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# A Microwave System for the Controlled Production of Local Tumor Hyperthermia in Animals

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*Abstract*—**A microwave system was designed and constructed which provides controlled, localized hyperthermia in the tumors of four experimental animals. The components of the system are a 2.45-GHz microwave source, a four-way power-dividing network and reflected power monitor, a temperature-controlled microwave power regulator, and small direct-contact microwave applicators. Adjustment of the temperature control results in elevated temperatures in the centers of tumors which can be maintained to within ±0.1°C without production of significant whole body hyperthermia. The temperatures at the edges of the locally heated tumors were found to vary within ±1.0°C of the center temperature. The system is currently being used to evaluate the therapeutic potential of sustained localized hyperthermia in small tumors implanted subcutaneously in mice.**

## I. Introduction

THERE IS continuing interest within the cancer-research community in the application of hyperthermia as an adjuvant to ionizing radiation and drug therapies [1], [2]. Both laboratory and clinical studies are proceeding to establish the efficacy of this combination treatment. The effects of local tumor hyperthermia can be investigated using small animal tumor models. These models have the advantages of well-characterized growth patterns and known sensitivities to drugs and other antitumor agents. In order to study the effectiveness of heat in treating these animal tumor models, it is necessary to develop an apparatus which produces a controlled and localized tumor hyperthermia.

Several techniques have been employed by previous researchers to use microwaves for the local heating of tumors. Gessler *et al.* [3], Allen [4], and Yerushalmi [5] used metallic screens to shield the bodies of mice and rats, restricting the microwave exposure from microwave diathermy applicators (types A and C) to the area of the tumor. Copeland and Michaelson [6] also used a metallic screen to shield the body of a rat, while the tumor was drawn through a hole cut in the screen. The entire rat was then irradiated with 2.80-GHz microwaves from an *H*-plane sectoral horn antenna. Robinson *et al.* [7] improved on these methods by simultaneously forcing warm air over the surface of the tumor during microwave exposure resulting in more uniform intratumor temperatures. Cater *et al.* [8] localized the exposure to the tumor by suspending tumor bearing thighs of rats in front of a waveguide (7.0×3.5 cm) operating at 3.00 GHz. Zimmer *et al.* [9] used direct-contact microwave applicators at 2.45 and 9.05 GHz to rewarm the local tumor areas of hypothermic

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Fig. 1. Photograph of the assembled microwave system.

mice and rats which were simultaneously administered an anticancer drug. Mendecki *et al.* [10] also used a small aperture (12×8-mm) direct-contact microwave applicator to provide local heating of mammary tumors in mice.

The microwave systems described above were designed so that only a single animal could be treated at one time. It would be helpful to be able to treat a group of animals simultaneously with a single system in order to more rapidly acquire statistically significant data without resorting to complete duplication of systems and controls. A technique for multiple animal exposure was developed by Robinson *et al.* [11] which allows the simultaneous exposure of nine mice in the far field of a microwave antenna. Each animal's body is shielded from the incident microwaves while the tumor is encapsulated in a large (15-cm-diameter) bolus of tissue-equivalent dielectric material. This method produces very uniform (±0.1°C) and reproducible temperatures within the tumor. Unfortunately, it requires a high-power microwave source and an anechoic chamber which entails considerable expense and space.

Another problem to consider in the development of a regulated hyperthermia system is the method of sensing the tumor's temperature. Conventional needle probes embodying thermistors or thermocouples cannot be used because they perturb the microwave field. The needle's point may concentrate the local fields, and the metallic shaft may heat from conduction currents which would result in a tumor temperature near the needle much greater than would exist if the probe were not present. In addition, the whole probe can pick up an artifactual current (for example, from rectification) that is independent of the tumor's actual temperature. Any of a number of noninteracting, nonperturbing temperature probes presently under development could avoid these problems, but none of these devices are available in the small size (diameter less than 0.5 mm) that is necessary for their use in small tumors. Thermocouple probes without metallic needles can be used in microwave fields if they are oriented orthogonal to the electric field and can be demonstrated to measure temperatures accurately.

