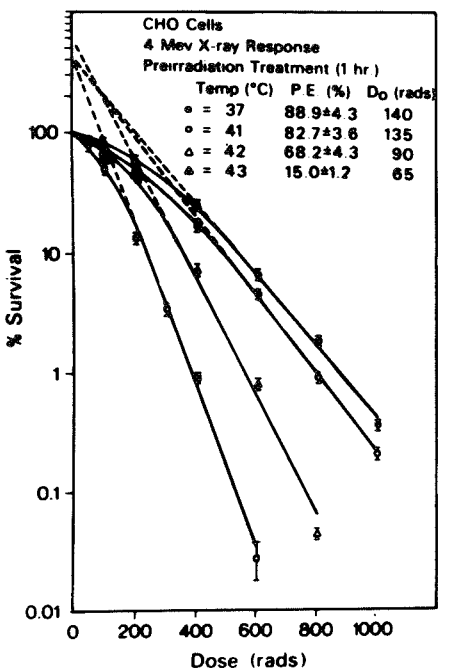


Figure 1.



Fractional survival (corrected for cellular multiplicity) of cells heated for various times at 45°C (upper curve, ●) or X rays (lower curve, ■). In this and the following figures curves were fitted to the data points by eye. Standard errors were smaller than the plotted points.

Figure 2.



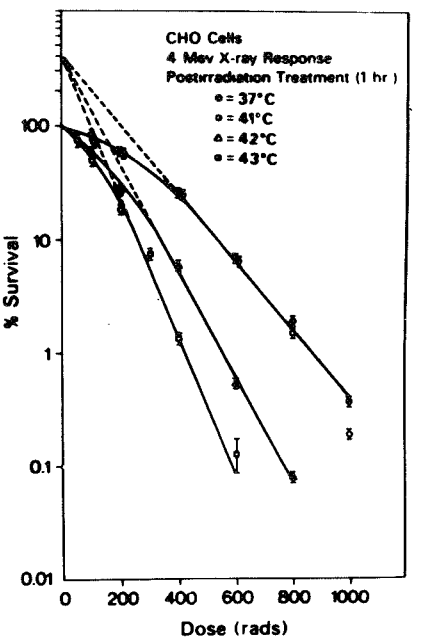
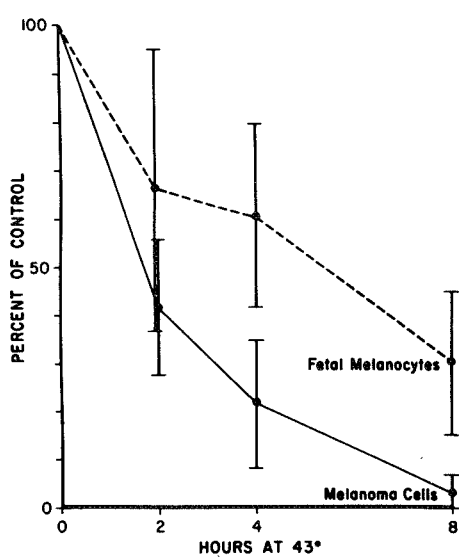
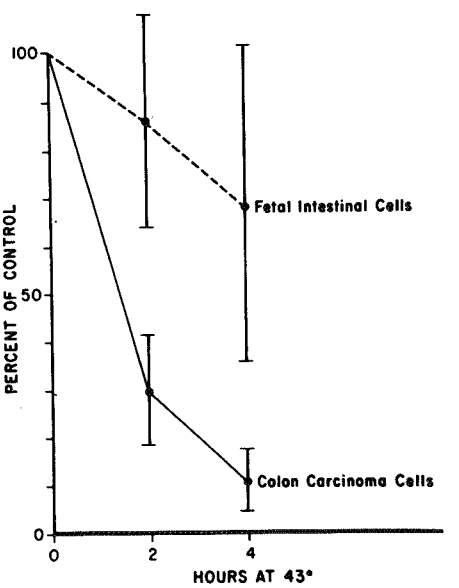


Figure 3.

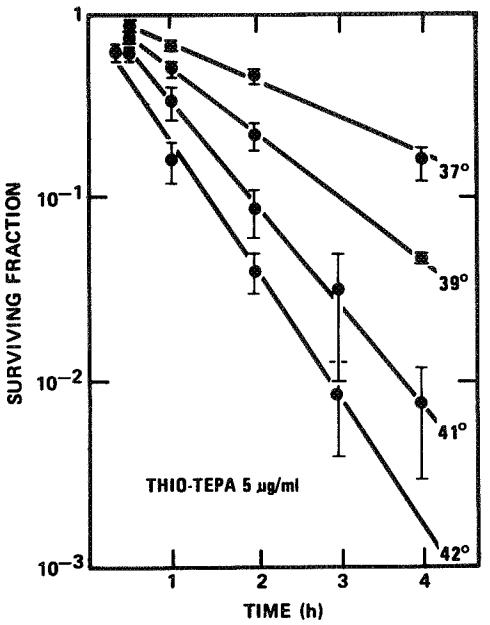


The percentage of surviving melanoma cells and fetal melano- as a function of the duration of exposure to 43° (mean ± S.D. of pooled iments given). Data from Table 1. At 4 and 8 hr, the difference in heat ivity between fetal melanocytes and melanoma cells is statistically icant, $p < 0.05$ and $p < 0.01$, respectively.

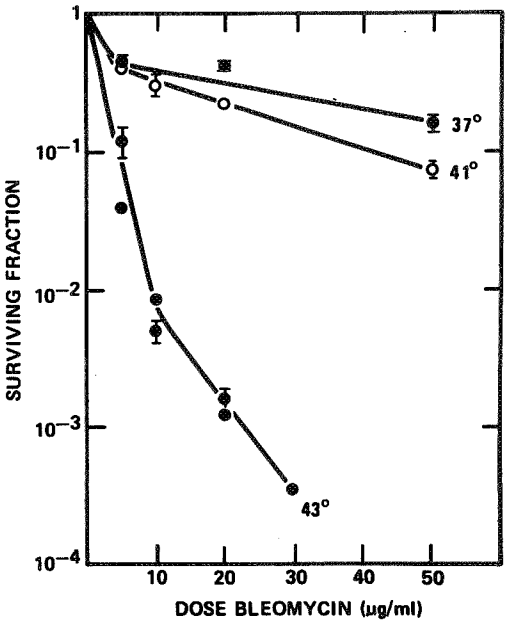


The percentage of surviving colon carcinoma cells and fetal intestinal cells as a function of the duration of exposure to 43° (mean ± S.D. of pooled experiments given). Data from Table 2. At 2 and 4 hr, the difference in heat sensitivity between fetal intestinal cells and colon carcinoma cells is statistically significant ($p < 0.01$).

Figure 4.

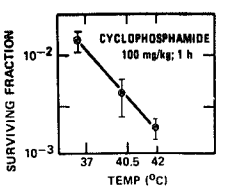


Effect of elevated temperature on the killing of V-79 Chinese hamster cells by thio-tepa (1).

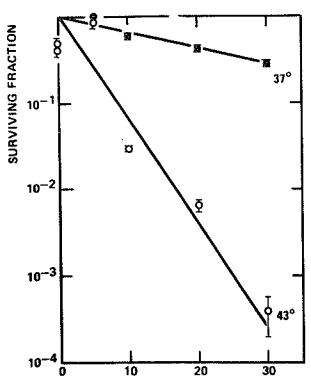


Effect of elevated temperature on the killing of HA1 Chinese hamster cells by bleomycin (6).

Figure 5.



Effect of elevated temperatures on the killing ("in vivo") of EMT-6 tumor cells by cyclophosphamide (Hahn, unpublished data)



Effect of 43°C on the cell killing "in vivo" of EMT-6 tumor cells by adriamycin (7).

Figure 6.

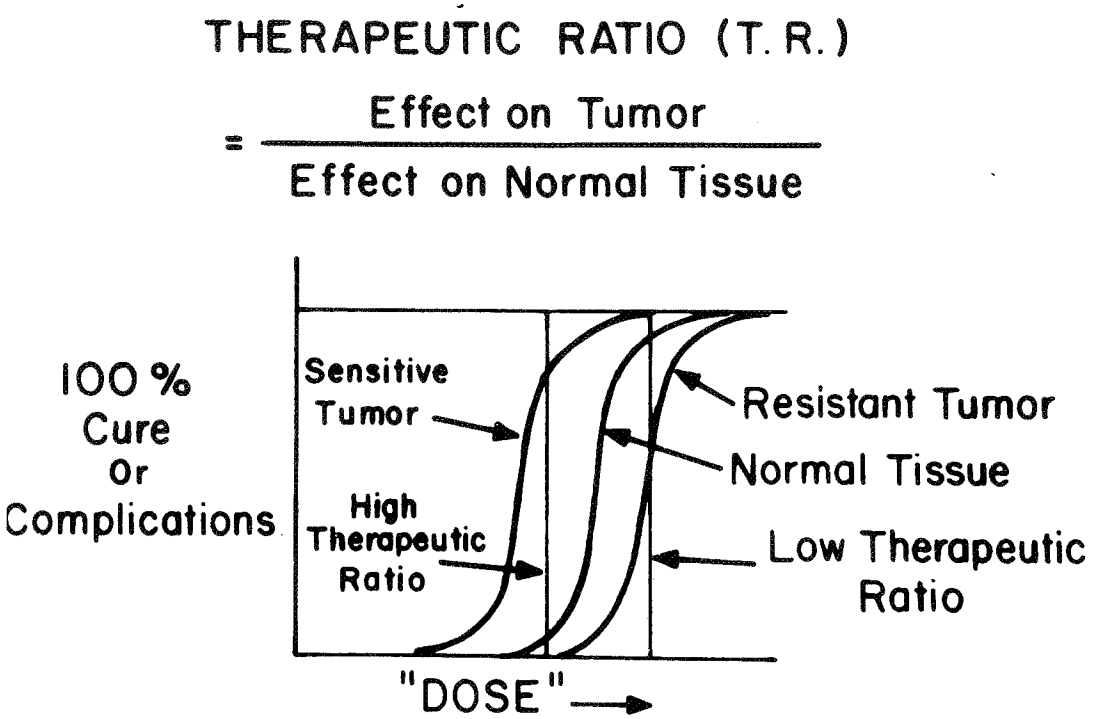
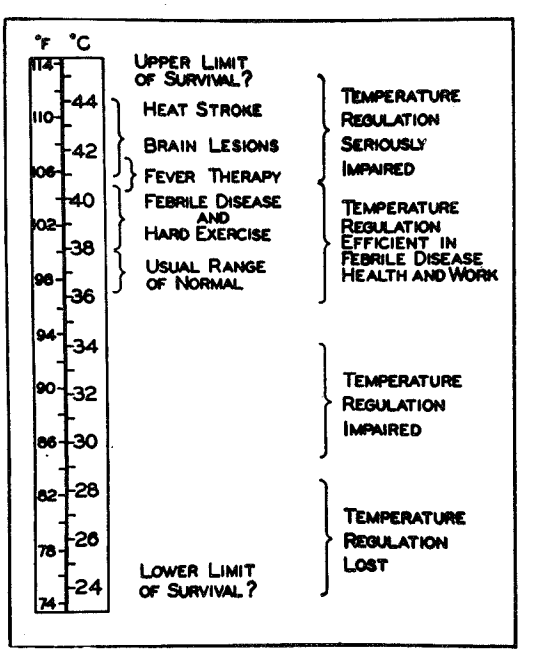
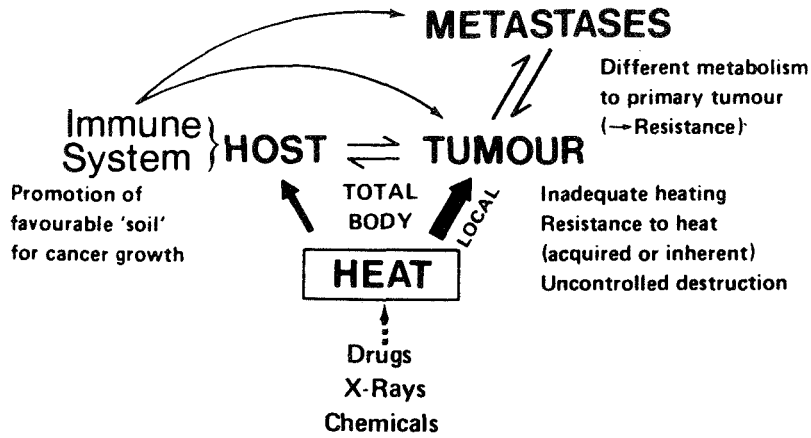


Figure 7.



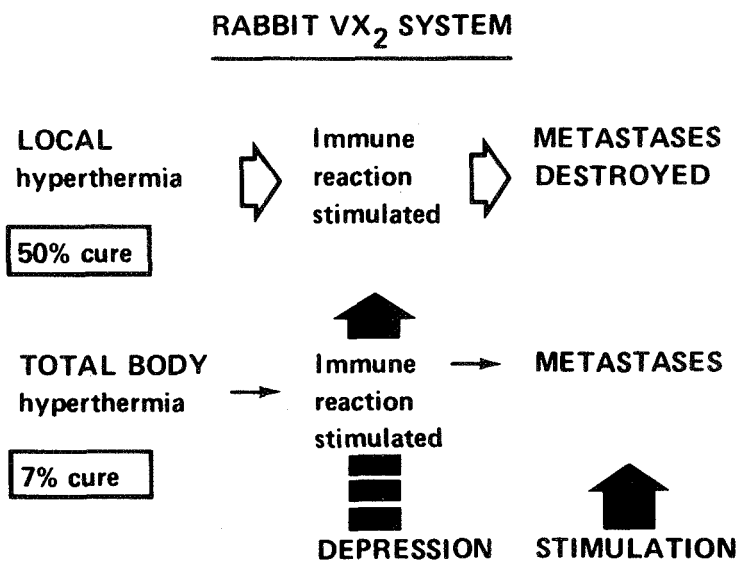
Approximate range of internal body temperatures in man with associated responses or consequences.

Figure 8.



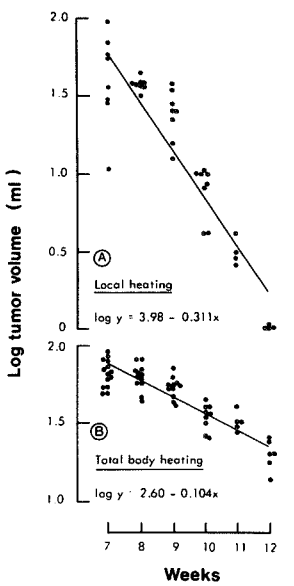
Host-tumor-therapy triad interrelationships govern therapeutic outcome. The possible hazards involving the host and the tumor when heat constitutes the treatment are indicated; 'potentiators' of heat (broken arrow) are viewed as affecting both these components.

Figure 9.



Scheme to illustrate the difference in results obtained in treatment of the VX2 carcinoma by local heating and total body heating in terms of postulated effects on the host immune system.

Figure 10.



Regression lines fitted to log tumor volume measurements from the 7th week following tumor inoculation. Local hyperthermia to the tumor-bearing limb (*A*), or total-body hyperthermia (*B*), was applied on Days 35, 36, and 37 after cell inoculation. The individual tumor volumes for all experiments shown in Chart 3 have been plotted, and the equation to the regression line in each case is given.

Figure 11.

Questions and Answers Following Baker's Paper

Singh: Why did you not go beyond 43° C?

Baker: That last study was not my particular study; but the reason for not going beyond 43° C is that as you start to increase the temperature in excess of 43° C, you begin to get cell killing and you lose the sensitizing effect of the radiation. The idea of the radiation is to increase the maximum potential very quickly. At higher temperatures you do not need radiation; you kill all the cells without it.

Merz: What were the drugs?

Baker: The drugs were cyclophosphamide and adriamycin.

Merz: What were the two before?

Baker: The two before were bleomycin and thio-tepa.

Singh: Dr. Baker, how is the heating done in the studies by Dr. Holt, for example?

Baker: Dr. Holt uses a circular array of some 12 radio-frequency generators operating at 414 megahertz. This radio frequency will heat a very large volume of tissue. The frequency is readily absorbed so that there is very effective heating. Dr. Pettigrew uses a liquid molten paraffin bath. He bags the patient in a plastic bag, intubates him, and uses spinal anesthesia. He depends on the heat of fusion of the paraffin as it goes from the liquid to the solid state, in order to produce the proper temperature to heat the patient. His patients are kept under these conditions for 6 to 14 hours, so it is a simple system. The German group uses infrared radiation for their total body hyperthermia. The group in Colombia at Bogota uses Coley's toxin, or its local equivalent, for inducing systemic hyperthermia. Other groups use different frequencies of radiation for local hyperthermia. The RTOG protocol calls for the use of 915 megahertz. We have tried both 2450 megahertz, and more recently 27 megahertz, radiation for inducing local hyperthermia.

E. Long: I did not catch, and perhaps you had it there, the amount of time that locally it was heated, or systemically it was heated, versus the amount of time for the X-ray radiation.

Baker: It turns out that as long as you are in a temperature range between 41° C and 43° C the effectiveness of your thermal enhancement -- or if you like, the thermal enhancement ratio -- is directly related to the duration. So you would, if you have a 41° C hyperthermia, like to sustain it for as long as you could. In this circumstance we are talking about some 3, 4, 5, or more hours. On the other hand, if you can get to a temperature of around 43° C, then probably 1 to 2 hours will give you the maximum therapeutic ratio.

E. Long: How does that compare to the length of time for the X-rays?

Baker: Well, the X-rays are conventionally delivered at conventional dose rates of perhaps 100 to 250 rads per minute. If your fraction size is as we have usually used, somewhere between 300 and 500 rads per fraction, then the duration of your radiation would be somewhere between 3 and 5 minutes. Yes, Dr. Atkinson.

Atkinson: Don, when I came in, you had a slide up of therapeutic ratios; and I did not quite get the story that went with them. Was that on in vitro or in vivo measurements? How was it measured?

Baker: I am not sure which slide we were talking about. I think this was an in vivo mouse mammary carcinoma system.

Atkinson: How was the damage to the normal tissue measured?

