Br. J. Cancer (1982) **45**, Suppl. V, 108

TEMPERATURE DISTRIBUTIONS IN TISSUES DURING LOCAL HYPERTHERMIA BY STATIONARY OR STEERED BEAMS OF UNFOCUSED OR FOCUSED ULTRASOUND

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Summary.—Temperature distributions resulting from insonation with stationary or steered beams of unfocused or focused ultrasound were measured in tissue-equivalent phantom, beef muscle *in vitro*, dog muscle mass, and transplanted murine tumours *in vivo*. Arrays of 4 to 6 thermocouples stepped through the volume of interest under computer control were used to measure the steady-state temperatures at 600 to 800 locations in both *in vitro* and *in vivo* experiments. The results were confirmed in spontaneous tumours in dog patients using fewer multi-thermocouple probes. Plane wave ultrasound was found to result in spatially non-uniform hyperthermia even in superficial tumours. The region of maximum temperature rise was small in extent and was situated at a depth which varied in the different models from 0·5 to 1·0 cm. Neither its location nor its extent could be varied by spatial manipulations of the transducer or by changing the insonation parameters except the ultrasonic frequency. A second region of hyperthermia was produced at depth by reflective heating if an ultrasonically reflective target, such as bone or air-containing tissue, was located below the target tissue. On the other hand, using available steered, focused ultrasound techniques, tumours (whether situated superficially or at depth) could be heated to a uniform, controllable temperature without undesirable temperature elevation in surrounding normal tissues. The use of steered, focused ultrasound permits deposition of energy to be tailored to the specific needs of each individual tumour. The small size of the focal region enables heating of tumours even when located near ultrasound reflecting targets.

HYPERTHERMIA, either alone or in combination with radiation or chemotherapy, is currently under evaluation as a modality in cancer therapy by many investigators. In treatment of disease localized to one or more circumscribed regions, local hyperthermia of the involved volume of tissue is preferable to whole body hyperthermia, as the local temperatures can be raised to higher levels without the toxicity and risks associated with whole body hyperthermia. Since the margin between the temperatures for therapeutic efficacy and damage to normal tissues surrounding the tumour is small, it is necessary that the temperature elevation be finely and rapidly controllable, be uniform throughout the tumour and drop off sharply outside the tumour volume. A non-uniformity of the hyperthermia temperature distribution may subject some regions in the tissue volume under treatment to undesirably high temperatures leading to thermal injury, while in some other regions the temperatures may be too low for therapeutic effect. The possibility that such low hyperthermia temperatures in the proliferating regions of the tumour may accelerate its growth rather than cause regression cannot be denied. Furthermore, with non-uniform intratumoral temperature distribution the "heat dose" to the tumour would also be indefinable and any correlation with effects in tumour, at best, would be only conjectural. Thus, ideally, not only should the magnitude of temperature elevation be finely controllable, but

also its spatial distribution in each of the three dimensions.

In a previous publication (Lele, 1980) it was shown that for induction of hyperthermia, in deeply situated tumours, non-invasively, and without undesirable temperature elevation in the overlying skin or mucosa, it is necessary to use focused ultrasound and to distribute the energy within the tumour around its periphery. Heat transfer considerations discussed later indicate that uniform deposition of heat throughout the target volume of tissue will invariably lead to excessive temperature build-up in its centre. Thus, in addition to focusing, some means for translocation of the focus in 3 dimensions around the target volume is necessary. Since the same considerations also apply to superficial tumours such a system can also be used for hyperthermia of superficial tumours. But, in order to circumvent the complexity of equipment needed for translocation, a stationary, plane wave (unfocused) ultrasonic transducer is commonly used in therapy of superficial tumours. The resulting temperature distributions are often measured at a single fixed location within the tumour, since in patients it is neither feasible nor advisable to make multiple insertions of the thermometric device. Therefore, temperature distributions resulting from ultrasound sources, as indeed with all other sources, need to be determined in prior experiments. This paper presents the results of temperature distributions measured in several media using both focused and unfocused ultrasound with stationary and steered beams and discusses their implication to clinical use.

MATERIALS AND METHODS

Experimental media

These consisted of tissue-equivalent phantoms (t-e phantom), cuts of bovine meat *in vitro* and the muscle mass in the gluteal, thigh or dorso-lumbar regions of the dog *in vivo*. Since the acoustical properties (*e.g.* ultrasonic attenuation and absorption coefficients and their frequency dependence, ultrasonic velocity and wavelength, acoustical impedance), thermophysical properties (*e.g.* heat capacity, heat conductivity and diffusivity, convective heat transfer through perfusion, *etc.*), as well as the anatomical and physiological characteristics (*e.g.* pattern of macrostructural organization with regard to homogeneity or anisotropy, degree and homogeneity of vascularization and its responsivity to temperature elevation, *etc.*) of tumours may be significantly different from those of these media, experiments were also conducted in large specimens of renal adenocarcinoma transplanted subcutaneously in the flank of the rat *in vivo*. In some experiments *in vivo* the rat bearing the tumour was placed inside the abdomen of an anaesthetized dog to simulate deep seated tumours.