It is possible to avoid many of these temperature-sensing problems by using a pulsed microwave system which measures temperature only during the period of time when the microwave power is turned off. Mendecki *et al.* [12] have developed a system which periodically applies microwaves to a tumor. During the part of the heating cycle when the microwave radiation is off, the temperature is measured. A decision is made, based on the measured temperature, to either heat or not heat during the next cycle. Joines *et al.* [13] have developed a similar system which also samples the temperature only during the time when the microwave power is off. Both of these control systems are currently in use in preliminary clinical experiments involving ionizing radiation and hyperthermia.

The design goal of this project was the development of an efficient system that could produce localized hyperthermia in small animals, which would be automatically regulated, and could be used on several animals simultaneously. The frequency of 2.45 GHz was selected because

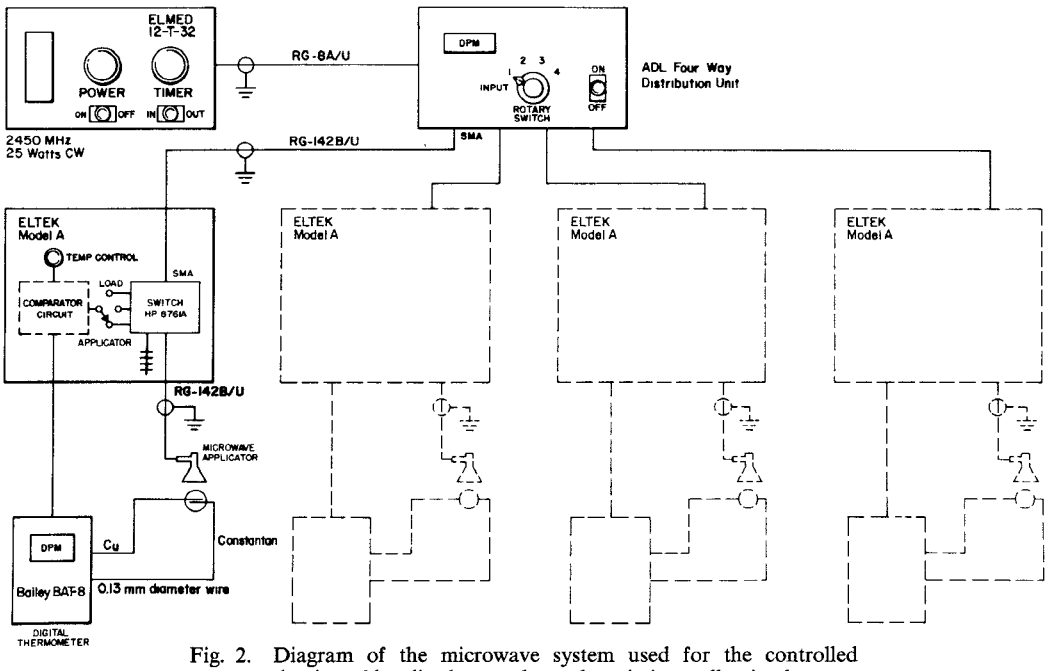


Fig. 2. Diagram of the microwave system used for the controlled production of localized tumor hyperthermia in small animals.