Baker: I understand, yes. This was the damage done to the skin. This was a skin reaction graded 1, 2, 3, etc., compared to local control of the mammary tumor. This was the ratio.

Singh: The temperatures that you are talking about are the entire mouse temperatures. They are not the temperatures of the region you are treating. Is that right?

Baker: Well, in some of the work I was referring to, we were talking about systemic hyperthermia and the temperature of the whole body. In other cases, it was local hyperthermia and the temperature of the tumor, or the volume that you are particularly concerned with radiating.

Singh: And that was that low for this treatment? It did not go higher?

Baker: No, no. Once you get higher than about 43° C, you begin to produce such an increase in sensitivity of the normal tissues that your therapeutic ratio is lost and there is no advantage.

Beebe: In these, did you measure the temperature of the tumor and of the tissue separately?

Baker: Yes. That is the way that we always try to do it. There are some considerable difficulties with making that measurement, as you can well imagine, because there are local areas where there is circulation, and for other technical reasons and physiological reasons, there are temperature gradients that exist.

Rosato: Dr. Baker, the incidence of cancer in undescended testes is known to be seven- or eight-fold greater than the normal situation. The assumption unproven is that this is the result of the exposure of the testicle to a higher temperature over a longer period of time in its intra-abdominal

position. Is there any literature, or any caveats, about the possible carcinogenic effect of hyperthermia, especially when applied over a long period of time?

Baker: No. This is information we do not have, but there are a couple of studies in which this is addressed indirectly. If you take an animal, a rat for example, and place him in a chronic, low temperature, 3 or 4 degrees above freezing, he compensates for this by increasing his metabolic rate. In fact, he will double it. He will live his whole life at twice its normal rate. Not only that, but he will compensate by increasing his core body temperature. His core body temperature will go up about 2 degrees, so now you have an animal whose core temperature is up 2 degrees, and it is up 2 degrees for the rest of his life. Now, the incidence of tumors in those animals is dramatically less, not more, so that this leaves the question still very much unanswered. But that is about the only comparison I can make for you.

CURRENT STATUS OF WHOLE BODY HYPERTHERMIA TECHNOLOGY

E. RONALD ATKINSON

ABSTRACT

Various techniques for the clinical practice of whole body hyperthermia (WBH) have been reported over the past 60 years. These techniques have involved the use of assorted exotic instrumental paraphenalia which had made WBH cumbersome and dangerous to apply. Recently, new insights into the production and control of WBH have been obtained at the Division of Cancer Treatment of the National Cancer Institute. As a result, WBH technolgoy has been vastly simplified to the point that current clinical trials at NCI demonstrate that WBH may now be safely performed at nominal whole body temperatures of 42°C, routinely, for four-hour periods. Using these techniques, patients have been and are being treated in a wide variety of disease states. It has become apparent that WBH, so performed, is simple enough to be applied by one or two paramedical personnel, as a bedside procedure, under the supervision of a physician. No elaborate equipment is required and the conditions of treatment are controlled and reproducible. Of great importance to the radiotherapy community, the patient, during this WBH, is accessible for adjuvant therapy and is free to be transported from place to place without support equipment.

If it may be assumed that 42°C is an effective radiosensitization temperature, it is apparent that we have, already at hand, a safe, simple and effective means to irradiate deep internal organs at this elevated temperature. In addition, mild WBH, at about 39°C, produced by these modern techniques, has been found to linearize and increase patient response to external heat sources to the extent that techniques of local hyperthermia may be greatly simplified.

Although limited data are available on the effect of 41°C local hyperthermia on tumor PO_2, no data are currently available on the effect of whole body hyperthermia on tumor blood flow, pH, PO_2 and oxygen response. This physiological data should be determined to allow predictions to be made of future clinical trials on the basis of collateral hyperthermia investigations.

TEMPERATURE UNIFORMITY IN HYPERTHERMAL TUMOR THERAPY*

George H. Harrison, J. Eugene Robinson, and George M. Samaras
University of Maryland School of Medicine

SUMMARY

C3H mouse mammary tumors heated by water bath or by microwave-induced hyperthermia exhibit a response that varies sharply with treatment temperature; therefore, uniform heating of the tumor is essential to quantitate the biological response as a function of temperature. C3H tumors implanted on the mouse flank were easily heated to uniformities within 0.1° C by using water baths. Cold spots up to 1° C below the desired treatment temperature were observed in the same tumors implanted on the hind leg. These cold spots were attributed to cooling by major blood vessels near the tumor. In this case temperature uniformity was achieved by the deposition of 2450 MHz microwave energy into the tumor volume by using parallel-opposed applicators.

INTRODUCTION

Our group has carried out a series of hyperthermia studies by using third-generation transplants of spontaneous mammary tumors on the flanks of C3H mice. The tumors were heated by immersion in water baths and considerable effort was expended to characterize tumor thermal uniformity under treatment conditions (ref. 1). The results indicate that the tumors were uniform in temperature to within about 0.1° C and were within about 0.1° C of the core of the water bath.

Data taken with this tumor and water bath heating showed (fig. 1) a dramatic effect of hyperthermal treatment on tumor radiosensitivity (ref. 2). The increase in radiosensitivity was a strong function of treatment temperature. In addition, a comparison of these tumor data with comparable data from normal mouse skin showed that a therapeutic advantage might be gained by ionizing radiation treatment at elevated temperatures (ref. 2). Data from other laboratories, primarily from tumors implanted on the mouse leg and also heated by immersion in water baths (ref. 3), show smaller therapeutic advantages for similar water bath temperatures and X-ray doses. In addition, heat alone provides a therapeutic advantage, treatment sensitivity depending strongly on temperature.

HEATING METHODS

To broaden our heating capability we have developed microwave heating techniques applicable to small laboratory animals. (See refs. 4 and 5.)

*Supported in part by ACS Grant PDT-33 and USPHS NIH Grant CA 18872-01.

One of our approaches has been to surround the mouse tumor with solid or liquid bolus material in plane-parallel-slab geometry and to irradiate with parallel-opposed microwave beams, in direct analogy to conventional radiation therapy techniques used with ionizing radiation. Microwaves at 2450 MHz are delivered by simulated TEM waveguide applicators, time multiplexed so that tumor heating occurs from opposite sides (fig. 2). By using the semi-solid Guy-type muscle phantom material as bolus (ref. 6), tumor heating nonuniformities were at least 0.3° C.

One difficulty is that there are unavoidable temperature gradients from surface to interior in solid bolus material. In a stirred heated liquid bolus, these gradients would be negligible. The liquid also improves thermal coupling between bolus and tumor. Therefore, we are currently using a heated solution consisting of 80% (w/w) isotonic and saline and 20% (w/w) ethanol. Electric properties of this solution closely approximate those of wet tissues at 2450 MHz. Even when unstirred, substitution of the liquid bolus has resulted in substantially improved tumor heating uniformity and a significant reduction in thermal inertia. Faster liquid heat-up may be due to the realization of a more favorable bolus coupling geometry rather than to calorimetric properties of the solution, although the liquid phase promotes convective heat transfer between tissue and phantom. The bolus material is maintained at a temperature slightly lower than the desired tumor treatment temperature, and microwave energy supplies the additional required increment in heating.

TUMOR TEMPERATURE PROFILES

The parallel-opposed microwave heating apparatus has been used to treat tumors implanted on the flank and on the leg. Temperature distributions were measured by drawing small thermistor probes (YSI 514, 524) through the tumor, along parallel lines at different distances from the bone and leg muscle. As in the case of water bath heating, uniform temperature distributions were achieved for the flank tumors, that is, constant temperature to within ±0.1° C, without the introduction of microwave power. In contrast, immersed leg tumors were quite nonuniform in temperature in the absence of microwave power. Figure 3 shows two thermal profiles taken through a leg tumor. The tumor was roughly ellipsoidal in shape and measured 15 × 12 × 8.5 mm along the three orthogonal major axes. The water bath in which it was immersed was maintained at 42.9° C. One profile was taken along a line near the leg bone, but well within the tumor. The second was taken about one-third of the way into the tumor on the side away from the bone. The profile shows marked temperature variations with temperatures measured as low as 41.6° and 42.2° C for the thermal scans near and away from the bone.

Figure 4 gives another example of the cold central region near the bone of a smaller tumor (10 × 8 × 5 mm) also heated by immersion, together with the more uniform thermal pattern of tumors immersed in liquid bolus and microwave heated. The liquid bolus was maintained at 42.9° C and the tumor with bolus was irradiated with a microwave power of 22 watts. Heating with combined microwaves and temperature-controlled liquid bolus much improved the thermal uniformity as is shown in the two top curves.

DISCUSSION

Temperature nonuniformity of the tumors heated by water bath can be attributed to two factors: Major vessels run down both ventral and dorsal aspects of the leg and act as heat pipes to locally cool the tumor. In addition, in order to reach the inner aspect of the tumor, heat must be transferred through the muscle and bone of the leg. The cooling effect of blood flow near the bone is also evident in the lower temperature achieved near the bone when the tumor was microwave heated.

Because of the strong dependence of thermal and radiation sensitivities on temperature, the cold spots which we see in these tumors would markedly affect any measure of tumor response. In assays such as tumor cure and tumor regrowth time, the measured response is probably characteristic of the lowest treatment temperature experienced by any significant fraction of the tumor under treatment. Thus, these tumors on the leg immersed in water baths at 45.0° C might more appropriately be compared with uniformly heated tumors immersed in water baths 1° to 1.5° C lower in temperature.

These observations might have some bearing on the discrepancies in biological hyperthermia data on different tumors subjected to apparently similar thermal treatments. They should stand as a reminder that careful thermal studies are even more important to thermobiology than good radiation dosimetry is to conventional radiobiology.

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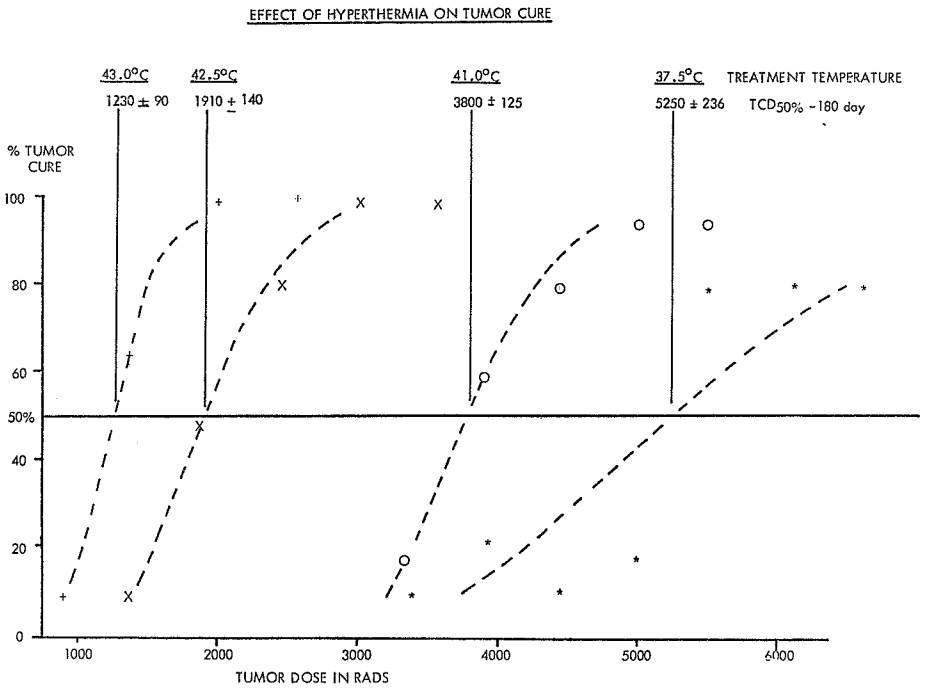
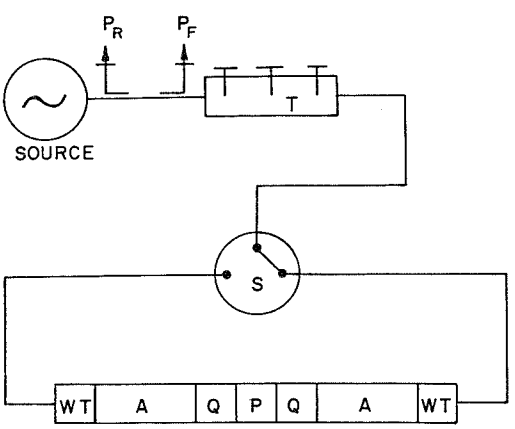


Figure 1.



P = FORWARD POWER
P = REFLECTED POWER
P = TISSUE EQUIVALENT MATERIAL + TUMOR
Q = QUARTER WAVE TRANSFORMER
A = APPLICATOR
WT= WAVEGUIDE TUNER
S = SWITCHING DEVICE
T = COAXIAL TUNER

Figure 2.

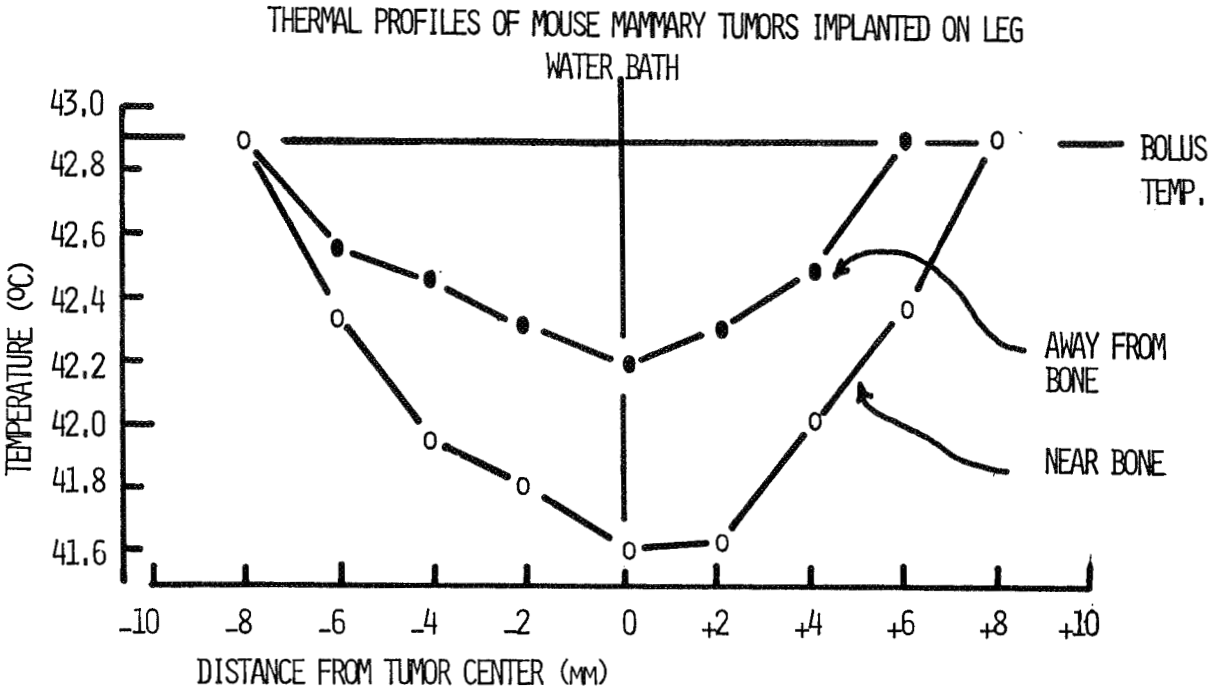


Figure 3.

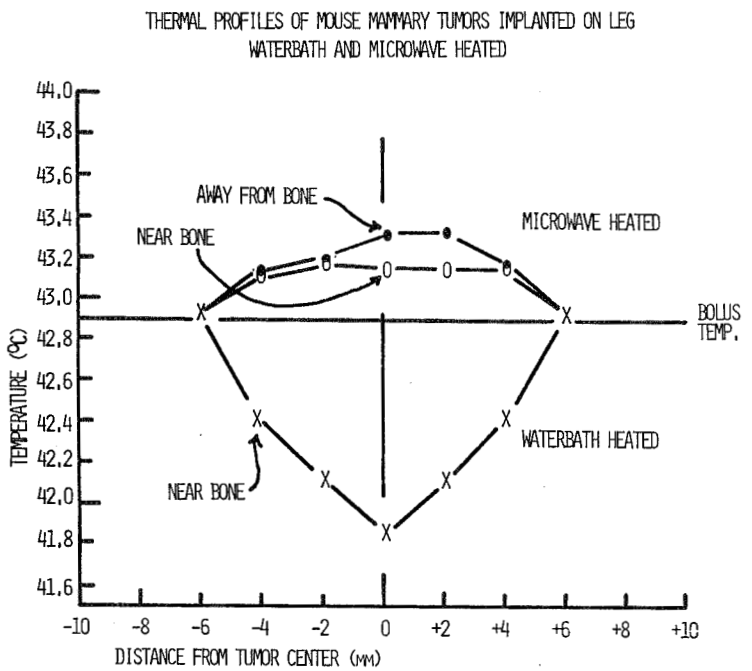


Figure 4.

Questions and Answers Following Harrison's Paper

Singh: Were these temperature measurements simultaneous with the heating?

Harrison: These were all from cooling curve measurements. We had very poorly characterized E&M fields, and we were using metallic hypodermic thermistor probes with thermistors. In fact, we did not dare attempt to make measurements with the microwaves on, so each and every datum point you see is an extrapolated temperature point from a cooling curve.

Carr: When you showed the apparatus on one of your slides, you showed that you were using two microwave sources simultaneously?

Harrison: No, not simultaneously. They switch back and forth. We have a timing circuit. We switch back and forth about every few seconds or so.

Baker: What was the composition of your solid, or semi-solid, bolus that you used?

Harrison: I cannot remember. It is the one that Guy uses that has polyethylene, powder, and water, or saline, I guess.