T-e phantom.—This was a gelatin-albumin-agar mixture similar to that suggested by Astrahan (1979*a*, *b*). Its ultrasonic intensity absorption coefficient, as compared to several biological tissues, is shown in Fig. 1. The molten mixture was poured into a jig containing 4 or more thermocouples spaced 10 mm apart in both vertical and horizontal planes. The t-e phantoms used were 15 cm in diameter and up to 15 cm in height and were mounted on a thick aluminium plate to simulate presence of bone at that depth.

Thigh of beef.—Fresh cuts of meat from the bovine thigh, selected for uniformity of its grain, 15 cm or more diameter and approximately 15 cm in height, with and without

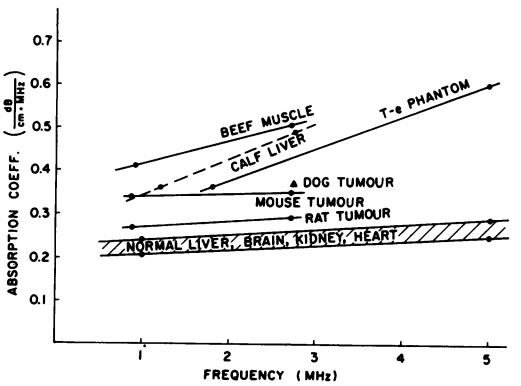


FIG. 1.—Absorption coefficients of the t-e phantom and typical mammalian tissues at different ultrasonic frequencies. The data shown as a cross-hatched band are from Goss *et al.* (1979).

the femur, were obtained from the slaughterhouse and stored in degassed normal saline, containing a mild bacteriostatic agent, at temperatures of 4 to 6°C for up to one week when not in use. The specimens were allowed to reach equilibrium with the ambient room temperature of 20°C and were massaged, to dislodge any gas bubbles, before experiments were performed.

Dog muscles.—Dogs weighing 35 to 55 kg were tranquillized with Acepromazine and maintained under light anaesthesia with i.v. pentobarbital sodium. Fluids were administered by a slow i.v. drip. The skin overlying the region under study was carefully shaved, cleaned with a detergent and massaged with ultrasound coupling gel to ensure good acoustical coupling.

Renal adenocarcinoma was transplanted s.c. in the flank of the Wistar-Lewis rats and was used in these experiments when approximately 10 × 8 × 10 cm in size. Tumours showing any signs of necrosis were rejected.

Ultrasound sources

X-cut quartz transducers 8 cm in diameter at fundamental frequencies of 0·6 and 0·9 MHz were driven either at the fundamental or its odd multiple harmonic frequency, yielding frequencies of 0·6, 0·9, 1·8, 2·7, 3·0 and 4·5 MHz. Central areas 1 to 6 cm in diameter were excited to change the effective transducer diameter for hyperthermia with plane wave ultrasonic fields. The entire transducer diameter was excited and the energy focused by plano-concave polystryrene lenses 6 cm in diameter for experiments with focused ultrasound. The insonation head was coupled to the t-e phantom or the tissue surface by degassed water contained in an open plastic bag.

Ultrasound source position and motion

The insonation head containing the transducer, without or with the lens, was mounted on a computer-controlled, 3-axis positioner (Fig. 2). This enabled alignment of the axis of the insonation head with any of the thermocouple junctions, or generation of oscillatory motions in X, Y or Z axes or of continuous motion in rectilinear or curvilinear trajectories. In the experiments described herein, oscillatory linear motions in X, Y or Z axes and circular trajectories were used.

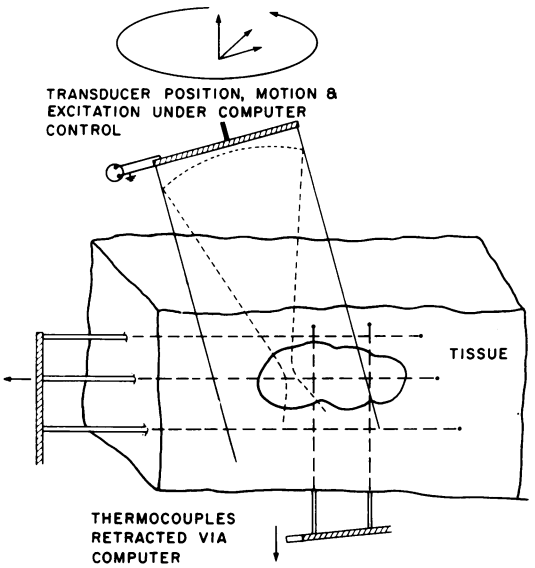


FIG. 2.—Insonation head positioning and thermocouple "stepping" system.