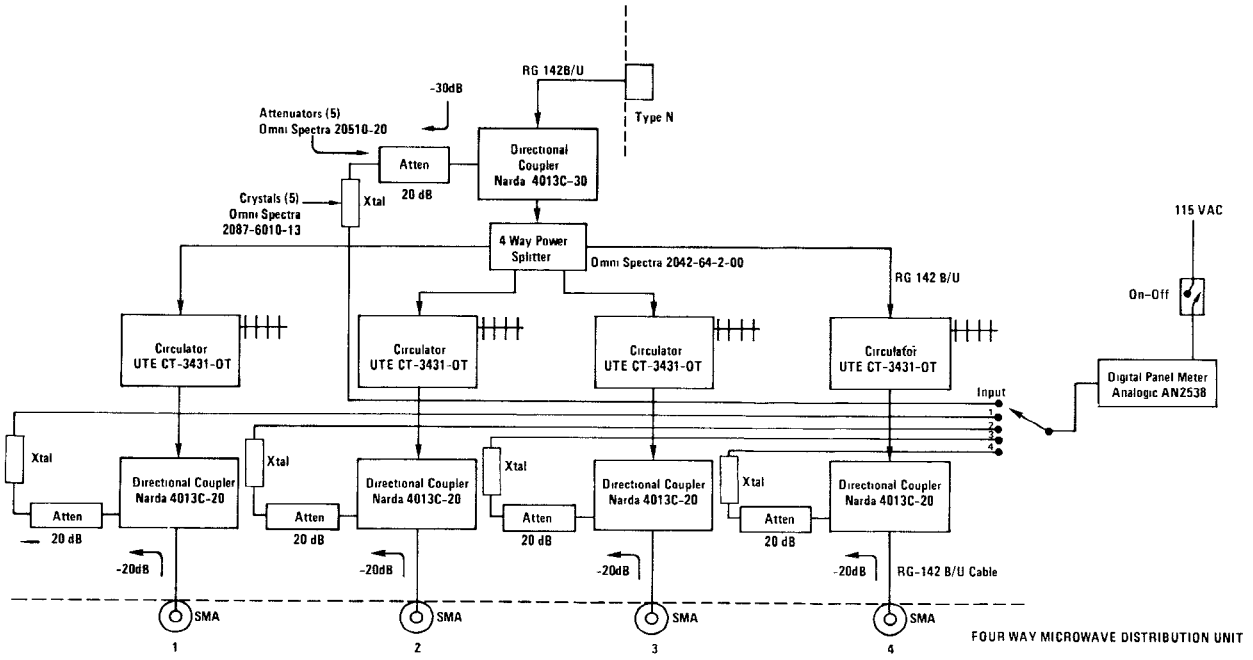


Fig. 3. Component diagram of the four-way power division and reflected power monitoring network.

of the availability of sources and its shallow depth of penetration which largely limits the absorption of energy to the region of the tumor. The design approach chosen was to construct a four-way microwave power divider and to provide a means for the regulation of each channel.

## II. Equipment

The assembled microwave system is displayed in Fig. 1. A complete block diagram is shown in Fig. 2. The system consists of a 2.45-GHz microwave source, a four-way power divider and reflected power monitor, temperature-controlled power regulators, small microwave applicators, and digital thermocouple thermometers. For applications requiring higher powers, the microwave source shown in Fig. 2 can be replaced by one which generates up to 50 W of CW 2.45-GHz power. The four-way power divider can display crystal detector voltages which indicate the input power to the unit or the amount of power reflected from each of the four microwave applicators. The configuration