THE EFFECT OF HYPERTHERMIA ON THE RADIATION RESPONSE OF CRYPT CELLS IN MOUSE JEJUNUM

John D. Wilson
Medical College of Virginia

SUMMARY

The effect of hyperthermia and/or gamma-radiation on the survival of intestinal crypt cells was studied in BDF_1 mice using a microcolony assay. Hyperthermia treatments, which in themselves caused no detectable cell lethality, inhibited the capacity of crypt cells to repair sublethal radiation damage. In addition, heat applied either before or after single radiation exposures potentiated lethal damage to crypt cells; the degree of enhancement was dependent on the time interval between treatments. At the levels of heating employed, DNA synthesis in the intestinal epithelium was significantly reduced immediately following exposure, but returned rapidly to normal levels. No further disturbances in cellular kinetics were observed for up to 10 days after heating.

INTRODUCTION

Current investigations into the use of local hyperthermia in the treatment of cancer can be divided into two basic approaches. In one, the application of relatively high temperatures (generally well above the thermal tolerance of normal tissues) is used to bring about the thermal death of malignant cells. Experimental evidence indicating that hypoxic cells may be differentially sensitive to thermal killing (refs. 1 and 2) makes this approach attractive since it has been suggested that radioresistant hypoxic tumor cells may be an important factor in cases where conventional radiation therapy fails to produce local control. However, recent reports (ref. 3) indicate that in some cases cells may also be protected against heat by hypoxia. In addition, significant technical problems remain to be solved in confining heat to the tumor volume and in accurately monitoring temperatures in normal and tumor tissues in order to achieve a favorable therapeutic index under clinical conditions. The second approach is to utilize lower temperatures which in themselves do not cause cell death, but when combined with conventional treatment modalities, for example radiation or chemotherapeutic agents, increase their effectiveness. At the present time, this approach is technically more feasible in terms of clinical application.

Fractionated radiation therapy alone is effective in the local control of many human tumors. The therapeutic advantage in these instances is believed to involve differences between normal and tumor tissues with regard to such factors as repair of radiation damage, proliferative capability, redistribution throughout the cell cycle, and reoxygenation of hypoxic tumor cells. It has been cautioned (ref. 4) that if hyperthermia is to improve the local control of

tumors, the ideal combination should exploit the beneficial effects of heat without compromising the factors which are the basis of the existing therapeutic advantage of fractionated radiation therapy. Thus, to achieve this goal it is important to determine the effect of hyperthermia on each of these processes in normal as well as tumor tissue.

This paper reports the results of some preliminary experiments on the response of normal tissue to combined radiation and hyperthermia treatments. Specifically, the effect of hyperthermia on repair of radiation damage and the effect of treatment sequence and interval between treatments were studied. The crypt stem cell compartment of the mouse intestinal mucosa was chosen as the biological test system. This is a cell renewal system of the type that is dose limiting for the acute radiation response in clinical situations. In addition, crypt stem cells have a sizeable capacity to repair radiation damage (refs. 5 and 6) making them ideal for studies on the effect of hyperthermia on repair processes.

MATERIALS & METHODS

General

Adult female BDF_1 mice 8 to 12 weeks old weighing 20 to 22 grams were used in all experiments. Each treatment group consisted of 5 to 8 animals selected at random. Groups were caged separately and maintained in controlled temperature and lighting conditions throughout the experiments. Food and water were available ad libitum.

For hyperthermia treatments, unanesthetized animals were loosely restrained in thin-walled, 30mm x 82mm plastic tubes. The animals were immersed in an upright position in an insulated water bath to approximately mid-thorax level. The walls of the restraining tubes were perforated with numerous holes so that the animals were in direct contact with the water. A commercially available constant temperature circulator was used to exchange the bath. By adjusting the thermostat, heater wattage and flow rate, a variation of $\pm$ 0.1°C from the desired bath temperature could be maintained throughout the treatments. In initial experiments, rectal temperatures were monitored during hyperthermia exposures using a recording thermistor.

Unanesthetized animals confined in a cylindrical lucite box received total-body gamma-irradiation at room temperature and in room air by using a conventional ^{60}Co teletherapy unit. The dose rate was 50 rads/min as determined by a Victoreen chamber placed in a mouse phantom positioned in the lucite holder.

Survival of intestinal crypt cells following radiation and/or heat treatments was determined by using the microcolony assay of Withers and Elkind (ref. 7). Three and one-half days after treatment, animals were killed by cervical dislocation. Segments of the jejunum were dissected out and fixed in buffered formalin. Histological slides of transverse sections taken at intervals along the length of the jejunum were prepared and stained with hematoxylin and eosin. Each section was examined microscopically and the number of crypts appearing around the circumference of the intestine recorded. Crypt survival for a given treatment was expressed as the average number of crypts per circumference

determined from counts of 4 to 5 sections from each of 3 to 8 animals.

Recovery (Repair) Experiments

Recovery from radiation damage was measured using the split-dose technique of Elkind and Sutton (ref. 8) and utilized by Withers and Elkind (refs. 5 and 6) in studies of the radiation repair capacity of intestinal crypt cells. In these experiments, animals were given two doses of radiation separated by varying intervals of time. Control animals received an equivalent dose as a single exposure. To test the effect of heat on repair of radiation damage, hyperthermia treatments were initiated as soon as possible (within 3 to 4 min) after the end of the first radiation dose. After the hyperthermia treatment, animals were returned to their cages at room temperature for various intervals before exposure to the second radiation dose.

Sequence-Interval Experiments

In experiments to test the effect of the order of hyperthermia and radiation treatments and the interval between treatments, animals were given an initial exposure of either heat or radiation then caged at room temperature for varying time intervals prior to the appropriate second treatment.

Effect of Heat on Stem Cell Kinetics

In order to examine the effect of hyperthermia treatments on crypt cell kinetics, animals were heated and at intervals up to 10 days after treatment, groups of 5 or 6 animals were injected intraperitoneally with 25 microcuries of tritiated thymidine (^{3}H-TdR). Thirty minutes later the animals were killed by cervical dislocation. Jejunal segments were then dissected out and immediately placed in iced, buffered saline. Sections approximately 5 mm in length were immediately slit longitudinally, rinsed in saline, blotted, and weighed to 0.1mg. The sections were then fixed overnight in acetic alcohol (1:3). The following day, sections were transferred to scintillation counting vials and solubilized at 55°C for 1 hr. Ten ml of scintillation cocktail were added and radioactivity determined in a liquid scintillation counter. Raw data were converted to dpm/mg wet weight of jejunum using quench correction data obtained from a quenched tritium standard set counted with the gut samples. Within certain limitations, these values are directly related to the number of crypt cells in the DNA synthetic phase (S-phase) of the cell cycle (ref. 9).

RESULTS AND DISCUSSION

Animals placed in the water bath for hyperthermia treatment required several minutes before their body temperature reached that of the bath. Figure 1 is a typical heating curve recorded from the rectum of an animal placed in a 42.1°C bath. Equilibration was obtained after 8 to 10 min. Once equilibration was achieved, it was maintained for the duration of the longest heating periods employed (30 min). Comparable results were observed at lower bath temperatures and with thermistors implanted directly in the lumen of the jejunum. A dis-

advantage of this method of heating is that the thermal tolerance of the whole animal is much lower than in techniques involving smaller heated volumes. For example, most of the animals heated for 30 min in a 42°C bath were moribund upon removal from the bath, and a significant proportion (up to one-third) died within 3 to 4 hr after exposure. The body temperature of these animals dropped rapidly to room temperature after removal from the bath; however, survivors regained their homeothermic capability by the following day. It has been reported that in mice heated under similar conditions, brain temperature may reach that of the bath even though the animal's head is well out of the water (ref. 10). Therefore, damage to areas of the hypothalamus responsible for integration of temperature control mechanisms may be involved. This post-heating response is almost certainly different from that following local heating techniques involving proportionately smaller tissue volumes. It must be considered as a possible factor in differences that may arise in the response of tissues to combination treatment under the two methods of heating. The dose response for thermal death as a function of bath temperature must increase very rapidly under the essentially whole-body heating conditions employed in these experiments since no early deaths were observed in animals heated for 30 min in 41.5°C baths; these animals rapidly regained their normal level of activity after heating.

The effect of hyperthermia on the capacity of crypt stem cells to repair radiation damage is shown in figure 2. The upper curve (circles) indicates the amount of recovery that occurred as a function of time between two radiation doses of 700 rads each. The crypt recovery factor plotted on the ordinate is the ratio of the number of crypts/circumference that survived the split dose (S_2) to the number of crypts/circumference that survived a single dose of 1400 rads (S_1). Maximum recovery, amounting to slightly more than a 5-fold increase in surviving crypts, occurred within about 4 hours. This split dose response is similar to those reported for a variety of biological systems. It is most often interpreted as indicating intracellular repair of sublethal damage inflicted by the first radiation dose (ref. 8), although other interpretations have been suggested (ref. 11).

The dashed curve (squares) traces recovery that occurred in animals heated at 42°C for 30 min immediately after exposure to 700 rads and then returned to room temperature for various times prior to a second 700 rad exposure. The maximum amount of recovery in heated animals was about 40% of that seen in animals held at room temperature between radiation treatments. No reduction in crypts was detected in animals receiving the hyperthermia treatment only. In animals receiving the second radiation dose immediately after the heat treatment, it was consistently observed that crypt survival was lower than in animals receiving the equivalent single dose. This resulted in a recovery factor less than one (square at one-half hr in fig. 2). This observation will be discussed below.

The effect of the length of the heat treatment on the extent of recovery is also shown in figure 2. The triangles show crypt recovery factors for animals irradiated with two 700 rad doses separated by 3 hours and treated immediately after the first exposure in a 42°C water bath. The numbers beside each symbol indicate the length of heat exposure in minutes. The hyperthermia treatment had to exceed 10 minutes before appreciable inhibition could be detected. This information is replotted in figure 3 as the percent inhibition of 3-hour recovery

as a function of heating time. After equilibration with the bath, inhibition of recovery increased rapidly with time reaching maximum value of about 60% inhibition at 30 min. Similar experiments were done to examine the influence of bath temperature on recovery (fig. 4). It is evident that recovery inhibition was highly temperature dependent and decreased from about 60% to less than 10% over a range of 2° C.

Reduced capacity to repair radiation damage after hyperthermia is a consistent finding in many biological systems. The denaturation of enzymes involved in the repair of radiation-induced lesions in DNA has been suggested as the mechanism involved in this inhibition (ref. 12). Unrepaired DNA damage may subsequently become lethal to the cell. Studies at the molecular level involving the effect of heat on repair of specific types of lesions (single strand breaks) support this hypothesis (ref. 13).

Results of experiments to examine the dependence of crypt survival on the sequence of combined hyperthermia-radiation treatments and on the time lapse between heat and radiation administration are shown in figure 5. The solid lines indicate crypt survival in animals heated at 41.5°C for 30 min at various times before or after a single radiation dose of 1200 rads. Crypt survival in animals which received radiation only (1200), heat only (41.5°) or neither treatment (C) is also indicated for reference. (The abscissa does not apply to these points.) When the interval between treatments was 2 hr or less, a hyperthermia treatment which was itself sublethal significantly enhanced the lethal effect of 1200 rads. Enhancement was achieved in both treatment sequences. The extent of potentiation was dependent on treatment interval, being greatest for no delay between exposures and decaying as the interval between treatments increased. The rate of decay of potentiation was nearly the same for heat applied before or after radiation; the loss of potentiation may have occurred at a slightly slower rate when heat followed radiation although further experiments must be carried out to confirm this. (In figure 5, compare the solid post-heat curve with the dashed curve representing the reversed pre-heat curve.) These time-dependent patterns of heat-radiation interaction in crypt cells differ from those reported for other biological systems. For example, heat potentiation of radiation damage in the skin of mice (ref. 14) and in cultured plateau phase mammalian cells (ref. 15) was found to decay more slowly when heat preceded radiation. In the latter case, it was suggested that repair of sublethal heat damage may be slower than repair of sublethal radiation damage. However, the mechanism of heat potentiation of radiation damage is not known. Although there is extensive evidence that heat can affect enzymatic radiation repair mechanisms, less attention has been given to the possibility that heat may modify either the radiation target itself or the initial radiation-induced lesions (ref. 12).

Heat potentiation of radiation damage in crypt cells (fig. 5) is probably the explanation for the consistent observation of a recovery factor less than one in split-dose experiments (fig. 2) in which both radiation doses and the intervening heat treatment were all given within a very short interval. In these cases, heat enhanced the effect of both the first and second radiation doses resulting in a lower level of crypt survival than that seen in animals receiving an equivalent single dose of radiation.

The data in figure 5 also suggest that as the time interval between treatments increased beyond 2 to 3 hr, heat may have protected crypt cells from radiation lethality. Crypt survival values for animals heated 2 and 4 hr before and 4 hr after irradiation were higher than for animals receiving radiation alone. The differences, however, are marginal and must be substantiated in further experiments.

The fact that the heat treatments employed in these experiments were sublethal in terms of crypt survival did not rule out the possibility that alterations in crypt stem cell kinetics might occur as a consequence of heating. Marked differences in the proliferative activity of the intestinal epithelium have been observed following exposure to radiation as well as chemotherapeutic agents (refs. 16, 17, 18, 19, and 20). In addition, it has been reported that cells in culture can be blocked at specific points in the cell cycle as a result of hyperthermia treatment (refs. 21 and 22). It should be assumed that such changes in cell kinetics could be important determinants of the response of renewal tissues to combined modality treatments. Thus, preliminary experiments were carried out to investigate the occurrence of altered crypt cell proliferation. Figure 6 shows the 30-min incorporation of ^{3}H-TdR into the DNA of intestinal crypt cells of mice heated for 30 min in a 42°C water bath as a function of time after treatment. Radioactivity (dpm/mg wet weight) of jejunal segments from heated animals is presented on the ordinate as a percent of control radioactivity of segments obtained from unheated animals. ^{3}H-TdR incorporation in this type of experiment is a direct measure of S-phase cellularity and is assumed to be indicative of the size of the proliferative compartment of the intestinal epithelium (ref. 9). The marked depression in ^{3}H-TdR incorporation which occurred in crypt cells sampled 1 hr after heating, however, was more likely a reflection of decreased DNA synthetic activity rather than a reduction in the number of S-phase cells. Recovery from this depression was rapid and the radioactivity of samples obtained from animals 12 hr to 10 days after heating fluctuated within $\pm$ 10% of control values. Therefore, although short-term changes in the rate of DNA synthesis may have occurred after the heat exposures employed in the combined modality experiments reported here, marked long-term alterations in crypt stem cell kinetics were not detected.

The results of these experiments indicate that caution must be exercised in clinical situations where it is proposed to use mild heating as an adjunct to conventional radiation therapy. If heating of the tumor volume results in increased temperatures in surrounding irradiated normal tissues as well, radiation damage there may be significantly enhanced and its normal repair compromised. An increase in therapeutic advantage thus may not be realized in combined hyperthermia-radiation treatment as a consequence of these alterations in tissue response.

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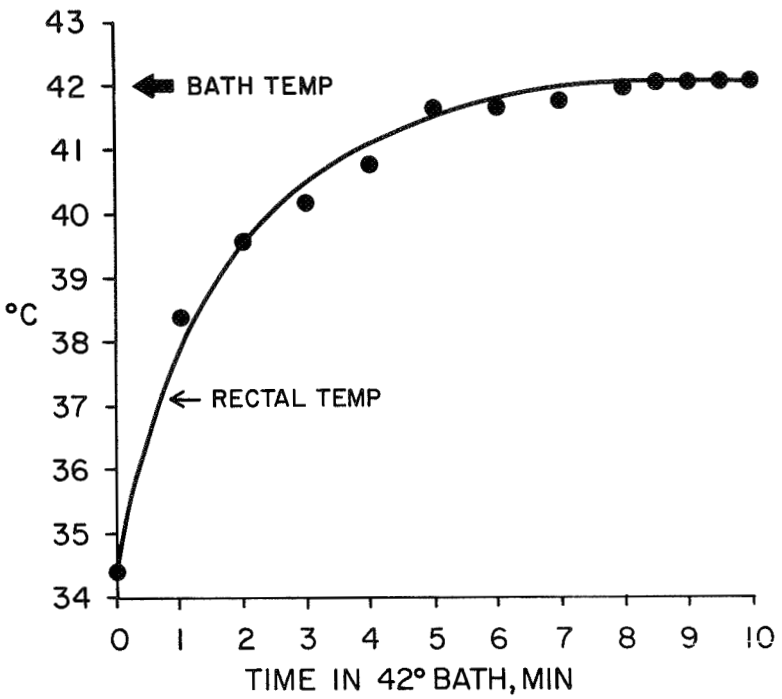

Figure 1.

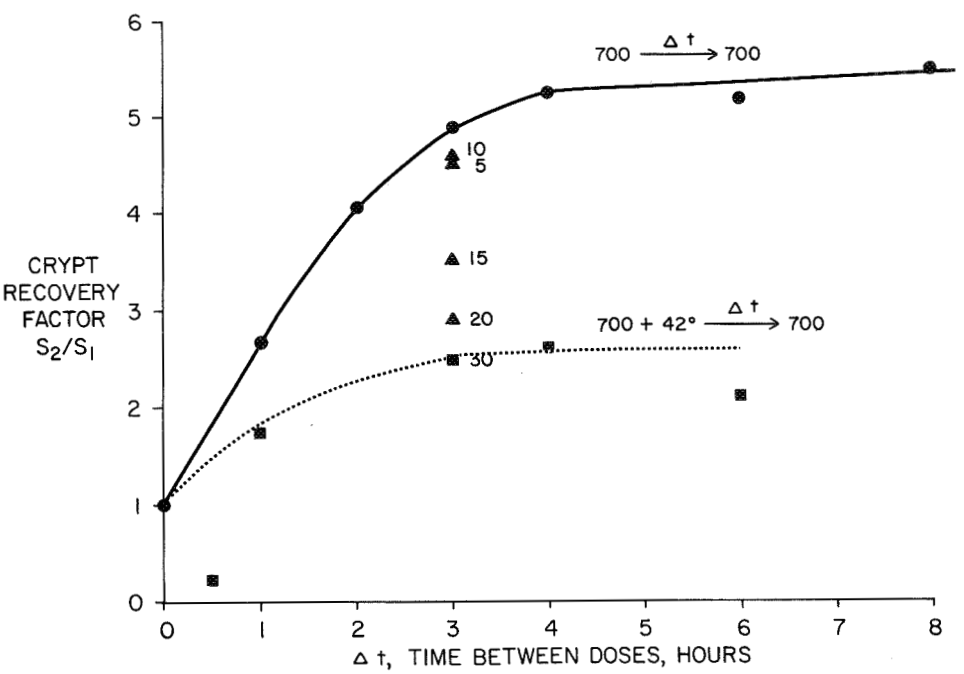

Figure 2.