Thermometry

Electrically insulated chromel-constantan thermocouples, 25 to 125 microns in diameter, either unsheathed or sheathed in 25 to 23 gauge insulated stainless steel hypodermic tubing (for insertion into dog muscles *in vivo*), were used for temperature measurement. Because of their small size compared to the ultrasonic wave length in the tissues (2·5 to 0·5 mm), they were essentially nonperturbing. Heat conduction along the thermocouples was also found to be negligible for the thermocouple diameters used. The bare thermocouples were threaded through the specimen and both their ends secured to a yoke. The sheathed thermocouples calibrated in mm were also inserted all the way through the specimen to ascertain their position and then retracted into the tissue. The yoke or the hypodermic tubing was attached to a micropositioner driven by a stepping motor (Fig. 2). In both instances, the thermojunctions could be retracted through the region of interest in steps of 0·01 mm or larger under computer or manual control. The thermocouple calibration was periodically checked at 3 or more temperatures against a thermometer, the calibration of which was traceable to N.B.S. The influence of heat conduction along the sheath on the accuracy of temperature measurement under steady-state conditions was determined in preliminary experiments and suitable correc-

tions were applied to the experimental data. For measurement of temperature distributions in the specimen, 4 to 6 thermocouples were placed in various planes through the volume of interest. After induction of hyperthermia, when the temperature had stabilized, these were retracted in 0·5 or 1·0 mm steps at intervals of 5 or more sec to allow for thermal equilibration at each new location. Usually one additional thermocouple was placed in the centre of the region and held stationary to monitor changes in the local temperature with time. For every thermocouple the temperature and the location of the thermojunction at each step was recorded on a multichannel strip-chart recorder and simultaneously digitized and stored in the computer. These data, from 600 to 800 locations within the sample, were utilized for construction of isothermal plots. The distribution of temperature was normally measured at a hyper-

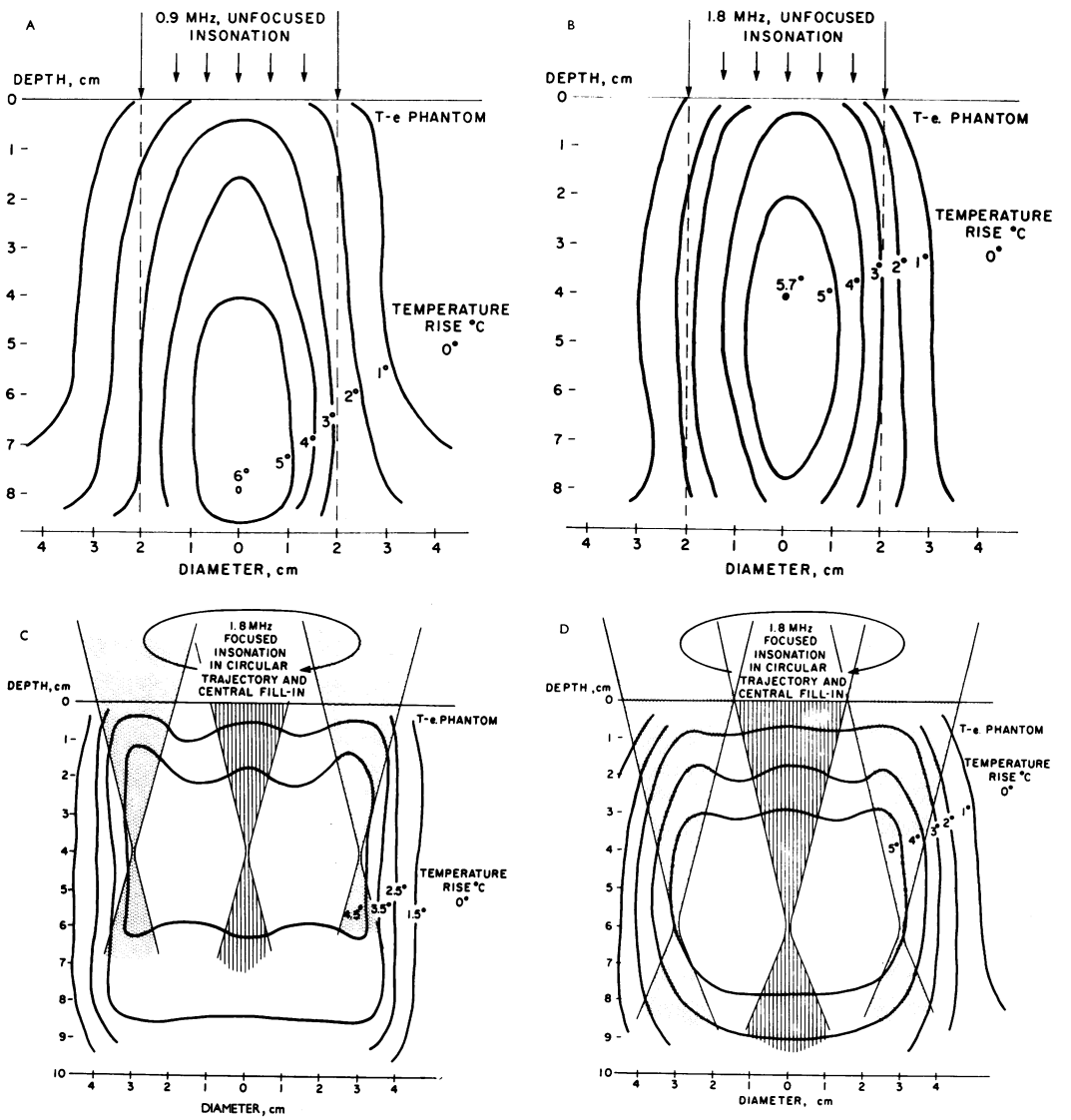


FIG. 3.—Temperature distributions in t-e phantom, plane wave ultrasound. A, 0·9MHz, B, 1·8 MHz. Focused ultrasound 1·8 MHz, focused at a depth of C, 4 cm, D, 6 cm.

thermia level of approximately 6°C above the initial temperature.