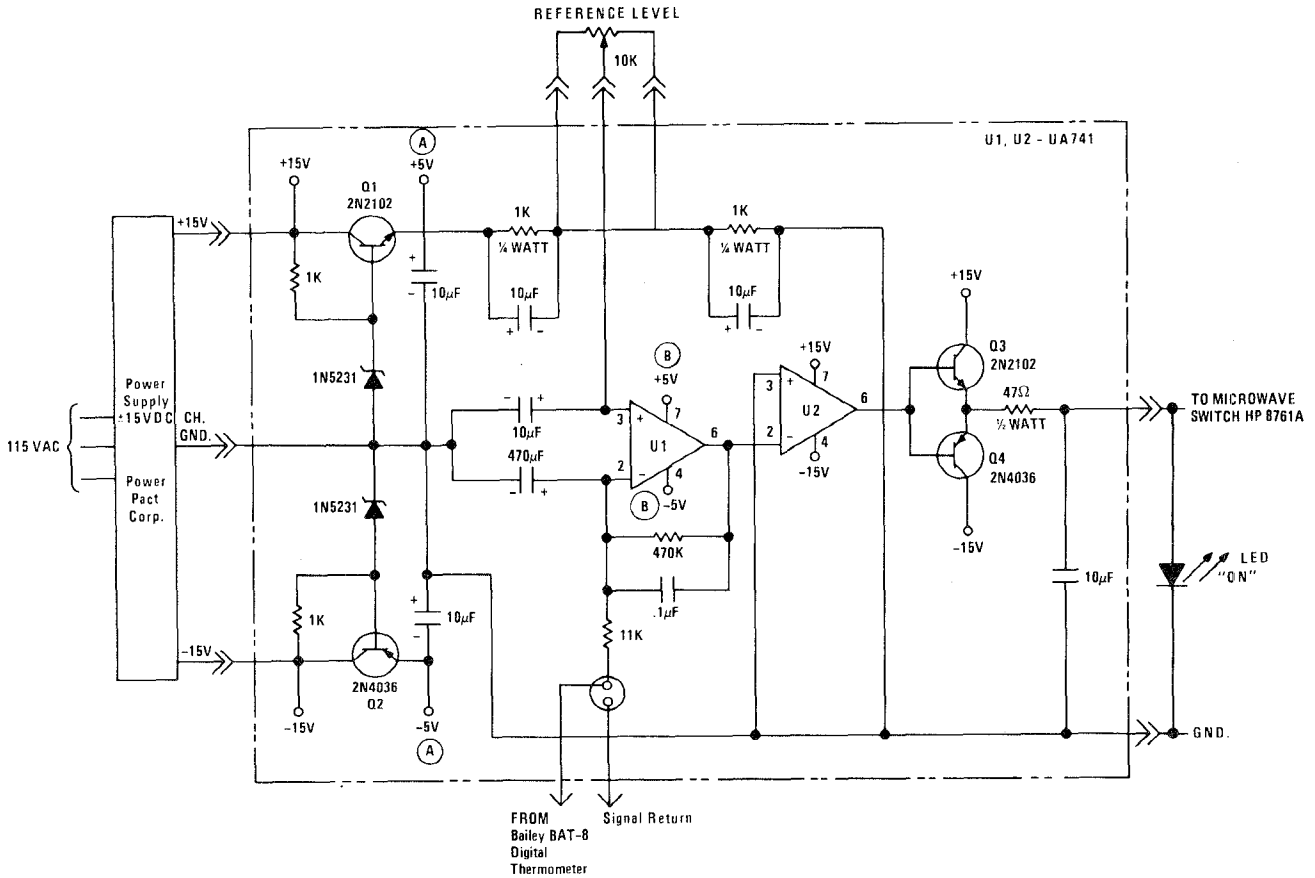


Fig. 4. Schematic diagram of the electronic control and comparator circuit contained in the temperature regulator.

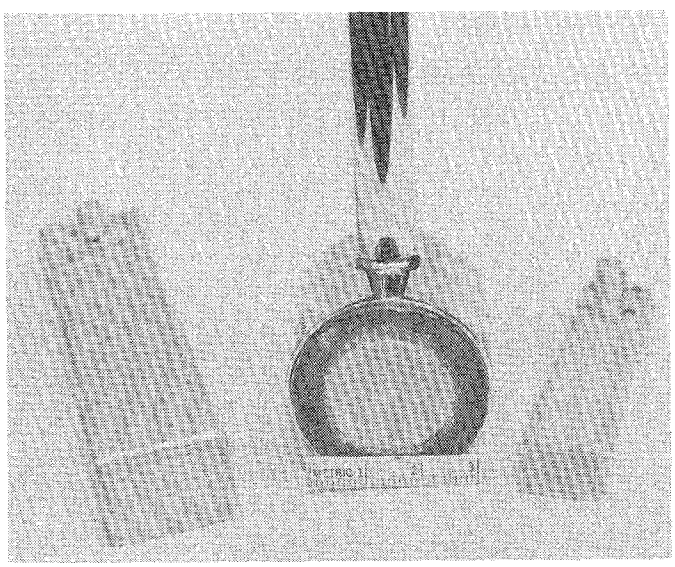

Fig. 5. Photograph of the small microwave direct-contact applicators.

of the four-way power divider network is shown in Fig. 3. The microwave switches (HP 8761A) direct the microwaves either to an applicator or to a matched load in accordance with the signal generated in the comparator circuit (Fig. 4). The power regulator (Model A, ELTEK Corporation, Gaithersburg, MD) receives a temperature-dependent input voltage from the digital thermometer (BAT-8C, Bailey Instruments, Saddle Brook, NJ) which it compares with the preset reference level to determine the correct state of the microwave switch. A manual single-pole triple-throw switch is provided on the power controller to force the microwave switch into either the applicator, regulate, or load state.