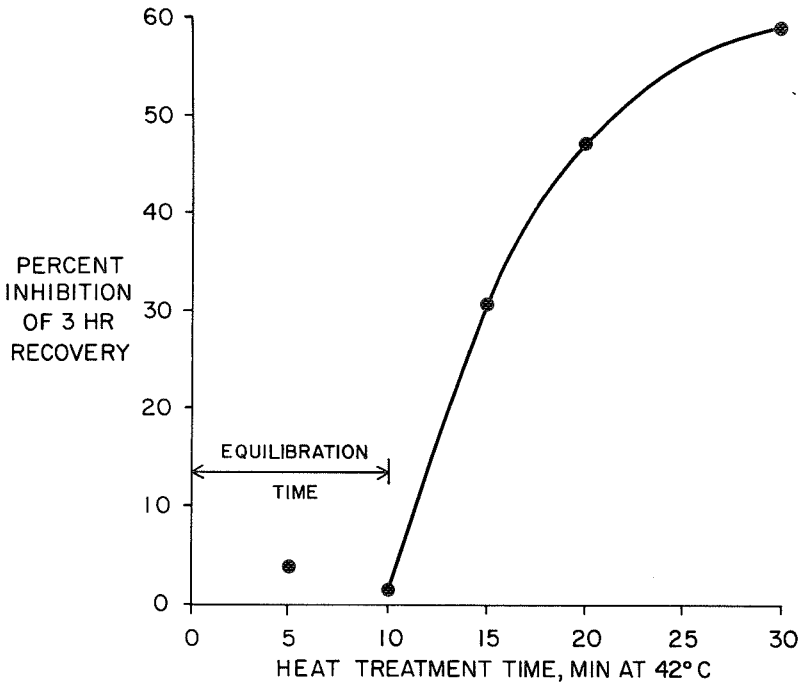

Figure 3.

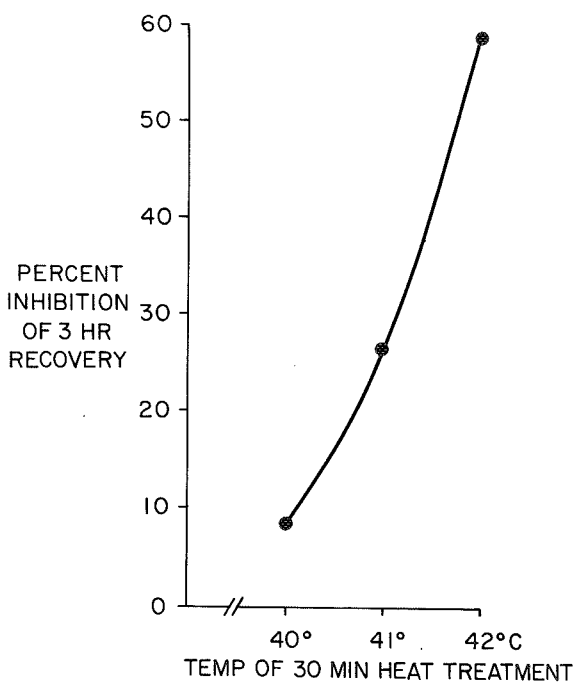

Figure 4.

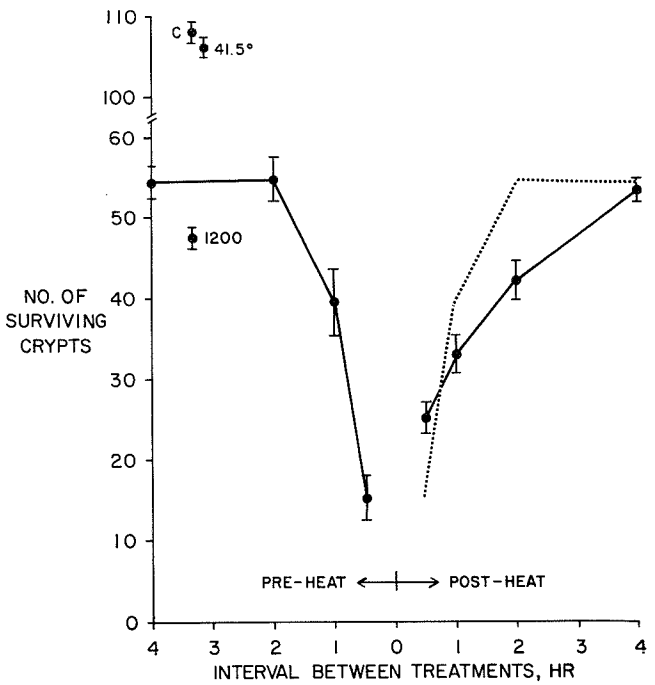

Figure 5.

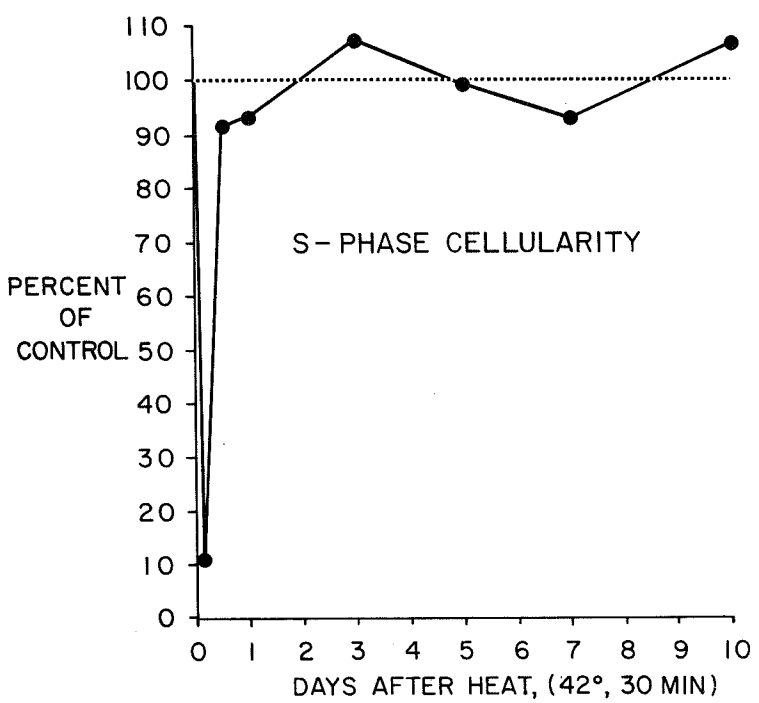

Figure 6.

A MICROANGIOGRAPHIC STUDY OF THE EFFECT OF HYPERTHERMIA ON THE RABBIT BLADDER

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Medical College of Virginia

Hyperthermia is now an accepted mode of treatment with radiation therapy and chemotherapy. Its use has been very restricted, and a wider use will encounter the same limitation as radiation therapy; namely, the tolerance level of normal tissue.

It is therefore worthwhile to devise a model to study the effect of hyperthermia on a normal tissue. The model selected was the rabbit bladder and the end point measured was the changes in the micro-vasculature of the bladder wall. It has already been demonstrated clinically that hot water bladder infusions will produce regression in bladder tumours (ref.1).

Material and Method

New Zealand white rabbits (male) weighing approximately 4 kg were catheterized and infused with sterile water heated to $43^{\circ}C \pm \frac{1}{2}^{\circ}C$. The water was heated in a coil in a heating bath and the bladder temperature was monitored with a thermistor threaded through the catheter. The water bath temperature was controlled by an automatic heating coil and cold water pump. An attempt was made to maintain sterility and the animals were anaesthetized with pentobarbital during the 15 minutes infusion time.

The animals were kept for periods varying from 7 days to 3 months, when microangiography was performed on the animals (ref 2).

The rabbits were anaesthetized and the abdomen opened to reveal the abdominal aorta which was then catheterized, and a 7% suspension of micro-opaque (barium sulphate) infused from a height of about 80 cm.

When the bladder vasculature was filled with contrast medium (about 2 hours), the bladder (which has been distended by filling with water) was dissected out and fixed.

The bladders are then cut into two halves and stretched. They are then set in a thin layer of paraffin and 30 Kvp radiographs taken of them on high resolution plates (Kodak).

Measurements

The normal bladders were used as a standard to establish three measurement criteria:

1. The number of vessels crossing a 1 mm line in the most vascular area.
2. The width of the vessels in the same area.
3. The tortuosity of the 5 most tortuous vessels between two terminal points separated by 5 mm .

It was in fact found that there was a close correlation between the scored results and a simple visual assessment based on experience in observing the samples.

It is important to avoid infection in the bladder because the appearance of the microangiogram of an infected bladder can closely resemble that of a bladder which has sustained some other injury such as radiation damage (fig 1).

Results

There is no evidence of any immediate change in the vasculature following the hyperthermic treatment. However, after 7 days, there was a noticeable slowing down in the rate of filling of the vessels with micro-opaque, and the vasculature is very sparse compared with normal samples.

In the case of the animals who were kept for 1 to 3 months post hyperthermic treatment, the appearance of the bladders was perhaps slightly hypervascular but not seriously abnormal, indicating that the immediate damage was repaired and that no medium term damage appears to result from a short hyperthermic treatment at a temperature which is sufficient to produce an enhancement of the effect of radiation on normal cells.

A present modification is that the anaesthetic has been changed to sodium brevital, which produces a shorter and shallow anaesthetized state and reduces the possibility of induced hypothermia, a condition which could possibly influence the results.

Figure 2 shows a normal bladder and figure 3 shows a slightly hypervascular post 3 months bladder.

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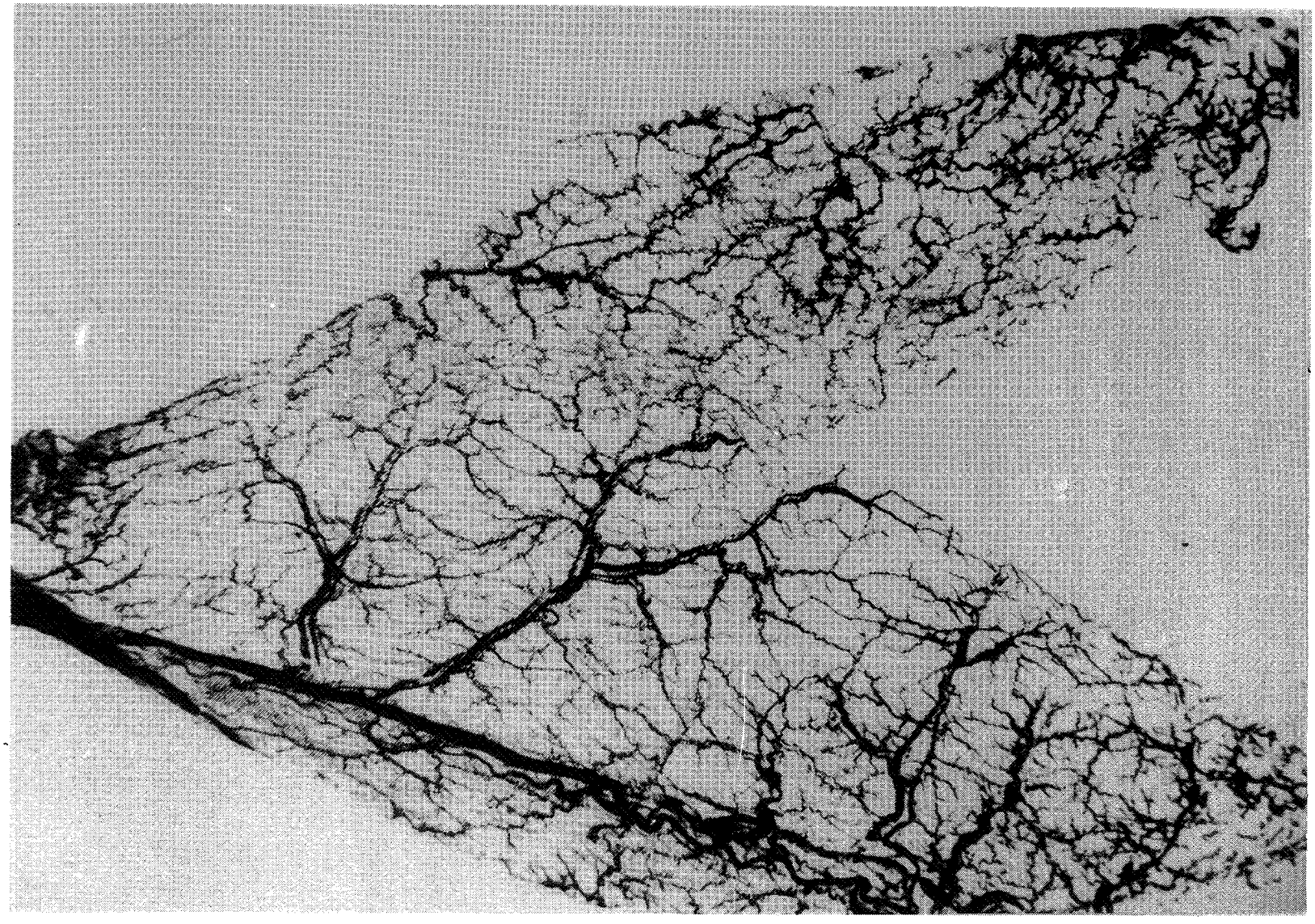

Figure 1.- An infected bladder.

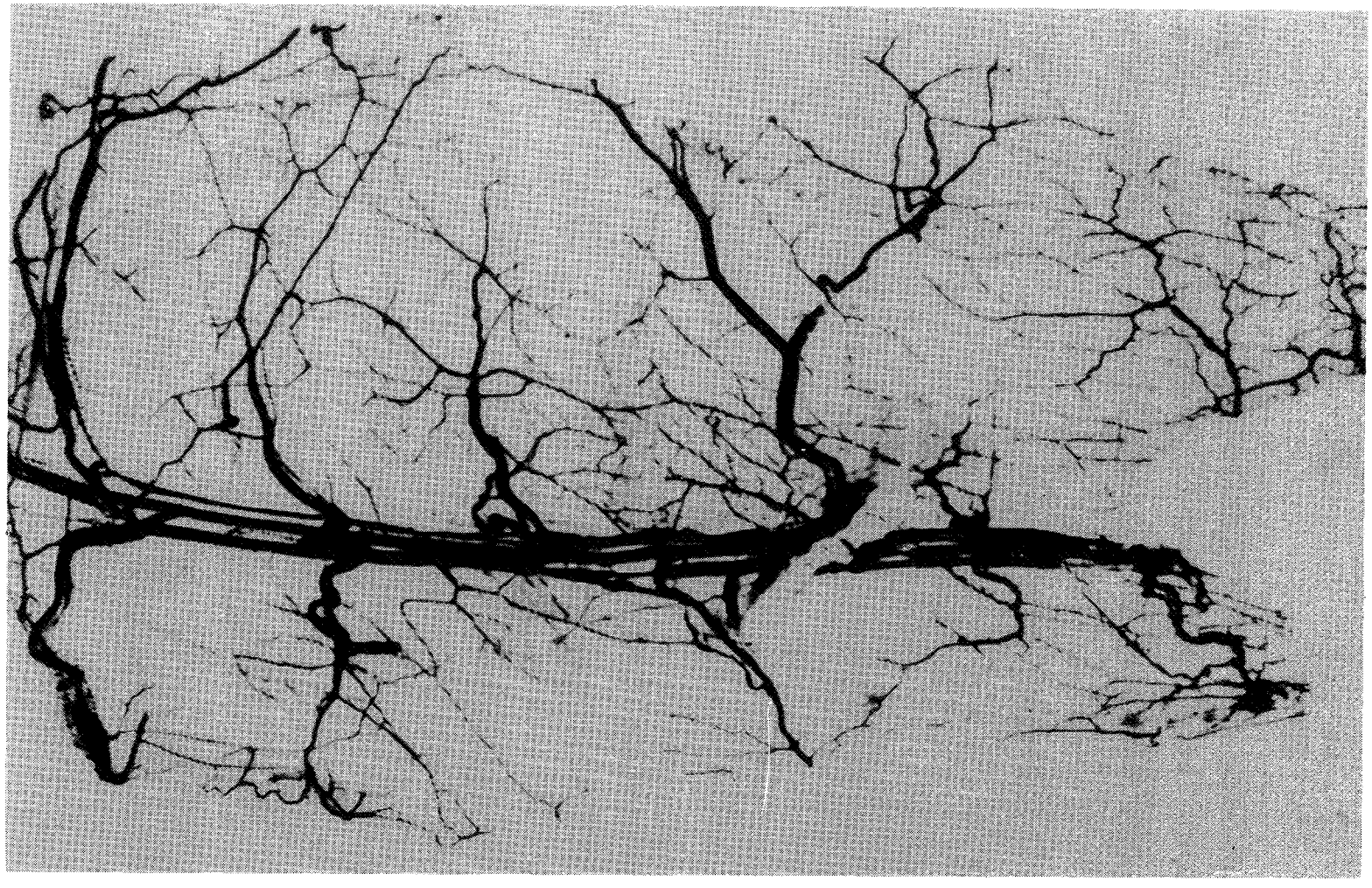

Figure 2.- Normal bladder.