RESULTS

The results are presented in the sequence of increasing complexity of the medium and are typical of those obtained in the course of experiments over 3 years. There was little variability in the distribution of temperature from specimen to specimen under any specific experimental condition. The temperature distributions presented below represent the steady-state distributions, *i.e.* after a steadily sustained hyperthermia was established in the target medium.

(*A*) *T-e Phantoms*

(i) *Plane wave ultrasound.*—The temperature distributions obtained by insonation with plane-wave transducers 4 cm in diameter at frequencies of 0·9 and 1·8 MHz, placed 1 cm from the surface of the phantom, are shown as plots of isotherms in Fig. 3A and B respectively. In addition to the regularity and symmetry of the isotherms, it should be noted that in each case the peak temperature is attained over a very small volume (hot spot) and that the axial location of the hot spot shifts towards the surface at the higher frequency of ultrasound. At any of the frequencies used it was not possible to shift the location of the hot zone higher or lower within the t-e phantom by raising or lowering the transducer. Transducer diameter also had no effect on the size of the hot spot.

(ii) *Focused ultrasound.*—The results obtained with focused ultrasound (Fig. 3C, D) are characterized by an absence of hot spots. Note that the temperature within the region of maximal insonation, which was 6 cm in diameter, is uniform. Furthermore, the depth or the axial location of the hot zone can be shifted up or down by changing the focal plane of insonation.

(*B*) *Beef muscle* in vitro

(i) *Plane wave ultrasound.*—The temperature distributions were similar to those obtained in the t-e phantom as regards the regularity and symmetry of the isotherms and the restricted volume of the tissue over which peak temperatures could be attained (Fig. 4A, B). The axial location of the hottest region, however, was relatively independent of the distance between the transducer and the specimen and remained at a depth of about 2 cm below the surface of the meat. Its depth was also less dependent on the ultrasonic frequency than was the case in t-e phantom. The isotherms tended to extend deeper into the tissue in the central region of insonation at the lower ultrasonic frequencies; but the temperature gradient in the tissue between the surface and the hottest region was always very steep, as evident from the close spacing of the isotherms (cf, Fig. 3 A, B in t-e phantom). Oscillatory motions of the transducer along X and Y planes, or along the Z axis, or in a circular trajectory, did not influence the pattern of temperature distribution.

In an attempt to avoid the build up of heat in the superficial regions of the tissue, two insonation strategies were evaluated. In one, insonation was performed using two, cross-fired, plane wave transducers, each angled 30° off normal so that their fields overlapped at a certain depth within the tissue. One of the transducers was driven at 2·7 MHz and the other at 1·2 MHz to provide increased "penetration depth". The resultant pattern of temperature distribution (Fig. 4C) is similar to those with single, perpendicularly placed transducers (Fig. 4A, B) except for a distortion in the symmetry of isothermal lines. The size of the region of maximum temperature rise was still very small and its location could not be shifted by varying the angles of incidence of the two ultrasound beams. Use of focused transducers, focused at the same region (isocentric insonation) or two adjacent regions within the tissue did not significantly alter the pattern of temperature distribution (4D). Occur-