The three types of direct-contact microwave applicators that have been used with this system are displayed in Fig. 5. Two are dielectrically loaded waveguide horn antennas. The third is a dielectrically loaded cylindrical microwave diathermy applicator (AT-502/7z, ELMED Inc., Addison, IL). The aperture dimensions of the horn antennas are 12×8 mm and 20×14 mm. The diameter of the cylindrical applicator is 35 mm. Coupling between the applicators and the tumors is provided by bolusing the tumor with muscle-equivalent dielectric phantom material [14]. The bolus is formed into a cylindrical shape approximately 35 mm in diameter and 10 mm in height which encapsulates the tumor.

The temperature in the heated tumors is sensed by the insulated thermocouple junction between copper and constantan wire (0.13-mm diameter). The junction is placed in the tumor by passing a 25-gauge needle through the

tumor and pushing the thermocouple wire through the lumen of the needle. The needle is removed and the junction positioned at the center of the tumor. Using this technique, the thermocouple wire can be oriented orthogonal to the predominant electric field of the microwave applicators, and observation of tumor cooling curves indicated that an accurate measurement of the tumor's temperature was obtained. The small, light thermocouple wires are easily secured, and the junction has been found to remain in position despite considerable movement by the animal.

The digital electronic thermometers used in this apparatus were periodically calibrated to an accuracy of $\pm 0.1°C$ in a large well-stirred water bath by using an ASTM 91C thermometer.

## III. Results

The performance of this system is illustrated by the data presented in Figs. 6 and 7. In Fig. 6, the results of a local tumor heating experiment are displayed. For this experiment, four $BDF_1$ mice with subcutaneously implanted Colon 38 adenocarcinomas were anesthetized with chloral hydrate (525 mg/kg). The tumors had been implanted two weeks earlier on the left flank of each mouse slightly forward of the rear leg and had reached an average size of 106 $mm^3$. The normal rectal temperature for these mice is approximately 37°C. The initial measurements of the rectal temperatures were elevated due to the excitement of the mice from handling. The rectal temperatures then dropped due to anesthesia-induced hypothermia. During the first 20 min, each mouse had a thermocouple implanted in the center of its tumor according to the procedure described in the previous section. A bolus of dielectric material was placed over the tumor and the applicator (ELMED AT-502/7z) placed in direct contact with the bolus. The average total input microwave power was first set at 40 W until the tumors were each heated to 43°C and automatic regulation began. The power was then reduced to 30 W and finally to 20 W for the duration of the experiment.

The temperature at the center of each tumor was maintained at $43.0 \pm 0.1°C$ for each mouse for 60 min. The rectal temperatures initially increased during tumor heating but leveled off near the normal rectal temperature of 37°C. These results demonstrate that a constant temperature was maintained at the center of the tumor without the production of significant whole body hyperthermia. In other experiments using this apparatus, the average rectal temperatures of the locally heated mice usually fell within the range of 36–38°C. Previous experiments [15] conducted without a tumor bolus required higher input powers and resulted in rectal temperatures of 41°C when the tumor was regulated at $42.5 \pm 0.1°C$.