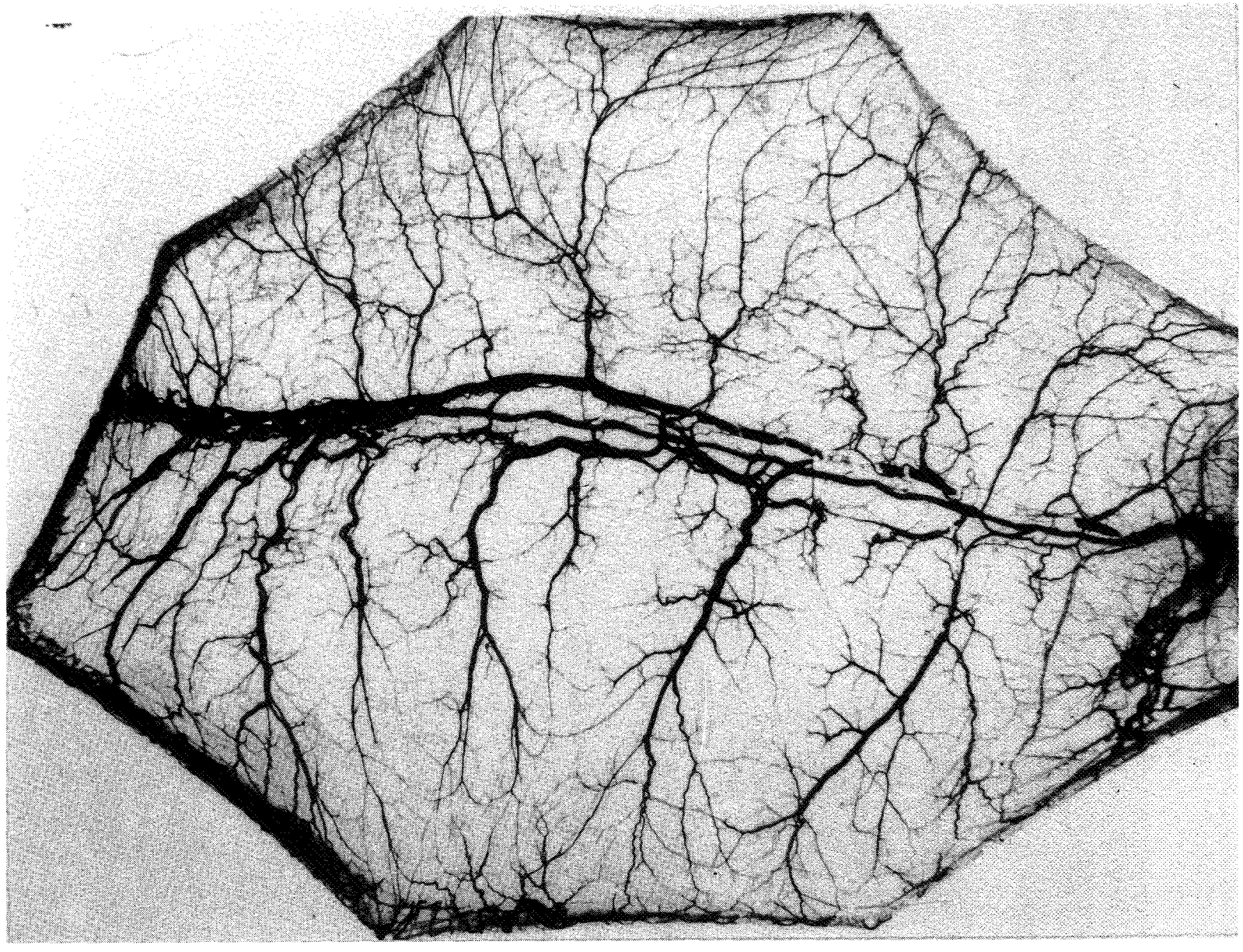

Figure 3.- Hypervascular post - 3 months hyperthermic treated bladder.

Questions and Answers Following Paper by Hietala, Howells, and Hazra

D. Cone: What was the composition of the so-called water that you infused with? Was it plain water, distilled water, or what?

Howells: It was sterile water.

D. Cone: Did it have a specific gravity, or pH control, or osmotic control?

Howells: It was plain, sterile water.

D. Cone: Could that have an effect?

Howells: I do not know. We were thinking of using saline, but we did not. We discussed this, but we did not really think that it had any significant effect.

THE COMBINED EFFECTS OF PULSED MAGNETIC RADIATION (DIAPULSE) AND CHEMOTHERAPY ON TUMOR BEARING MICE.

THE MEASUREMENT OF RODENT PALATAL EXPLANTS AS A DEVICE FOR MEASUREMENT OF THE BIOLOGIC EFFECTS OF NONIONIC RADIATION (EMR)

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Medical College of Virginia

and

Dominick P. DePaola
Fairleigh Dickinson University

SUMMARY

The aim of this program is to study the effect of nonthermal pulsed magnetic radiation on tumor growth and embryonic development.

Simultaneous treatment utilizing pulsed radiowave (diapulse) and cancer chemotherapy significantly extended the life span of BDF_1 mice with Lewis lung transplanted carcinoma. In comparison with nontreated controls, the combination of hydroxyurea and whole body nonionizing EM radiation (at 27.12 MHz) produced differential enhancement of longevity depending on power output. The highest power (38 mean watts) had the greatest effect. Hydroxyurea combined with highest power output achieved by pulsing the radiation 600 times per second; at a 3.9% duty cycle, peak watts = 975 produced the mean extension of life 67% greater than that of the group treated with hydroxyurea alone.

The stress involved in confining mice to holders and subjecting them to both nonionic radiation and chemotherapy produces significant variability in tumor growth. To achieve biologic quantification of EMR effects in vitro methods are necessary. We have studied palatal explants from 14 day old mouse embryos suspended in tissue culture as the EMR target. Histologic readouts of EMR effects can be obtained in 48 hours. This technique is difficult because of problems in timing mouse pregnancy to obtain properly dated embryos for quantitation of EMR effects of nonionic radiation on cellular differentiation, migration, adhesion, and destruction.

The effect of EMR on palatal explants and tumor growth can hopefully shed light on the significance of frequency windows vs. temperature effects, and provide significant information relevant to the use of nonionic radiation in the study of developmental birth defects as well as tumor growth.

INTRODUCTION

As discussed in our previous papers (refs. 1 and 2), the evidence supporting biological activity on nonionizing radiation based on either athermal or relatively low thermal mechanism needs serious evaluation. The diapulse instrument was studied because of its commercial availability and unverified reports of clinical anti-tumor activity. Diapulse has relatively low thermal effects as compared with diathermy despite similar reports of clinical usefulness in the treatment of injury.

This study was prompted by a report by Bassett et al., 1974, of inhibition of the transplanted METH-A sarcoma in mice by pulsed low energy electromagnetic fields (EMF). This led us to study the effects of pulsed magnetic radiation on tumor growth, normal development and drug metabolism in mice (refs. 1 and 2).

MATERIALS AND METHODS

The diapulse instrument operates at 27.12 MHz carrier frequency. Besides the commercial availability of this source of EMR (F.D.A. clearance is necessary), another immediate advantage was the existence of several field analysis studies and reports of its clinical use and biologic application (P. W. Neurath and J. Li, Personal Communication, 1974 and ref. 3).

Diapulse's theoretical design is based on the concept that pulsed high instantaneous power output (on the order of 280 to 975 watts peak), with relative low duty cycles (0.15% to 3.9%, depending on pulse repetition rate), should permit heat dissipation from tissues during the off-phase (1600 microsecond width or greater). In addition, the higher peak power levels of this instrument were designed to be capable, theoretically, of inducing tissue effects that could not be found with diathermy tolerance because of heat damage.

The diapulse generator used a fundamental frequency of 6.76 MHz, provided by a crystal, which is doubled and mixed with the output of a multi-vibrator stage. Power of the mixed stage is amplified, doubled and coupled to the 10 cm treatment head. Pulsed modulation as selected from 80 to 600 cycles per second is applied to the amplified stage to regulate the radiation supplied to the treatment head. As maximum settings, the treatment unit supplied 974 instantaneous watts with a 3.9% duty cycle, each pulse lasting 65 microseconds. This yields a highest average power output of 38 watts. These measurements were taken with a P80 probe placed on the inverted radiation head (1.3 cm removed from pancake coils) by means of 585A tektronic oscilloscope.

P. W. Neurath and J. Li (Influence of pulsed and continuous fields of a diapulse unit on peripheral circulation when applied to the abdominal region. Unpublished manuscript, personal communication with Medical Device Division, F.D.A., 1974), in a study to determine the magnetic and electrical field intensities of a diapulse instrument, reported similar measurements. A range of 10 to 45 volts/cm and an approximate 10 gauge field is seen at the surface of the head.

TUMOR STUDIES

Lewis lung carcinoma was obtained in the ascites form from serial passage in BDF_1 female mice and injected as a 10^6 saline cell suspension subcutaneously into the flanks of mice of the same strain obtained from DBA paternal, C57 maternal parentage. Details of study are reported in our previous papers (refs. 1 and 2).

The purpose of this experiment was four-fold: (1) to determine the effect of a single drug, hydroxyurea (HU) or cytoxan (CTX), upon the tumor; (2) to determine the effect of a single drug plus irradiation 160-3 (approximately 4 mean watts) (low;lo) or 600-6 (38 mean watts) (high;hi) upon the tumor; (3) to determine the

effect of a combination of drugs (HU+CTX) upon the tumor; and (4) to determine the effect of a combination of drugs (HU+CTX) plus irradiation upon the tumor. The observed parameter was relative to change in lifespan of experimental animals over controls. Eight mice, matched as to age, sex, and weight, were treated in each group.

Chemotherapy

For more detailed analysis of methodology as relates to chemotherapy and dose timing of drug administration in relation to diapulse whole body irradiation, the reader is referred to our previous publication and our Airlie House Conference presentation (refs. 1 and 2).

Palatal Explants

The palatal processes are explanted following dissection from timed-pregnant Swiss Webster mice at day 14 of gestation in a 1:1 (V:V) mixture of Tyrode's hose serum. The explants are then positioned with the nasal surface resting on a millipore filter (0.3μm) porosity that is placed in contact with a nutrient agar-gel medium consisting of Hank's BME containing 1% agar, 1% dialyzed fetal calf serum, and 50 μ/ml penicillin-streptomycin. All cultures were incubated at 37°C in a humidified atmosphere of 5% CO_2 in air and harvested at 24 or 48 hours following exposure to nonionic radiation. At harvest, explant cultures were fixed for electron microscopy and fusion was assessed according to the criterion of Smiley and Koch, 1971, and DePaola et al, 1974. (refs. 4 and 5). Mouse embryos are dissected at 14 days gestation and rabbit embryos at day 16.

Chemotherapy Results

There were two baseline controls. The first control group who were administered no drugs of any sort had an average lifespan of 36.86 days. The second group administered sodium pentobarbital to screen out effects of anesthesia on

experimental groups had an average lifespan of 37.8 days which was not significantly different.

Hydroxyurea Groups

The group receiving HU alone showed an average lifespan of 45 days with an increase of 22.1% over the controls at a significance level of 0.5. The group receiving HU plus irradiation at 160-3 (lo) (4 mean watts) showed an average lifespan of 38.75 days representing an increase of 5.1% over controls at a significance level of 0.75. The group receiving HU plus irradiation at 600-6 (hi) (38 mean watts) showed an average lifespan of 74.3 days representing an increase of 101.9% over controls at a significance level of 0.001.

Cytoxan Groups

The group receiving CTX alone showed an average lifespan of 60.5 days representing a 64.1% increase over the controls at a significance of 0.05. The group receiving CTX plus irradiation at 600-6 showed an average lifespan of 64.17 days representing a 74.1% increase over controls at a significance level of 0.01. The group receiving CTX plus irradiation at 160-3 showed an average lifespan of 76.14 days representing a 106.6% increase over controls at a significance level of 0.005.

Multiple Drug and Irradiation Groups

The group receiving a combination of HU and CTX showed an average lifespan of 21.67 days representing a 41.2% toxic decrease in lifespan compared with nonchemotherapy controls. The group receiving a combination of HU and CTX plus irradiation at 160-3 showed an average lifespan of 50.86 days representing a 38% increase over nonchemotherapy controls and a significance level of 0.01 from the HU and CTX controls. The group receiving a combination of HU and CTX plus irradiation at 600-6 showed an average lifespan of 37.5 days which is an increase of only 1.7% over nonchemotherapy controls.

The groups in order of decreasing importance (experimental groups compared with control groups): combination CTX and irradiation 160-3 showing increased lifespan (I.L.S.) of 106.6%; combination HU and irradiation 600-6 showing I.L.S. of 101.9%; combination of CTX and irradiation 600-6 showing I.L.S. of 74.1%; CTX alone showing I.L.S. of 64.1%; combination of HU, CTX, and irradiation 160-3 showing I.L.S. of 38%; and HU alone showing I.L.S. of 22.1% over controls. The combination of HU and CTX without irradiation showed a decrease in lifespan of 41.2%.

Similar studies with bleomycin given at these same radiation power levels and pulse frequencies were not significantly different from the nonchemotherapy controls or the bleomycin alone controls.

In no case was weight loss a factor, nor did pentobarbitol by itself exert any therapeutic influence on the results seen. There was no evidence of body temperature elevation on assessing rectal and subcutaneous temperature by thermistor following power termination in a matched BDF_1 mice group.

Palatal Studies

This program is in progress and unfortunately technical problems related to timing of mouse pregnancy and palatal harvest suggest at this time that as a biological assay of nonionic magnetic radiation, this method of biologic assay has variables equal to that of tumor growth studies in the living mouse.

DISCUSSION

In our previous study (ref. 1) in unanesthetized mice, growth of Lewis lung carcinoma tumors were either enhanced or inhibited depending on the scheduling of the EMR exposure used. Pre-tumor inoculate irradiation, one hour daily for one week, resulted in a 49% inhibition in mass at post-tumor inoculate day 14 and 45% inhibition at day 26 after exposure to a 6 mean watt (160 pps/585 watts) power level. However, extended scheduling using daily irradiation for 13 pre-and 6 post tumor inoculate days, at the same power level, resulted in a contrasting 20% stimulation in tumor growth and the use of higher power levels was associated with greater increased growth of tumors of 54% and 51% (15 mean watts produced by 400 pps/585 watts and 38 mean watts by 600 pps/975 watts, respectively, given for 13 pre-and 14 post-tumor inoculation days). In contrast, anesthetized mice receiving identical treatment (160 pps/585 watts daily seven pre-and six post tumor inoculate days) demonstrated a greater inhibition of tumor mass, 67%, in comparison with the unanesthetized animals, 20%. This may indicate an effect of temperature elevation in view of our data demonstrating heat retention in irradiated anesthetized mice (ref. 1).

Simultaneous treatment utilizing pulsed radiowave (Diapulse) and cancer chemotherapy significantly extended the life span of BDF_1 mice with Lewis lung transplanted carcinoma. In comparison with nontreated controls, the combination of hydroxyurea and whole body nonionizing EM radiation (at 27.12 MHz) produced differential enhancement of longevity depending on power output. The highest power (38 mean watts) had the greatest effect. Hydroxyurea combined with highest power output achieved by pulsing the radiation 600 times per second; at a 3.9% duty cycle, peak watts of 975

produced the mean extension of life 67% greater than that of the group treated with hydroxyurea alone.

The stress involved in confining mice to holders and subjecting them to both nonionic radiation and chemotherapy produces significant variability in tumor growth. To achieve biologic quantification of EMR effects, in vitro methods are necessary. We are now testing palatal explants from 14 to 16 day old mouse or rabbit embryos suspended in tissue culture as the EMR target. Histologic readouts of EMR effects can be obtained in 48 hours. This technique might enable us to quantitate EMR effects of nonionic radiation on cellular differentiation, migration, adhesion, and destruction. The effect of EMR on palatal explants can shed light on the significance of frequency windows against temperature effects and can provide significant information relevant to the use of nonionic radiation in the study of development birth defects as well as tumor growth.

The importance of nonionic low thermal radiation is seen in the recent IV International Bioelectrophysiology Meeting at Woods Hole. Low energy nonionic radiation effects have been seen to stimulate bone repair (refs. 6 and 7 and C.A.L. Bassett, personal communication, 1977), derepress frog embryo cells and convert them to fibroblasts (ref. 8), and produces dendritic outpouchings in cultured neuronal cells (ref. 9) and control dorsal ectoderm migration in spinal cord development (ref. 10). The energy levels for these effects are infinitesmal and unrelated to heat production and evidence by references 11 and 12 and others (ref. 8, 10 and 13) support that this condition is associated with calcium flux (refs. 14 to 16) and may require frequency windows (specific frequencies) for selected effects to be seen. Calcium ionophores (ref. 8, 10, and 13) can mimic at

least some of the effects reported for low energy electromagnetic fields on cell physiology.

In view of frequency window data indicating that low energy pulsed EMF can affect a variety of biologic systems with stimulation of bone repair and inhibition of tumor growth, further work remains to be done in testing varied frequencies for optimal effect. This is important in view of Holt's (ref. 17) report of increased survival of head and neck cancer where microwave at 434 MHz combined with radiotherapy was reported to increase 2 year survival of recurrent head and neck epidermoid cancer. Holt insists that the frequency of 434 MHz is critical for results seen.

Our future work will explore frequency window effects ranging from 8 to 400 MHz. With new instrumentation from Bassett's group and NASA, we will avoid the high energies that produce heat effects although, as was seen in the diapulse system using a pulsed magnetic field, minimal heat was generated in both the in vivo mouse tumor system and in tissue culture palatal explants.

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Questions and Answers Following Regelson's Paper

Beebe: Did you consider the effect of the diurnal cycle on the susceptibility?

Regelson: Well, that is obviously a factor, but all our work was done during the day.

Beebe: Was it done routinely in the morning?

Regelson: Yes. Routinely, our timing was fixed so that as a variable we did not change it. Once we locked in, we were locked in. Incidentally, the light cycle in the mouse room was controlled.

FOCUSSED MICROWAVE RADIATION THERAPY FOR DEEP TUMORS[1]

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SUMMARY

Elevated temperature increases the efficacy of ionizing radiation and certain chemical agents in the treatment of some cancers. The use of heat as an adjunctive therapeutic modality in radiotherapy can, in some cases, yield a marked increase in radiosensitivity of malignant tissue with only a slight change in the radiosensitivity of surrounding normal tissue (refs. 1 to 3). In contrast, the use of heat with chemotherapeutic agents increases absorption and chemical reactivity in both malignant and surrounding normal tissue (ref. 4). Probably, the most effective means of heating, especially in the case of deep tumors of the head, neck, abdomen, and limbs, will be to focus the temperature elevation in the region of the tumor volume. As an adjunct to radiotherapy, this procedure will limit the thermal load and any increase in radiosensitivity in the surrounding normal tissue. As an adjunct tc chemotherapy, it should increase absorption and chemical reactivity in the tumor volume - thus, a means of "steering" systemic drugs to desired target sites.