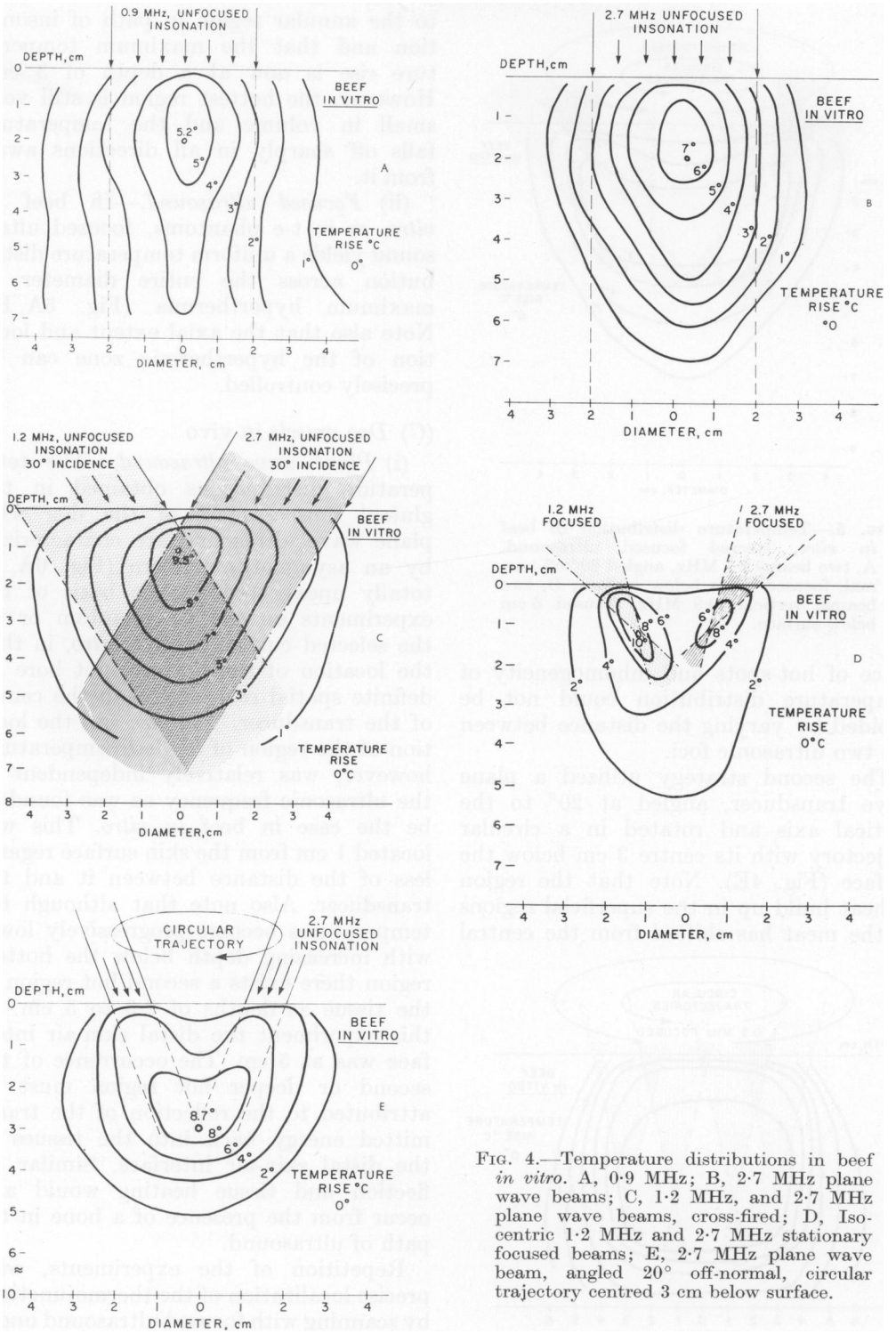


FIG. 4.—Temperature distributions in beef *in vitro*. A, 0·9 MHz; B, 2·7 MHz plane wave beams; C, 1·2 MHz, and 2·7 MHz plane wave beams, cross-fired; D, Isocentric 1·2 MHz and 2·7 MHz stationary focused beams; E, 2·7 MHz plane wave beam, angled 20° off-normal, circular trajectory centred 3 cm below surface.

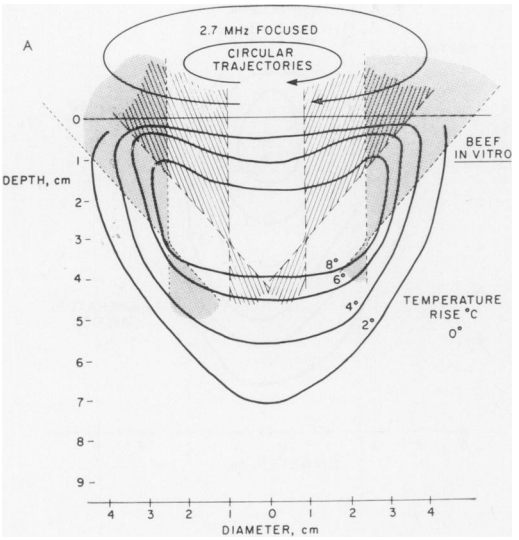
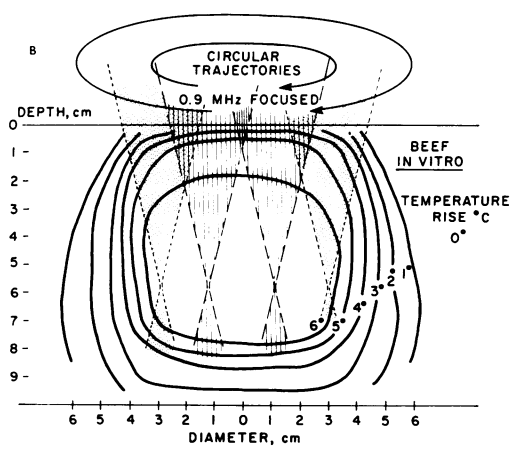


FIG. 5.—Temperature distribution in beef *in vitro*, steered focused ultrasound. A, two beams 2·7 MHz, angled 20° off-normal, focused 3 cm below surface; B, two beams, vertical, 0·9 MHz, focused 6 cm below surface.

rence of hot-spots and inhomogeneity of temperature distribution could not be avoided by varying the distance between the two ultrasonic foci.

The second strategy utilized a plane wave transducer, angled at 20° to the vertical axis and rotated in a circular trajectory with its centre 3 cm below the surface (Fig. 4E). Note that the region of heat build up in the superficial regions of the meat has shifted from the central



to the annular region in path of insonation and that the maximum temperature rise is now at a depth of 3 cm. However, the hottest region is still very small in volume and the temperature falls off sharply in all directions away from it.

(ii) *Focused ultrasound.*—In beef *in vitro*, as in t-e phantoms, focused ultrasound yields a uniform temperature distribution across the entire diameter of maximum hyperthermia (Fig. 5A, B). Note also that the axial extent and location of the hyperthermic zone can be precisely controlled.