In order to measure intratumor temperatures, experiments were conducted with thermocouples placed at different locations within and surrounding a tumor. Three 0.05-mm-diameter wire thermocouples were formed into a

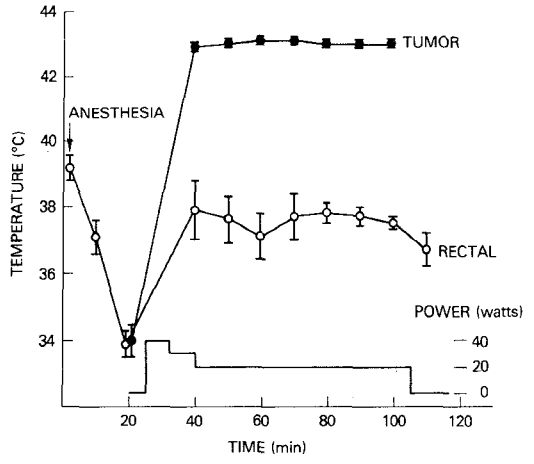


Fig. 6. Graphs of the average tumor and rectal temperatures measured in four mice during a local hyperthermia experiment. Each average is presented with its corresponding standard deviation. The approximate total power utilized during the experiment is also displayed.

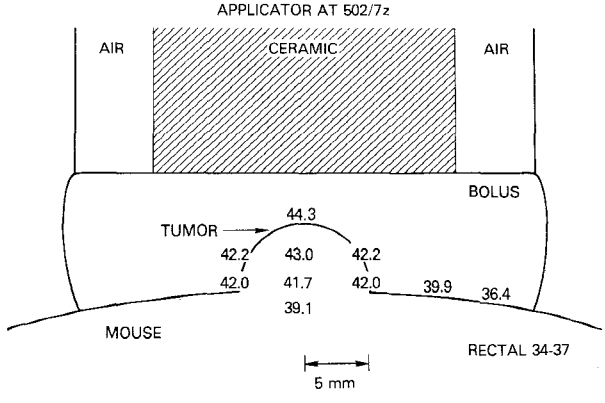


Fig. 7. Diagram of the steady-state temperatures measured in degrees Celsius found in and around a bolused tumor whose center was maintained at $43.0 \pm 0.1°C$.

bundle to measure temperatures at ±5 mm from the center of a tumor, while thermocouples formed from 0.13-mm-diameter wire were used to measure temperatures on the top, in the middle, and on the bottom of another tumor. In other experiments, temperatures were measured in the peritoneal space beneath the tumor as well as at various distances away from the tumor. All measurements were performed while the center of the tumor was maintained at 43°C and after steady-state temperatures had been established. The thermocouples were oriented orthogonal to the electric field of the applicators and checks for interference were frequently made by cycling the microwave power on and off.

Previous studies [15] using unbolused tumors indicated that sharp temperature gradients existed in locally heated tumors. When the center of an unbolused tumor was regulated at 42.5°C, steady-state temperatures of 39°C were measured at ±5 mm near the edges of the tumor. These intratumor gradients occur in the unbolused tumor because the ambient air temperature surrounding the tumor is approximately 20°C below the tumor temperature and the heating patterns of the applicators fall off

sharply away from their centers [15]. Thus another function of the tumor bolus, in addition to improving the applicator-to-tumor impedance match, is to provide thermal insulation for the tumor from the ambient room temperature.

The results of a series of temperature measurement experiments within and around bolused tumors are presented in Fig. 7. This figure illustrates the usual experimental configuration of mouse, tumor, bolus, and applicator in a schematic manner. The temperatures measured at different locations are indicated on this diagram. All the experiments were performed on Colon 38 tumors approximately $10 \times 5 \times 5$ mm in size using a $35 \times 9$-mm cylindrical bolus and the cylindrical applicator. Since the temperatures listed in Fig. 7 were obtained from different tumors, they are only indicative of the actual temperature gradients existing in any given tumor of this size. In general, however, a uniformity of $\pm 1.0°C$ was found to exist throughout the tumor, while outside of the tumor the temperatures were seen to decrease quite rapidly.

## IV. Conclusion

A 2.45-GHz microwave system for the production of multiple-animal local tumor hyperthermia has been described. The experimental system can be used to produce local tumor hyperthermia without the induction of whole body hyperthermia. An intratumor temperature uniformity of $\pm 1.0°C$ was demonstrated.

## Acknowledgment

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The rectangular microwave horn antenna applicators were designed and fabricated at the RCA David Sarnoff Research Center, Princeton, NJ, by R. W. Paglione and M. Nowogrodski.

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