In order to obtain focussed microwave heating at depth, we have borrowed from therapeutic radiology the concept of superposition of separate radiation beams (ref. 5). The application of this multiple-beam paradigm to microwave diathermy offers the potential of generation and control of spatio-temporally complex thermal fields deep within the body. Our prototype system consisted of two parallel-opposed simulated TEM applicators operating at 2450 MHz with power time-multiplexed either between the treatment beams or off to an air-cooled load (ref. 6). Our current system is programmable (microprocessor controlled), capable of supporting 16 miniature applicators(ref. 7) and controlling the output power of each applicator, while monitoring forward and reflected power, temperature, and physiological parameters (ref. 8). While currently being operated at 915 MHz, the control system is frequency-independent and will be operated at a lower frequency when clinical trials commence.

By using the dual-beam system, we found that the central axis tissue temperature profile is parabolic as would be predicted by superposition of energy deposition in tissue. In tumor regrowth studies, using C3H murine mammary carcinomas transplanted to the flank, we have found that the delay in regrowth following treatment compares favorably with our previous water bath studies(refs. 1 to 3).Our programmable system is under evaluation and software development. It is currently being used to study the efficacy of focussed heating in a feline brain through measurement of electric and resultant thermal fields (with Narda and Ramal implantable probes).

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At present, the major limitations of the use of microwave diathermy for cancer thermotherapy is the equipment's ability to heat deep tumors while sparing the intervening tissue. With development of equipment and techniques for focussing the heat to the tumor site, we expect to improve the utility of localized microwave-induced hyperthermia as an adjunct to radiotherapy and chemotherapy in the clinical management of some cancers and especially malignant brain tumors.

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Questions and Answers Following Samaras' Paper

Singh: What is the beam size, the physical width, if you will, of the beam?

Samaras: I am going to try and bring that up in the next point. The applicators that we are using are these dielectrically-loaded "waveguides." This was presented at the Airlie House meeting last September, I think. It was by Dr. Chung and me. What we have done is that we have taken a 1 centimeter by 2 centimeter bar of titanium dioxide and painted on the surface with DuPont de Nemours conductive paint a waveguide, in effect. So, we have an applicator the size of an X-band waveguide with a cutoff frequency at 700 megahertz. For the preliminary experiments, or for the laboratory preclinical experiments, that we are doing, we are operating at 915 megahertz and using feline brain. Does that answer the question about the aperture size sufficiently?

Regelson: There might be another way to approach this. That is, the technology is here, and it is done clinically to introduce arterial catheters to include portions of the blood supply to regions of the brain. We are doing this now. If anyone is interested, I could provide you with starch microspheres, which are digested by amylase. When introduced intra-arterially, they can give you a reversible occlusion that can be timed, depending upon how we polymerize and what size of the spheres we give you. I can make them available to you, but in the brain the speed of the depolymerization would be too long for it to be used. It could be used in other organ systems. But, you could use balloon catheters; and by denying arterial supply you will decrease heat dissipation, and thus you might get hot spots. I wonder whether or not that might be another way for you to do this, apart from the focusing technique that you are so interested in.

Samaras: You mean in conjunction with that or as an alternative?

Regelson: Well, you could radiate the whole head; but by taking the region of the tumor, you can localize the blood supply to a degree. You then put a balloon catheter up in there. You occlude for within the 5-minute period that you can occlude without severely damaging normal tissue. Or, you can go beyond that because your regional localization can be that good. Then, you whole-brain radiate with your microwaves, expecting that the area that does not have the arterial supply is going to get hotter. I wonder whether that is an option that you could use.

Samaras: What about the time, though?

Regelson: Well, I mean, again, you have to work it out empirically, and the only way you are going to do it is to try.

Samaras: No, I am saying if you could only occlude for a period of 5 minutes, that might not be long enough.

Regelson: No, you can go beyond that, but you are going to get an infarct. O.K. So what you want to do, of course, is to get a gradient effect related to the area of involvement. I think that is the way you can go provided you closely control the time that you produce the occlusion. You would get a real hot spot, I would think, because you are not getting arterial blood profusing the area, and the temperature is going to stay there.

Samaras: To diffuse the heating, yes.

Singh: Apparently, you are going to have a predetermined temperature in the region where the tumor is. Would that be just like trial and error, or would you have a way of actually controlling it?

Samaras: We hope that we are going to be able to monitor intratumor temperature in the animals, certainly, with a temperature probe in the center of the tumor. In the human patients down the line, ultimately most of these people will have been through a craniotomy, and it will be no problem. They have a burr hole there that you can drop the probe into. Did I understand the question properly?

Singh: Well, yes, but I am not fully sure if I did get the answer; but since it is down the line, I suppose that is alright.

Samaras: What I am saying is, yes, we expect to be monitoring the core temperature of the tumor on line while we are doing the heating. It is to close the loop.

OPEN DISCUSSION

Session 1: Methods of Heating

Moderator: George Samaras

Samaras: Well, I guess the first thing that I would like to bring up about methods of heating, and I think one that is controversial, is the difference between whole-body heating and localized hyperthermia. Does anyone want to make any comments about that?

Regelson: I would just like to address a question in regard to methodology. There is work in basic biology in relation to the use of poikilothermic cells in tissue culture; for example, one very good model is the fat head minow. You deal with a fish, and you grow its cells, and it can grow at room temperature. Now, when you raise the temperature, you drive cell division at different rates. People have studied DNA and RNA synthesis in relation to these relationships. Is anybody utilizing these models in relation to microwave effects?

Samaras: Not that I know of. Does anyone have any comments to make about that?

Singh: No, but I think I might ask a different question. Is not the whole-body heating, in fact, being used by default? I mean, if one could have localized heating, or focused heating, one would not want to do whole-body heating. Is that not right?

Samaras: Well, that has always been my feeling. But, Ron Atkinson, who is one of the international proponents of whole-body heating, could help us with that.

Singh: Oh, perhaps, we should ask Dr. Atkinson then. Would there be any reason why you would want whole-body, as opposed to localized, heating?

Atkinson: Well, let me say that in the treatment of disseminated disease, it would be most desirable to treat systemically, rather than locally. For this reason we have been very much interested in whole-body hyperthermia. Of course, you are restricted, we think, to temperatures below or at 42° C. This is a limitation of the whole-body heating method. I think if you would have asked me this question a year ago, I would have said: "Local hyperthermia is much easier to do than whole-body." I think back about the last year's experience I have had with whole-body hyperthermia, and I have to absolutely reverse that position. While playing around with local hyperthermia for a year, I ran into all sorts of difficulties in temperature measurement, control localization of the heat, and the various problems which I am sure you are all familiar. I can say that it appears that whole-body hyperthermia is quite a bit simpler, at the present stage of technology, than local hyperthermia. Have I answered your question?

Singh: Yes, you did. But, if you could focus it reasonably easily, would you prefer to localize?

Atkinson: Yes, except for the fact that the interest in cancer treatment, or a large portion of the interest in cancer treatment, is in treating disseminated disease, rather than local disease. There exists, already, radiotherapy and surgery as treatment modalities for localized disease.

Samaras: Ron, could I ask you a question, please? What about the problem of thermal uniformity, though, in whole-body hyperthermia? You do not really have true thermal uniformity in heating the whole body. We were discussing that on the plane ride down. How do you? You were talking about disseminated disease and trying to raise the whole body to 42° C. Do you think that gives a therapeutic benefit?

Atkinson: Yes, let me say this. If we talk about nominal 42° C whole-body hyperthermia, this is referring to 42° C tissue temperature. Blood temperature, typically, will sit at about 41.8° C; and skin temperature, at around 40° C, or perhaps slightly higher than 40° C. The tissue temperature, we believe, is quite uniform, except, perhaps, in specific organs, in which it is higher. The best we can tell at the present time is that these are higher than the nominal tissue temperature of 42° C. We feel confident that no part of the patient -- with the possible exception of the actual skin surface, which we are cooling to maintain the patient at his temperature so that we do not have thermal runaway -- is below 42° C. I think this is a fairly safe assumption. If I could say the same about any local hyperthermia treatment, I would say that the state of the art in local hyperthermia had exceeded this capacity.

Samaras: The reason I asked the question was because of the possible stimulatory effects when you are below that temperature. If we are talking about 42° C in one region with a malignancy and 40° C or 40.5° C, in another region with a malignancy, then you are not getting, at least from the laboratory experiments, remission.

Atkinson: Well, we have carefully looked for evidence of stimulatory effects of subtherapeutic. We have not found any ourselves, nor have we seen any instance of this being reported in the literature. Occasionally, you hear of unpublished reports where there are indications on the basis of a few trials that some of the animals appeared to have a decrease in life span. But, if I look at where the arrow bars are and the number of animals involved, I have not seen any. Certainly none of this has been published. We would like very much to know if this is a real effect. In the FDA testimony and hearings that we have had about the use of diathermy in the treatment of malignancy, the FDA tried to pin this down. They could not succeed in coming up with any evidence that there is a deleterious effect in the treatment of cancer. I am not an expert in metastasis, but there certainly is an increase in cell shedding of tumors at elevated temperatures. Naively, I initially thought that this indicated an increase in proliferation. But, it turns out, I am told, and I have no direct experience with this myself, that this is not necessarily indicative of an increase in metastasis. Indeed those experiments that have

been done indicate that with exteriorized rat ovaries, for instance, in one experiment I have in mind, although tumor cell shedding increases at elevated temperatures, there is no corresponding increase in metastasis. So, it is still a somewhat open question, but it is a matter that does not give me serious concern.

Shaeffer: Dixon and his colleague in Great Britain have published results relating to the Yoshida tumor in rats, and I also believe the VX2 carcinoma in rabbits, in which, when they gave what they considered to be inadequate doses of hyperthermia, there were demonstrable differences or increases in the number of hematogenous metastases. And, when you are heating your patients, you know they have to pass through some critical level of suboptimal hyperthermia on the way up to the desired temperature and also as they cool down. I was wondering what comments you might have about this; i.e., about the enhancement of metastasis by suboptimal or subtherapeutic hyperthermic levels.

Atkinson: I was unaware of the Yoshida, but I knew about the experiment with the VX2 and the rabbit, and it was a one-rabbit experiment; that is, only one of his rabbits survived the whole-body hyperthermia. So, I do not know about that. I shall ask about the Yoshida, though. I would be interested to know.

Shaeffer: I was referring to the Dixon and Muckle paper.

Harrison: You could ask the same question about local hyperthermia. Robinson did a mouse experiment to look for lung metastasis, and we are in the process of writing it up. We see that there is no change with heating, or else a decrease in metastasis. I also think of Szmigielski's work in Poland. He seems to have some hard evidence that localized hyperthermia actually stimulates some mechanism which inhibits metastatic growths elsewhere from the treated volume.

Samaras: On the other hand, though, to be fair to both sides, you are absolutely right that whole-body hyperthermia, right now, is the only game in town. It is so much so that we are planning on cranking up clinical trials with whole-body hyperthermia for brain tumors in conjunction with the BCRC.

Regelson: There are people involved in local hyperthermic approaches clinically.

Samaras: Are they treating brain tumors?

Regelson: They are not treating brain tumors, but other tumors. Durant has successfully, well not quite successfully, treated a patient of mine with schwannoma, metastatic to lung. Unfortunately, he did not radiate the lung parenchyma itself, but he treated a substernal mass which decreased 50 percent by volume. This confirms Holt's work in Perth; he reported on a schwannoma in the head and neck region that melted away with his 434 megahertz machine. As I was saying to Ron earlier, I think that somebody from the NCI with sophistication should take a look at Holt's program in Perth because you cannot discount Holt. Anybody who is reporting 65-percent, 3-year survival of recurrent head and neck cancer, post radio-therapy following heat, is somebody you have to pay attention to. He is either the biggest liar in the business,

or he has got something that has to be looked at. He claims he has enough numbers now for this to be valid, and somebody has to go to Perth and look at this, instead of ignoring the man. We have got to do something about it because it might speed up the rate at which this gets into the clinic.

Samaras: Well, I think that people in Indiana are going along quietly doing some of this work, and probably their results should be able to answer some of those questions. I think they are working at the same frequency, but not with Holt's machine.

Atkinson: I am a Cochairman of the Fourteen University Cooperative RTOG Protocol for local hyperthermia in the treatment of cancer. Most of the participating institutions have started pilot studies. The protocol was just issued about a month ago by the American College of Radiology under NCI sponsorship. We are expecting some good data to be generated over the course of the next year or so for local hyperthermia. You are quite right. To my knowledge, there is only some very preliminary experimental work going on in local hyperthermia for brain tumors, however.

Singh: May I ask a question, Dr. Atkinson? Has there been any important use of ultrasound for local hyperthermia?

Atkinson: Yes, I can suggest two persons to contact in regard to this at Sanford University. George Hahn is working with Jane Marmur in the use of ultrasound clinically for local hyperthermia. They can give you the details. I just simply know that it exists, and I know more about George's animal studies than I do the clinical work. I have not visited him since he started.

Regelson: There is a big program with Bowman-Gray with ultrasound for clinical use in conjunction with radio-therapy.

Carr: With regard to local versus whole-body, if you could locally heat a tumor, what would be the upper limit, or what temperature would you want to heat it to? I know that you are limited because of damage to surrounding tissue. If you could heat locally, what temperature would you strive for?

Samaras: Well, our feeling at Maryland from Robinson's animal experiments is that probably about 44° C to 45° C is ideal.

Carr: What is the problem of going higher, if you did not damage the surrounding tissue. If you could locally heat only a tumor, what would be the problem in going to a higher temperature?

Samaras: I think that, rather than decreasing repair following radiation damage, or increasing the effect of chemotherapeutic agents, you would merely be cauterizing the tumor. I do not know the answer to that question.

Carr: Regarding whole-body versus localized, just what temperature are you going to limit yourself to?

Samaras: Can you answer that question Don?

Baker: I can only say that I have spent a little time with Dr. LeVeen in New York. His idea is to get the tumor temperature up into the mid 50° C range. He does this with the idea that he can destroy the tumor cells without any use of any other modality. He depends on the fact that the tumor is unable to dissipate the heat as rapidly as the normal tissue. So, on this basis he trys to get tumor temperatures into the mid 50's. Apparently, he has succeeded, at least occasionally, in doing this.

Samaras: I had a question about that myself. Except for the necrotic center where you do not have that much vasculature, how about the highly vascularized periphery and the possibility of leaving behind even one live tumor cell to start the whole cycle all over again? How does he handle that problem?

Baker: I cannot really answer your question definitively because I do not know what he says. But, as far as I could tell from spending some time and watching him treat two or three patients, it seems that the method he was using was effective -- only if there was a significant vascular defect in the tumor, and if the heat dissipation was much less there than in the surrounding normal tissues which contained the path of the radio beam. So, presumably, in highly vascularized tumors, his method would produce no significant advantage. But, his argument is that nearly all the tumors that he was dealing with were selected on the basis of their histology and had indicated poor circulation.

Beebe: LeVeen feels that tumors are very poorly profused compared with surrounding tissues -- on an order of 10 percent. That is the basis for his feeling that they cannot dissipate the heat. And, he feels this is true for tumors in general, regardless of what type. Also, in one of his papers, in 1976, he selected four or five different types of tumors.

Samaras: I am not an oncologist or a pathologist, but I was under the impression, from the work at Harvard of Judah Folkman, that at least in the exterior regions the tumor attracts the blood supply to it and, in fact, becomes highly vascularized. So, I do not quite understand how the two can be happening simultaneously.

Baker: Well, if you generate a large amount of heat, then you are going to have a temperature gradient, and this may simply overpower that narrow rim of vasculature.

Samaras: I see. That is certainly a possibility.

Baker: Incidently, I saw a case record of one brain tumor that he did treat, and he got complete remission. The whole thing became a cyst, which was drained out; and the patient is alive.

Samaras: I would like to bring up what Dr. Atkinson was talking about earlier in terms of the legal aspects of doing clinical trials. I am involved with some localized clinical trials in microwave hyperthermia for skin cancers at Maryland. I am looking into the legal liability because I fabricated

the system that is going to be used in treating the patients. We got a reading from the State Attorney General's Office saying that I would be held personally liable for the treatment and also for the product liability. That is something that I think should be taken into consideration by people who are not covered by insurance policies; e.g., non-clinicians, or nurses.

Regelson: What about informed consent? Are you not covered by your investigations committee with informed consent?

Samaras: The clinical trials are approved by the Human Experimentation Committee. At least in the State of Maryland, the informed consent is not a consent to negligence or to accidents. So, that does not cover you, in the least.

Regelson: Well, if you have an accident, that is another story.

Samaras: Well, that is all we are talking about. We are not talking about deliberately going and hurting someone. Yes, Sir.

Hobson: I have been involved in this for a long time. The informed consent does not, in any way, relieve you from responsibility. The legal principle, I am told, and I am not a lawyer, is that no one can sign away his rights to claim that he has been damaged as a result of particularly unorthodox procedures. So, you have no protection for the investigator from the patient who has signed an informed consent.

Samaras: And, if one of the investigators also happens to be the manufacturer of the machine, you have double jeopardy.

Shaeffer: I would like to move on now to the next session, Thermal Measurements. The moderator for this session will be Dr. Jag Singh from the NASA Langley Research Center. Dr. Singh.

THERMAL MEASUREMENTS IN HYPERTHERMIA

Moderator: Dr. Jag J. Singh, NASA Langley Research Center

Introductory Remarks by the Moderator:

Several papers presented in the morning session had cited the need for accurate temperature measurements - both for thermal bath (whole body) studies as well as localized heating induced by electromagnetic radiation. Langley scientists, at the request of clinical researchers at EVMS, MCV, and the Veterans Administration Center, have been studying this problem for some time. The thermal measurement problem can be approached in two ways:

1. Temperature Measurements Concurrent with Diathermy. These measurements require that the "thermometer" not interfere with the heat distribution or interact with the heat-inducing radiation. The following two noninvasive techniques fall in this category: (a) microwave radiometry, (b) acoustic thermometry.