(*C*) *Dog muscle* in vivo

(i) *Plane wave ultrasound.*—The temperature distributions obtained in the gluteal muscle mass of the dog with plane wave ultrasound are characterized by an asymmetric pattern (Fig. 6A, B) totally unexpected on the basis of the experiments on the t-e phantom or on the selected cuts of beef *in vitro*, in that the location of the hottest spot bore no definite spatial relationship to the centre of the transducer. The size and the location of the region of highest temperature, however, was relatively independent of the ultrasonic frequency as was found to be the case in beef *in vitro*. This was located 1 cm from the skin surface regardless of the distance between it and the transducer. Also note that although the temperatures become progressively lower with increasing depth below the hottest region there exists a second hot region in the tissue at depths of 2·5 to 5 cm. In this experiment the distal skin-air interface was at 5 cm. The occurrence of the second or deeper hot region must be attributed to the reflection of the transmitted energy back into the tissues at the distal skin-air interface. Similar reflection and tissue heating would also occur from the presence of a bone in the path of ultrasound.

Repetition of the experiments, with precise localization of the thermojunctions by scanning with focused ultrasound under

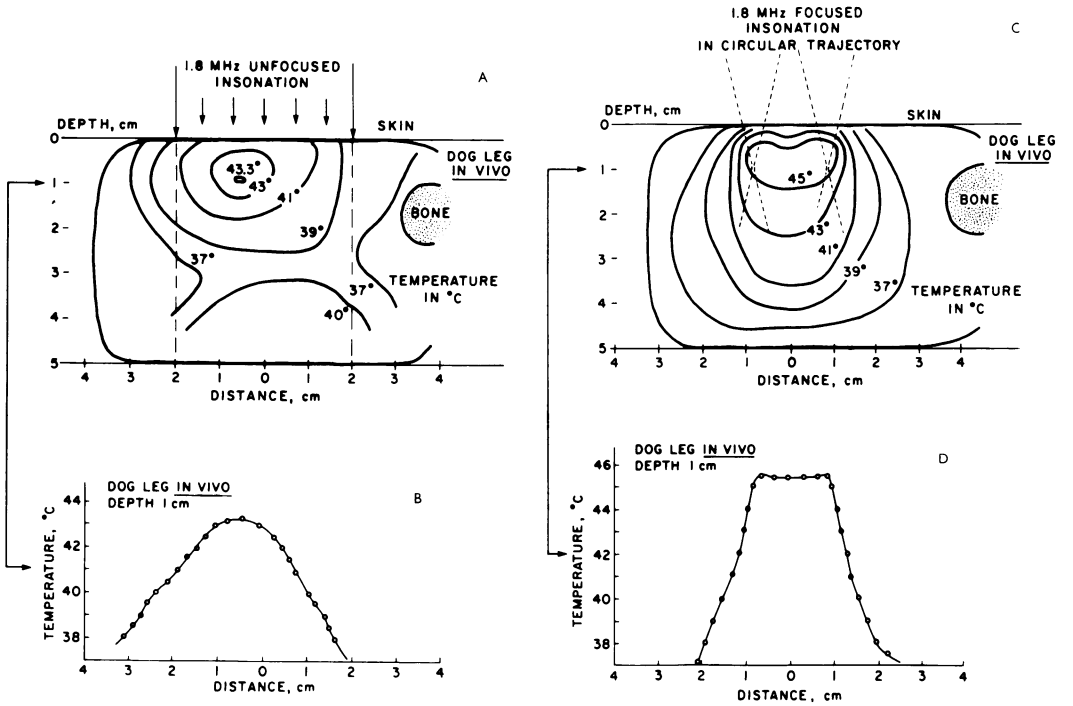


FIG. 6.—Temperature distributions in gluteal muscle mass of dog *in vivo*. Plane wave ultrasound, 1·8 MHz. A, isotherm plot; B, temperature distribution at 1 cm depth. Steered, focused ultrasound, 1·8 MHz at 1 cm depth, C, isotherm plot; D, temperature distribution at 1 cm depth.

computer control, confirmed the asymmetry of the isotherms relative to the position of the insonating transducer (Fig. 6B). The degree and the direction of the asymmetry varied, to some extent, with the region in which hyperthermia was induced. In order to determine the reason for the asymmetry, the thermocouple tracks were examined by slicing through the tissue *post-mortem*. It was found that the thermocouples traversed a number of different muscle groups and intervening connective tissue and muscle sheaths. In contrast to the selected cuts of beef *in vitro*, the fascicles and fibres of dog muscles were oriented in different directions. Tissues such as the muscles, the nerves or the white matter of the central nervous system, with a conspicuous directionality in their pattern of organization, display anisotropy with respect to propagation of ultrasound (Lele, 1975). Fig. 7 shows the intensity distribution patterns of the focal region of a 2·7 MHz focused transducer in water and in muscle along and across the direction of its fibres. The difference in the shape of the focus along and across the muscle attests to differences in ultrasonic propagation velocities, which could lead to beam diffraction. Similarly differences were found to exist in absorption coefficients measured along and across the muscles. These differences in ultrasonic absorption, together with the highly directional nature of the blood flow confined to each individual muscle and the absence of blood flow across the fascial sheaths, may account for the asymmetric patterns of temperature distributions in these experiments.