2. Temperature Measurements Following Diathermy. Invasive thermometers - such as thermocouples and thermistors - can be used for such measurements.

The noninvasive techniques - microwave/acoustic radiometry - are ideal for measuring the temperature of the suspected tumorous region as well as providing a feedback signal to control the heating level.

Langley is currently involved in the development of a microwave radiometry system for microwave hyperthermia. We are also developing a thermocouple-based controllable RF heating system to provide a predetermined level of heating to test mice. Proper orientation of the thermocouple leads as well as the use of an RF filter eliminate the interference from the RF field in the test region. I will be glad to discuss our work in detail if the audience so desires.

This session is now open for general audience participation.

Session 2: Thermal Measurements

Moderator: Jag J. Singh

Singh: Several papers presented in the morning session cited the need for accurate temperature measurements, both for thermal bath (whole-body) studies and for localized heating induced by electromagnetic radiation. Langley scientists -- at the request of clinical researchers at the EVMS, MCV, and Veterans Administration -- have been studying this problem for some time. The thermal measurement problem can be approached in two ways. The first approach is to make temperature measurements concurrent with diathermy. These measurements require that the "thermometer" not interfere with the heat distribution or interact with the heat-inducing radiation. The two noninvasive techniques, microwave radiometry and acoustic thermometry, fall into this category. The second approach is to make temperature measurements following diathermy. Invasive thermometers, such as thermocouples and thermistors, can be used for such measurements. The noninvasive techniques, microwave and acoustic radiometry, are ideal for measuring the temperature of the suspected tumorous region, as well as providing a feedback signal to control the heating level. Langley is currently involved in the development of a microwave radiometry system for microwave hyperthermia. We are also developing a thermocouple-based, controllable RF heating system to provide a predetermined level of heating to test mice. Proper orientation of the thermocouple leads, as well as the use of an RF filter, eliminate the interference from the RF field in the test region. I will be glad to discuss our work in detail, if the audience so desires. This session is now open for general audience participation.

Samaras: Obviously, I would like to be able to measure the temperature simultaneously so that we could use it to close the feedback loop. It would be preferable if we could have something like three-dimensional microwave thermography.

Singh: That is a very good idea. Maybe, Ken Carr could address that one. How far are we from providing the simultaneous temperature measurement for microwave hyperthermia?

Carr: Okay, I think the microwave radiometry is equivalent, of course, to infrared. Only, hopefully you would be able to look below the surface. Now, for any hot-body radiator the optimum emission frequency is in the infrared. However, in getting to the surface you go through a great deal of dispersion, so what you are really measuring in infrared is the surface temperature, but what you would like to do is look deeper. The deeper you look -- or the closer to the tumor, or the hot spot, you are measuring -- the more accurate will be the reading you get. Now, you would like to measure temperature simultaneously. For this you would have to be operating at two different frequencies. Also, you would have to separate the two systems because, if you are going to be heating, your microwave radiometer is a very sensitive device, and you would wipe it out. One thing that I caution everyone on in using these microwave generators that you are using is that they are called dirty generators. They call such rich in harmonics

because it sounds better and sells the instrument better. But, the harmonics you do not want! The harmonics, of course, would wipe out instrumentation at the higher frequencies. So, all your measurements should be made with proper filtering, so you are not getting some unknown side effect of some harmonic you did not plan on. In most of the microwave generators, the second harmonic level is susceptible to the maps that you are looking at. Also, it is only 3 or 4 dB down from the fundamental in a lot of these devices, and so you should really filter. But, I would agree with George. I would want to measure temperature simultaneously and close the loop. But, to do that you would be using two different frequencies.

Singh: Let me just make one comment. That is, I think you can do the IR, as well. It is true that you can make only a skin temperature measurement. But, if you had a light guide -- let us say, for example, a silicon dioxide light guide, that is going right into the region you want to look at -- and a proper band pass and a wavelength in the range of about half a micron to 5 - 6 microns, then you can use a regular IR detector, a gold-doped germanium detector, cooled to liquid helium temperature. It will work very well.

Carr: Well, you get a trade-off. In other words, as you go higher in frequency, your tumor, or your hot spot, is emitting more energy.

Singh: Well, yes, you are quite right, but you can easily make the calculations. For black-body radiation the range is reasonable enough. It is well outside the minimum limit that we need, in order to get above the background-level signal from this IR detector I was talking about. Well, I think it is a good thought, though, that, if you can use microwaves, then IR should not be ruled out.

Beebe: I was thinking about your suggestion, Ken, on two different frequencies. Perhaps, you could use the same frequency and just momentarily turn the radiation off from the therapy and measure the radiation that is then coming from the tumor. That way, you could use the same frequency, if it turned out to be an optimal frequency.

Carr: That is true. If you could duplex -- in other words, be heating one point and then, of course, sensing another -- that would certainly be adequate. Normally, you would probably like to keep the heat constant. You could certainly duplex.

Buckley: Yes, Ken, why not just pulse it? My gosh, you do nanoseconds in terms of electronics. The body is not that good of a heat-transfer agent. Just pulse the thing in nanoseconds or microseconds.

Carr: That is true. And, by the way, once you start heating, if you do get the differential in heat which you have all said you do between the surrounding tissue and the tumor you are heating, then the target, or the tumor, stands out more. It becomes more pronounced and easier to find with sensoring devices, so it makes the loop easier.

Singh: Very good. Let us see. Dr. Atkinson has something to say.

Atkinson: If you are referring to the microwave radiometry, indeed the pulsing technique would be quite effective. We have found that the pulsing technique is slightly effective in adversely placed thermocouples. The problem there, however, is that the electric field heats the transducer selectively to the tissue, and that is what I mean by an adversely placed thermocouple. However, an on-off technique is effective; and, where safety is not a major consideration, such as in animal experiments, it is indeed quite feasible to use pulsing.

Singh: Well, but in the case of Mr. Carr, he was not really using any detector inside. It was simply the emission from the hot spot. Dr. Samaras?

Samaras: There is one hangup with the duplex technique, and that is you need at least 5 to 10 seconds for your integration time on your radiometer. But, I think that, on the order of low-hertz duplexing, microseconds is a little bit too fast. But, I think that, on the order of low hertz, you could probably handle it simply because of the heat-transfer characteristics of the body.

Carr: Yes, you could. Actually, you would be running basically CW for a longer period of time, and then you would switch over and sense because you could certainly duplex with long time durations on the heating and short time durations on the sensing and get around it. It is a very good point.

Singh: Well, I think in addition to microwave, both for heating and for sensing, some reported clinical studies seem to have used RF power, or frequency in the range of a few 10's of megahertz. I think, if you are doing that, then you have a way of handling the problem, even with the thermocouples, of the temperature measurement. With the RF current, for example, you do not have the problem of interference of the electromagnetic field with the detector because you can have the field direction normal to the conductor length. And, if you do have that simultaneous readout from the thermocouple, then you could use a closed loop and maintain the temperature you want.

Carr: It is very difficult when you have dispersion, particularly in a complex structure like the human body, to try to maintain orthogonality of the detecting device. Dispersions in these media are very complicated. It is not like radar in free space, where it is reasonably homogeneous. The body is not.

Singh: I think you are quite right, but we deliberately use RF current. We just use two electrodes across the test subject. The only problem is the heterogeneity of the medium.

Carr: The lower that you are forced to go on frequency, the more difficult it is to focus because most important of all, you are looking for spatial resolution.

Singh: You are right. It is not focusing; it is simply plugged. It consists of just two electrodes. The RF current provides actually resistive heating.

Carr: That is correct. Okay.

Singh: Well, are there any more comments?

Harrison: About the ultrasonic thermometry, I am under the impression that if I wanted to ask questions about that, I call up Pat Lele at MIT. Is anyone besides him doing any work? I would like to know.

Singh: Well, I suppose Dr. Atkinson might address that. I do not know personally.

Atkinson: I do not know if Pat Lele is doing any work in ultrasonic tomography for temperature measurement. I do know that there was a group at the Mayo Foundation doing this. John Greenleaf and a fellow by the name of Johnson were involved. I am trying to recall his first name. Johnson has a 5-year career development award from the National Cancer Institute, and he is at Utah right now working on the techniques. They split off into two groups, one at Mayo and the other at the Utah Department of Bioengineering.

Singh: I think one additional advantage of the sound wave would be that it would be a lot easier to focus -- much easier than, for example, the microwaves. Yes, Dr. Regelson?

Regelson: As I mentioned earlier, to my knowledge the biggest clinical program that I know of in ultrasound is at Bowman-Gray in Winston-Salem. The Reynolds people, the tobacco people, have given them a very fancy ultrasound machine, which has been in clinical tests for at least 6 years. I was on a project-site visit there, and it is being actively used. But, what has happened with it, I do not know. I do not keep up with that literature.

Singh: Was it part of acoustic holography? Was that machine used for holography, as such, or was it for hyperthermia?

Regelson: To my knowledge, as I recollect it, it was the ultrasound itself that was given special virtues. Some years ago I remember the Germans were using ultrasound in combination with radiotherapy and claiming that they were focusing ultrasound in head and neck tumors, for example. They got an improved therapeutic differential. This was felt to relate not so much, as I recall, to heat, but to blood flow, increased hyperemia, which, of course, could have some relation. But, there is an intrinsic mystique to ultrasound, independent of the fact that it raises temperature.

Singh: Well, there is, in addition to just the temperature rise associated with the incidence of ultrasound, that nonthermal effect which is a little more marked with the ultrasound. The nonthermal effect that we have heard earlier today is more marked, more of a problem, with the ultrasound than it is with the microwaves, or any other E&M form of radiation. Is that not correct?

Regelson: I would just like to get to know that guy who was playing the guitar and got all those cockroaches and mice to leave! Do you remember that?

Singh: They were probably frightened away. Well, temperature measurement is certainly a challenging problem. At Langley we were approached by the local medical community, the Eastern Virginia Medical School and MCV, to see if some of the NASA technology could be transferred to help out. I think we have a couple of groups at Langley. There are representatives of both the groups here, as a matter of fact; they are Ed Germain and Richard Couch. They are setting up a closed-loop system which uses RF heating. And, I suppose the idea there is to be able to maintain a constant temperature, or dial any temperature you want, for any length of time you want. Also, you can probably put six, seven, or more animals at one time into the inside that encloses where you are trying to maintain a high temperature, or where you are passing a current. In addition to that I think we also have this contract I referred to with Microwave Associates, Inc. I do not know if that is in effect already, or not. I think some of the NASA technology can help out, and at Langley we are, indeed, cooperating as much as we can. Certainly the use of microwave radiometers can help. We have had Skylab and Nimbus 5, and I suppose in these programs we developed the radiometers. And, I think we are certainly willing to lend one to Microwave Associates. So, in addition to that promise, I do not know what else I can tell you. Perhaps, you will raise the question of what type of help you can get from us, and we shall see if we can come up with some answers. I can assure you that we shall give it consideration. Are there any problems? Dr. Atkinson?

Atkinson: May I raise the question of how you are going to know where the microwave thermal radiation is coming from internally from the clinical subject or the animal? This has been a real impediment to microwave thermometry, to my knowledge. The facts of extremely poor spatial resolution due to internal scattering, heterogeneous organs, bones, and long wavelength make the precision -- even in two dimensions, let alone in the third dimension, or along the Z axis -- as to where it is coming from difficult. Even in two dimensions, localizing where the radiation is coming from is difficult. I believe these are fundamental basic-research problems that should be undertaken. It is well to talk about possible future applications of this to something like hyperthermia, but I do not think that the beginnings have even been made. There are many fall-back positions. The tool might be useful if it were developed for tissue characterization, for various screening diagnostic procedures, or for a very nice adjunct to diagnostic radiology. But, I personally feel that it is a little far down the line for us to talk about microwave radiometry in hyperthermia.

Singh: Well, I think you do have a good comment. But, is it not already in use, for example, at Falkner Hospital, where they are using 1.30313 gigahertz? I think their spatial resolution is less than a centimeter. And, they claim that they can see a tumor the size of about 1-centimeter diameter. I think maybe that is one of the goals that we have in connection with what we are going to do.

Carr: The work at Falkner Hospital has mostly been done at 1.7 gigahertz and 3 gigahertz. They are now considering going to a higher frequency. There are tradeoffs between spatial resolution and frequency. As you go higher in frequency and approach the infrared frequency, of course, the emission from the target, or from the tumor, becomes greater. For good spatial resolution at the higher frequencies, however, the depth of the tumor below the surface would push us toward the lower frequencies. So, you do have some tradeoffs. Now, the fact is that you may not be able to get all the advantages, and you will have to make some tradeoffs. You may not be measuring the temperature of the tumor itself; but you may be measuring it at some distance away from the tumor, which is certainly closer than being at the surface. You will be able to get a definition of where the tumor is. And, I think, once that you have learned to locate the tumor this way, you will also know more about how to apply heat to the tumor because it should be the reverse of what you have learned.

Singh: Well, that is true, yes. But, I think in answer to that question of how do we localize it, it is a very strong function of the temperature, the microwave emission from that point. And, of course, I think it will certainly be the hottest part that will emit the most. By simply scanning across, you should be able to sense the spot where the tumor is. You are not going to be able to localize it, I agree, but you can spot it below the surface, at least. Dr. Regelson?

Regelson: Again, I wish somebody would tell me why the mice's tails fall off in association with diapulse! What is there about the base of the tail that creates a burn?

Singh: I do not know, but did you have standing waves of some sort?

Regelson: I do not know. It is a tail wave, whatever it is! But, another interesting thing relates to what I was talking to Don Cone about. Don Cone, of course, is interested in sodium relationships. Salt concentration in tumors is very high. Is there anything about microwave in relation not only to the water content which people have talked about but also to things like sodium concentration? Can these be factors that could be related to manipulation? Or, could this explain differential effects?

Singh: Well, I do not know. But, let me give you an analogy. If you have just a circuit element and you make a small break there somewhere, there is intermittent sparking there and the spark heats the most. Are you having some such thing at that point where the tail joins the body? Do you have, for example, a sudden change in the impedance, or a sudden change in the resistance, there due to ionic concentrations? Don?

D. Cone: Not to my knowledge.

Regelson: The only thing you have got, of course, at that point is that the tail vertebra become continuous with the pelvis, and you have got one big bone, whereas before you had small separate bones.

Singh: I think that before I can really answer the question, we shall have to look at the whole problem. We shall have to look at the actual layout and see what is involved. I do not think that I can off-hand answer the question. Maybe that is going to be a little difficult. In view of the fact that the temperature measurement was one of the hottest problems, I am rather gratified to see that you do not have the problem, that you are satisfied with the things you have, or that you know your own bag.

Shaeffer: I was kind of surprised that no one brought up anything about using liquid crystal type measurements. That might be the way to go. We have to move along here. The next topic for discussion is Preclinical Experiments, and this session will be moderated by Dr. Tim Merz from MCV.

Session 3: Preclinical Experiments

Moderator: Timothy Merz

Merz: Since I have no preclinical data to present, I am obviously the logical person to moderate this session. At the meetings in Wisconsin, there was considerable time spent discussing tolerance to heat. I have not heard that mentioned. I would be interested in hearing more about that. Also, peculiarly enough, everybody is talking about Holt's experiments with heat due to 434-megahertz microwave radiation. He was very careful to point out in Wisconsin that he did not think heat had anything to do with his results. He also said that essentially he gave very low orders of radiation, like 600 rads, for the total treatment; and he did not think he raised the temperature past 39° C, as I recall. He thought there was a tremendous component from the microwave radiation itself and that 434 megahertz was the magic number. I would also like to hear anything from anybody on this. Yes?

Atkinson: With regard to Holt's paper, I chaired his session in Wisconsin, and I also attended a presentation he made at Airlie House. I would like to point out that his evidence that he is dealing with a nonthermal effect is based exclusively upon the fact that he packs the patient in ice and places the 434-megahertz antenna around the patient and then, when he takes the antenna away and looks with an IR thermograph, he finds that the skin is indeed cold. Now, this is a technique that has been widely used to prevent skin burning with deep-tissue heating. This is far from being evidence that he has not heated the tissue. I think this would be an excellent way to heat the tissue without heating the skin. So, I do not know that we can really conclude that Dr. Holt has observed a nonthermal effect, or that he has any evidence that he is looking at a nonthermal effect.

Merz: I do not think there is any doubt about that, but that is definitely what he reported at the time. There is a possibility, which has been mentioned several times by my colleague, Dr. Wilson, that the damage that we are looking at in terms of what we call enhancement of radiation damage by hyperthermia is, indeed, to some extent an enhancement of damage, rather than an inhibition of repair. I think most of us are stuck on the repair capability change, and not on the damage. That is another thing that one of you might want to talk about.

Regelson: One of the things that I was impressed with about Wilson's presentation is the fact that he got a protective effect, or that he might have, rather than a synergistic effect. I am reminded of Emanuel Farber's work with alkylating agents and cyclohexamide pretreatment in rodents, where he protected the intestinal epithelium by interfering with protein synthesis. Chemotherapeutic lethality to the gut requires RNA and protein synthesis, and, if you impede it with something like cycloheximide, you could protect against nitrogen mustard and, as I recall, actinomycin D. I cannot remember which other chemotherapeutic agents were involved, but you prevent slough-off of the intestinal mucosa by blocking protein synthesis. So, it is possible that you

have some sort of relationship like this operating. Has anybody studied free radical formation in association with heat?

Merz: I have heard talk of it. I have not read any papers, though.

Regelson: A fellow by the name of Slater in London and a number of other people have followed through on this thing. The concept of tissue damage as a function of free radical formation is a general phenomenon in biology that is suddenly coming into its own. There are a number of people now who are administering free radical scavengers and antioxidants. They claim that they are protecting the myocardium from ischemia and protecting the brain from total ischemia. They utilize agents like dimethyl sulfoxide, which is a free radical scavenger.