Neither the pattern of temperature distribution, including reflective tissue heating, nor the size and location of the hottest region could be significantly altered by linear or circular motions of

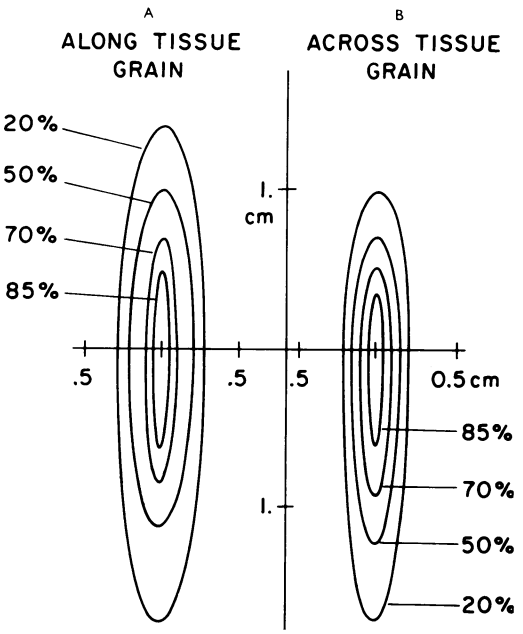


FIG. 7.—Intensity distribution patterns of a 2·7 MHz ultrasound focus, A, in skeletal muscle oriented parallel to (along) the ultrasonic beam; B, in skeletal muscle oriented perpendicular to (across) the ultrasonic beam.

the insonating transducer in X, Y or Z axes.

(ii) *Focused ultrasound.*—In sharp contrast to the asymmetry of isotherms with plane wave ultrasound, the temperature distributions are regular in pattern (Fig. 6C, D). They are comparable to those obtained with focused ultrasound in the t-e phantom and beef *in vitro* (Figs 3C, D, 5A, B). As in the case of these two media the spatial extent and placement of the hyperthermic zone could again be controlled precisely. There is no reflective heating below the single region of hyperthermia. The temperature distribution across the region of hyperthermia is uniform. The symmetry and uniformity of temperatures must be attributed to the fact that in this case focused energy at high intensity is deposited in small volumes of muscle tissue and the heat generated diffuses radially by conduction. Since the focused transducer is continuously moving, any given location at the

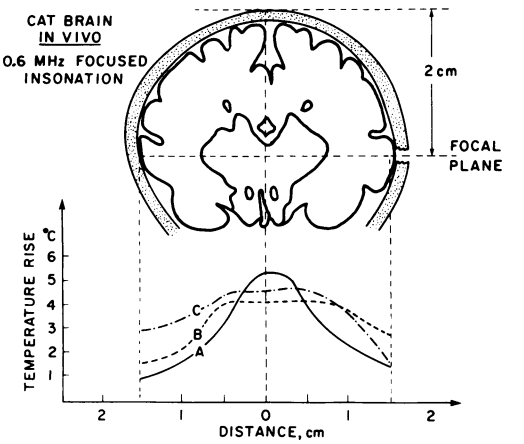


FIG. 8.—Temperature distributions in the brain of cat *in vivo*. Transcalvarial insonation, focused ultrasound 0·6 MHz. In A and B, the insonation beam was angled so that its axis was normal to the calvarial surface. The focal trajectory was respectively 1 and 2 cm in diameter. In C, insonation was performed vertically down—normal to the Horsley–Clark plane. The trajectory was 1 cm in diameter.

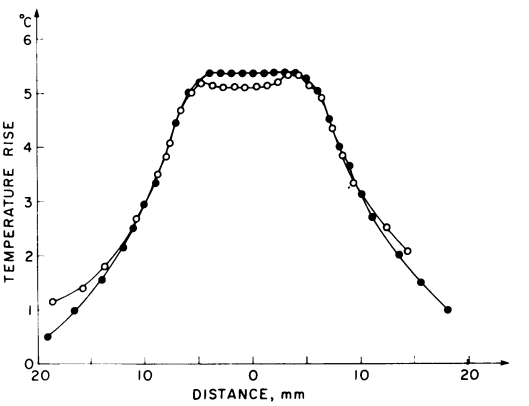


FIG. 9.—Temperature distributions in the brain of cat. Transdural insonation through a craniotomy. Focused ultrasound 2·7 MHz. ○, *in vivo*; ●, *post mortem*.

periphery receives the heat dose intermittently and there is more time for heat flow and equilibration. Anisotropy or directionality of the blood flow would cause only a displacement of the hyperthermia pattern and not non-uniformity of temperature distribution.

Comparable results were obtained in the brain of the cat with transcalvarial insonation (Fig. 8) or insonation through a

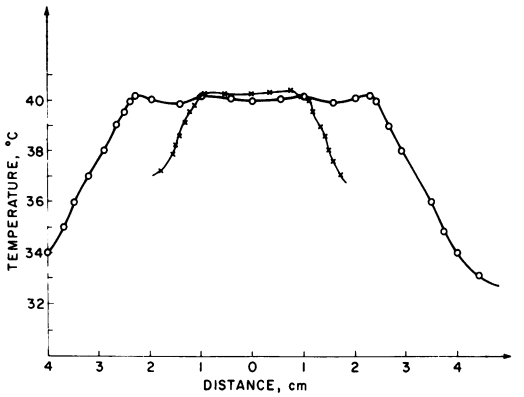


FIG. 10.—Temperature distributions in a flank implanted tumour in rat *in vivo*. Plane wave ultrasound, 1·8 MHz.

craniotomy (Fig. 9), *in vivo* as well as *post mortem*. Note that the uniformity of the hyperthermia is not affected by the presence or absence of blood flow, although more power was required to attain and sustain the desired temperature *in vivo* with blood flow than *post mortem*.