Merz: About the protein synthesis, I think there is an enormous amount of evidence that, in some systems, you tend to protect against damage by inhibiting protein synthesis. This happens if you are dealing with a potentially lethal dose of radiation, or if you are dealing with an enzyme which tends to cut things out severely when its trying to open up for repair. But, there is also an enormous amount of data which would tell you that, under other circumstances, you get anything but protection. You get considerable damage by cutting out protein synthesis because, when you cut out protein synthesis, you cut out, in many instances, the polymerases that are going to repair the damage. Anybody else? Jim?

Shaeffer: I was a little late in arriving this morning, and I did not hear all of what Dr. Baker had to say. I was wondering whether a few years back somebody might have referred to hyperthermia as a poor man's LET source. I know that Gene Robinson had done some work along these lines. I was wondering if, since we have Dr. Harrison in the audience, he might comment on the oxygen enhancement ratio using hyperthermia.

Harrison: Dr. Baker showed the reduction OER as the temperature goes up, and that was the data of Robinson, I think. It has also been shown by some other people. That does seem to be cheaper than a pi meson generator.

Shaeffer: It is cheaper by quite a few dollars, at least!

Merz: It is cheaper by about ten million dollars!

Harrison: On the other hand, is OER really important in clinical radiation therapy?

Merz: That is another good question.

Harrison: I do not know what is happening with the neutron trials, and I do not know if that is going to be the best reason for hyperthermia, or not.

Regelson: Has anybody looked at heat protective agents, like people look at antifreeze. I recall some paper, but I have not kept up with them, in regard to calcium tissue content reflecting heat death. I am also thinking of some

of the work that Cornforth reported years ago on heat shock, where you take blood cells, freeze them, thaw them, and then measure the hemolysis. I know there is literature there. I wonder whether anybody has looked to find the pre-fatty acid, lipoprotein ratio in the membrane that seems to govern this. Some people have made membrane models of this kind. Does anybody know anything about this? This is becoming increasingly important. For example, complement antibody cell lysis is inversely related to fatty acid incorporation. If the fatty acid incorporation protects from complement cell damage, then it is quite possible that protease lethality, or lipase lethality, protects the cell surface. Could the stability of the surface to heat reflect on something like this? Is anybody working with models of this kind? Or, has anybody reviewed the literature relevant to this?

Singh: How does hyperthermia compare with other forms of treatment like fast neutron, or pion, therapy? Does it match, for example, pion therapy?

Merz: Well, I do not really understand the question. You can get survival curves with hyperthermia, if you want to take the temperature up enough to essentially where the tolerance effect can be seen. But, when you are talking about the enhancement of radiotherapy and radiation damage by hyperthermia, these are different. You cannot compare the two.

Shaeffer: We come now to the last segment of the open-discussion part of this symposium, Clinical Trials. This session will be moderated by Dr. William Constable from the University of Virginia Medical School.

Session 4: Clinical Trials

Moderator: William C. Constable

Constable: All I have heard is that we really do not know what we are doing with hyperthermia. I am really not sure whether there is even a place for clinical trials yet, let alone a place for using it. Although, if you look back, you realize that the radical mastectomy was introduced without a single clinical trial, and also that, within about 6 months after discovery, X-rays were being used therapeutically without a clinical trial. Perhaps, we should consider whether there is any place for using heat and radiation, empirically on the evidence that we have at the present time. If so, what would this situation be? Now, Dr. Baker has been involved in some of this work in San Francisco. I was wondering if he would mention some of the experience that they have had there with treating lesions with heat and radiotherapy in a controlled clinical trial.

Baker: There was a clinical trial, admittedly not quite controlled and not entirely within the boundaries of the RTOG protocol, conducted in San Francisco. The idea was to investigate feasibility. One aim was to find out if it was practical, in fact, to set up in a practical radiation therapy department a clinical hyperthermia program. There were a couple of questions we needed to answer. Not so much the biological consequences, as those I think we can deduce from the amount of literature presently available, from past experience, from preclinical trials, from animal studies, and so on. But, was there a practical point to this in the sense of cost-benefit to the department? To begin with, there was the initial outlay for the kind of equipment and facilities that were needed. And, that represents a fairly large dollar tag, although not quite comparable to that of a new linear accelerator. For each treatment, you are tying up a treatment room between 1½ and 2 hours. You are also tying up a full-time, highly paid technician for that same length of time, at least. You are tying up physician time by a factor of five, compared to a conventional radiation therapy treatment. You are then confronted with all the medical legal problems associated with the use of this modality. There are all the problems associated with consent forms and whether or not they are valid at all. There is the question of who is responsible legally. All these things have been mentioned briefly by Dr. Atkinson; and they are horrendous problems, when you happen to be the person whose name is on the line. There is also the budget problems in terms of nurses, nurse time, and usable supplies. And, if any of you are anticipating getting into the hyperthermia business in a local radiation therapy department, then I suggest you very carefully cost-account the program before you get it started. We have done that, and the bottom line gets to be quite large.

Constable: Don, do you not think, however, that we have enough clinical information now to suggest that it could be used in very specific circumstances, such as in the treatment of superficial masses that, perhaps, have been unsuccessfully treated previously and for which there are no other treatments available?

Baker: There is no question, in my mind, about its effectiveness. You know, I have seen some rather remarkable regressions of local tumors that have been refractory to all the conventional modalities. I have seen them very successfully treated by small doses of radiation and hyperthermia, or even by hyperthermia alone. So, there is certainly a place for it. I think the question is not really that; but, rather, can we afford to use it? It is not a question of is it effective, or can we use it? We certainly can use it. But, can we afford to use it? And, that is the bottom line that involves both the legal aspects, as well as the time and cost.

Constable: Certainly, we have been approached by community hospital radiotherapy departments for advice on how they can set up their hyperthermia programs. So, the information that has been getting into the press from exuberant M.D.'s who have been researching in this field has had its effect. And, these people are now feeling they want to get into this area, which is essentially still a research area. With regard to the documentation of palliative responses, this is very difficult in radiotherapy. I am not even sure if you can run a controlled trial in this area. We have, I think, one patient who is sort of a control. The patient had a melanoma; we treated it with conventional levels of radiation. It did not respond at all to the radiotherapy. Six months later, when Dr. Baker arrived, we treated it with another 12 hundred or so plus heat; and the thing just melted away. That is a rather surprising thing to happen. I do not know how that could be explained, except on the basis that heat does have an effect. Dr. Atkinson?

Atkinson: With regard to the question of the cost of research in hyperthermia, I think that this is, indeed, a real problem. We, in generating the RTOG protocol, seriously looked at just what information we could get for the minimum cost and minimum development. The highest priority that we could establish was to determine whether or not there was a therapeutic advantage to the use of heat in conjunction with radiotherapy. For this reason, we chose to limit the patient population to those patients having superficial lesions. With regard to the instrumentation required to produce, monitor, and control the heating, it appeared that for superficial lesions the 2½-gigahertz radiation, with a penetration depth of only 1 to 2 centimeters, would be adequate. And, also, this lent itself to a clinical trial with a minimum risk associated with deep bone heating. We were rather skeptical about the safety of using more penetrating radiation. And, also, we considered the fact that 2½-gigahertz machines are commonly available in hospitals. The cost of the instrumentation among the various participants in the RTOG protocol, I believe, came to about $5,000 per organization. You are quite right, however, that this is a labor-intensive method. The labor costs about $50,000 to $75,000 per man year. We felt that it would probably involve the full-time work of at least 1½ men to execute the protocol that we had outlined. But, it is research that is expensive, not particularly hyperthermia research. The instrumentation is not terribly expensive. We have been talking about some very exotic, secondary and tertiary, research goals that might be associated with hyperthermia, far down the line. I wonder whether they are really essential to the investigation of hyperthermia. Sure, they are interesting biological and clinical investigations, but their

relevance to hyperthermia is, in my-mind, sometimes very often in question. Hyperthermia, I think, can be used as a good front for other research activities. There is absolutely nothing wrong with this, as long as we recognize this to be what it is.

Constable: Do you think that there is a place for hyperthermia in palliative situations outside your particular clinical trials?

Atkinson: Well, we are doing a whole-body hyperthermia clinical trial. We are just terminating phase 1, which was primarily to investigate toxicology, to establish the feasibility, to determine the patient selection criteria, and what not, for the chemotherapy trial, which we have just undertaken. And, we have only done two treatments, as a matter of fact. A few weeks ago we started on the chemotherapy in conjunction with whole-body hyperthermia, so it is really too soon to say. We have seen some objective evidence of remission in the whole-body hyperthermia with heat alone. I am not an oncologist, so I refer you to the medical oncology branch of NCI for more information on this. But, we were rather surprised that the heat alone apparently was effective in some treatments, that is, as effective as it turned out to be.

Constable: So, in fact, what we are saying is that it is not all smoke. Maybe, there is a little bit of fire under there.

Atkinson: Well, we are hoping from this RTOG protocol to answer this question very definitively. That is, is there a differential increase in susceptibility to radiation damage between tumor and normal tissue? That is the major problem that we are addressing. There are 14 participating universities in this protocol. We are 2 months into the protocol now, so we do not have any data yet. Let us see, last month the pilot studies were presented. These were just primarily start-up investigations, from which there are no real data. I think that it is extremely important that we address this question. I do not think it can ever be answered by in vitro tissue culture work because, after all, almost any stress, including raising temperature, decreases the viability of the cell. We can talk about pH; we can talk about CO_2; we can talk about nutrient levels; we can talk about anything you add to make life uncomfortable for the cell. The question is: "What controls can we compare it to in tissue culture?" There really are not any. In animals the tumor systems that we know the most about are the murine systems, and these animals are extremely susceptible to the effects of heat. So, we are almost excluded from the beginning from dealing with these animals in an effective, evaluable manner, such as is used in chemotherapy. If we go to large animals, there are no controlled tumor systems. What has motivated me, anyway, at NCI are the various semi-anecdotal clinical experiences that have been appearing in the literature over the past 50 years, with increasing frequency in the past 10 - 12 years. And, that is primarily the way I have been justifying and rationalizing the conduct of clinical trials. We are quite conservative at the National Cancer Institute. It was with great difficulty that we did get the four protocols that we have for hyperthermia through our various committees.

Constable: Anas, did you want to comment on the RTOG trial and hyperthermia?

El-Mahdi: I think I would like to comment about the whole issue of the treatment of cancer, actually. There is a big gap between the basic scientists and the clinicians. If it is going to be expensive and very sophisticated, such that you need something like 10 scientists to treat one patient in 1 week, then forget it. This is true -- even if you are going to cure all cancer! If you are not going to have a simple instrument, for the clinician, then forget it. Do not waste your time now. The hyperthermia reminds me of the oxygen. We went through that a few years ago. Everyone was speaking about hyperoxygen, oxygenation of the tumor, sensitivity, and so forth. But, once it entered the clinical field, it died because of the extensive time, effort, and the kind of material we were using. If the RTOG is going to confine itself to the skin tumors only, they better forget about that. We are not interested in the superficial lesion, even if they said there was a 100 percent cure rate from heat and radiation. The people dying these days from cancer are the people with cancer of the lung, of the breast, of the colon, of the deeply-seated tumor, or of disseminated tumors. We can cure the superficial ones. I can take them out. I can cure them by many means. I do not need hyperthermia for superficial lesions. But, if a patient comes in with a huge axillary mass, no one can do anything about it. So, I think we need a little bit of not focusing heat, but focusing thinking, with all due respect to the sophisticated work coming from you researchers. It has become like a fashion now. The whole country is going into hyperthermia. The whole country is going to radiosensitizers. And, there is a very, very, big gap. I think we are declining in treating cancer, not progressing.

Atkinson: With regard to the RTOG protocol, I quite agree that a superficial metastatic lesion, or tumor, is obviously treatable by surgical means, or by any number of means. You say that you would not need hyperthermia for that. But, tell me, would you not like to know before you treated a lung-cancer patient, or subjected the patient to a risk of radiation pneumonitis, whether or not a superficial metastatic lesion in the lung was susceptible, or differentially susceptible, to hyperthermia?

El Mahdi: Well, you yourself said that in the last 50 years there has been a lot of data in the literature which indicates that heat by itself can cure some kinds of cancer. There are many things I want an answer to. For the scientists, can you in a simple way heat a deeply seated structure? I hear people speaking about one by one millimeter, and all that. That is not the issue! The issue is a big tumor down there in the abdomen of that human being, for example, in the pancreas. I do not know if I can heat it. We agree, in general, from the data available that, perhaps, heat by itself, or heat and chemotherapy, or heat and radiation, may do something. We agree about that. But, we have not solved the problem of delivering the heat. We do not know the effects of different kinds of heat -- wet heat, dry heat, or which wavelength we are going to use to heat a particular tissue. Everyone is speaking about the normal tissue in animals, but no one is speaking about a particular normal tissue in animals, like the lung tissue. Is the effect the same as in the spinal cord, as in skin, as in intestines, as in kidneys? We know all the differential effects of radiation and of chemotherapy. With

chemotherapeutic agents the toxicity to the bone marrow is different than the toxicity in the gut. So, there are many, many things. We are rushing, you know, and I am sorry about that because out of that rush we may lose a chance of finding the cure for cancer. We will get too many scattered data, and everyone will get disgusted, throw heat away, and go to another fashion. We do not follow up a single aspect and find the real answer for it.

Atkinson: I really do not follow your logic. I do not want to make this a dialogue, but I feel compelled to comment. You are, on the one hand, saying that we should be focusing upon the very expensive, but technically trivial, problem of deep internal organ heating -- before we have even established the validity of the treatment modality. I think that this should be approached in a systematic method, such as to conduct a clinical trial with evaluable lesions. One of the difficulties that we are having in our whole-body hyperthermia protocol is answering the question of how can we tell if we are, indeed, doing a patient a benefit? And, how can we quantitate this? This is a serious problem. For a superficial lesion this is easily measurable. That is why we chose this approach. Certainly we are not saying that the method, if it is effective, will be restricted to superficial lesions. But, this does seem to be the best way, which we can come up with at the present time, to determine whether or not it is effective and to justify, and I seriously mean this, the expense involved in the technically trivial problem of deep internal organ heating. But, I think that, if we jump into deep internal organ heating, it might be years before we ever answer the question of whether it is even effective. And, I look at the hyperbaric oxygen chambers that are being excessed from hospitals all over the country. I see what happens when you get a little drunk with technology and start getting equipment without determining whether it is effective, or how it is best to be used. That was a serious mistake, and I would not like to see the RTOG do such again.

Constable: I think this is correct. Dr. Baker and I have been looking at the methods you can study clinically, and the only thing you really can come up with is multiple lesions on the surface, at the present time. As we said, there may be enough general information in the literature to justify using it in certain palliative situations. But, to try to quantitate that, as with your whole-body hyperthermia, is almost impossible. So, I think we have to go along with the skin testing just now; and, if there is something in that, then, perhaps, the exotic things we have heard may justify themselves in due course. Dr. Samaras, did you want to say something?

Samaras: I take exception to the fact that deep heating is technically trivial. Clearly, we have to balance cost-effectiveness and budgeting, on the one hand, and the development of technology, on the other. But, I cannot see that deep heating by any methodology -- including whole-body hyperthermia, which, at least in my mind, is still questionable as to how uniform the heating, or how well we control the heat, say at the head of the pancreas, or in the center of the brain -- is a technically trivial problem. I think that it is a very difficult problem. And, I think in order to solve these problems, if you do want to solve these problems, you are going to have to expend the resources necessary.

Merz: I would like to add that I think it is extremely important to pick the right tissue and to go at it systematically. I recall not too long ago a catastrophe. I think about Stanford, where they studied the effect of bromodeoxyuridine as an analog and as an adjunct to radiotherapy. In my mind, they picked a lesion, a modality of treatment, and a fractionation system which have denied the use of bromodeoxyuridine to anybody else who may ever want to use it, because it was so disastrous. I think that it is a necessity that we look at the right lesion in the right way, so we can really determine whether or not this is really useful.

Regelson: Before the meeting ends I just want to talk about another approach that does away with microwave instrumentation, or external heating from a variety of techniques, to raise temperature. We are starting to do some collaborative work with Slater from London. Slater, as you may know, has found that, if you give dinitrophenol with the right displacing agents, you get heat off the albumen, depending on the animal species you use. You can raise the temperature of a rat, for example, to 44° centigrade, by uncoupling oxidative phosphorylation. In fact, you get instant rigor mortis because you have a tremendous accumulation of lactate. We have suggested that this be used as a method to meet the energy crisis, by putting it in rat poison. If you have rats in your walls, you get a lot of heat! But, it represents a very interesting option, and it is extremely intriguing because uncouplers of oxidative phosphorylation have been around for some time, not only in platelet physiology, but also in tumor work. Perhaps, some of the effects of warfarin, the coumadins, and some of the quinoline derivatives may work in this way as antitumor agents. So, we are very, very much interested in this.

Constable: Are there any more questions?

Singh: You have debated the usefulness of hyperthermia. Has the medical community agreed that it has a merit; and, if it has agreed, why does hyperthermia work? What is the basic reason? Why does, for example, hyperthermia render tumorous cells more liable to treatment by X-radiation or chemotherapy?

Constable: I think that most clinicians would think that it does have something in it, to a greater or lesser degree. But, I do not think that we can go beyond that at this time. With regard to how it works, you have heard all the people talking today. Dr. Atkinson may again be the best one for telling us the latest theory on that. I have always thought that it was the hypoxic cells in the middle that we were getting at.

Singh: Well, I have heard the arguments both ways; and I did not hear anything that says why it works, if it does work.

Constable: Dr. Atkinson, how do you think it works?

Atkinson: Well, I was just asking the question of how X-radiation works. Would you care to dispose of radiotherapy departments because this question has not been fully elucidated? I call attention to the fact that we do not even know how aspirin works! Also, penicillin was in use for a great many years, 20 years approximately, before any inkling was discovered of what its

mechanism of action was. I think that, if we had sought to define the mechanism of action of old suggested therapeutic modalities before it was determined whether they were, in fact, therapeutic modalities, then we could have paralyzed medical research around the world.

Constable: Yes, I trained with Ralston Paterson, and I remember him teaching us that radiotherapy is, in fact, an empirical science, an art I suppose. Although we have gathered and garnered radiobiologists around us by the scores and although we just now, possibly, know how it works, our methods have not really changed. So, it may not be entirely necessary to answer that question before getting on with the clinical studies.

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