(*D*) *Rat tumour* in vivo

(i) *Plane wave ultrasound.*—The temperature distributions (Fig. 10) closely resemble those in beef *in vitro* (Fig. 4) rather than those in the muscle-mass of the dog *in vivo* (Fig. 6). As in these two media, the size of the hottest region is very small and its location in depth was fixed and could not be changed by changing the distance between the transducer and the skin or by change in the ultrasonic frequency.

(ii) *Focused ultrasound.*—Uniform and controllable levels of hyperthermia could be produced in volumes of tumour 6 to 8 cm in diameter and up to 8 cm below the surface, with the equipment available. Fig. 11 shows data from 2 such experiments. Note the sharp fall-off of temperature away from the region of hyperthermia at the rate of approximately 0·3°/mm.

Rat tumour in vivo *placed in the abdominal cavity of dog* in vivo

These experiments were conducted to simulate tumours located deep in the body; *e.g.* those of abdominal viscera. A computer plot of the temperature profiles measured by one stepped thermocouple, representative of the results obtained in other experiments with multiple thermocouples, is reproduced in Fig. 12. The temperature in the abdominal wall muscle

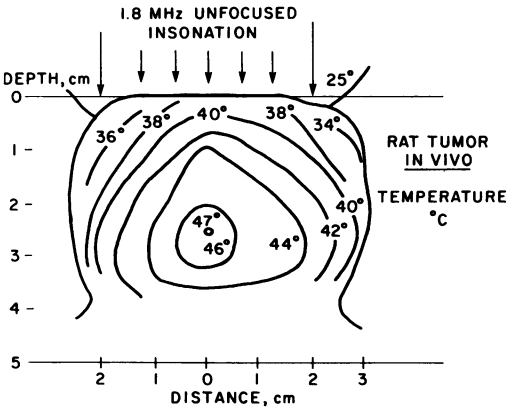
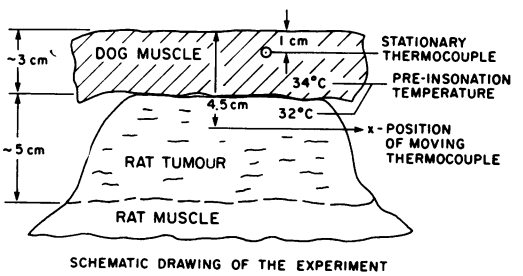


FIG. 11.—Temperature distributions in a flank-implanted tumour in rat *in vivo*. Steered focused ultrasound, 3 cm depth. ×, 2 cm diameter; ○, 5 cm diameter.



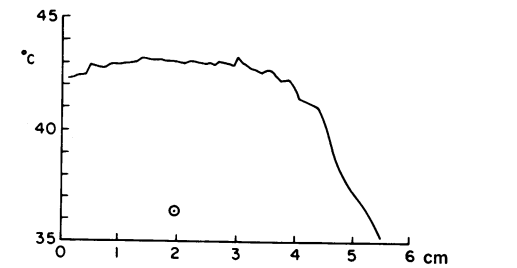


FIG. 12.—Temperature distribution in a flank-implanted tumour in rat *in vivo* placed in the abdominal cavity of dog *in vivo*. Tumour tenperature was measured with a stepped thermocouple. Temperature in overlying dog tissues was continuously measured with a stationary thermocouple.

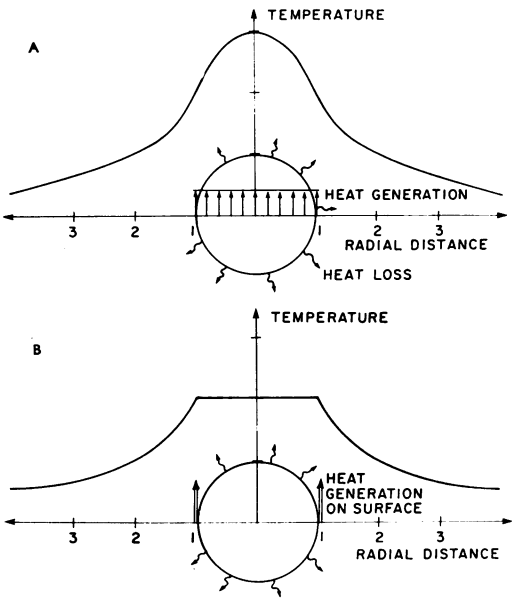


FIG. 13.—Schema of temperature distributions in a tissue volume subjected to A, spatially uniform heat deposition; B, heat deposition at the perimeter.

overlying the tumour in the insonation path was measured by a stationary thermocouple. Note that, though the temperature in the tumour was raised by 11°C, the temperature rise in the overlying muscle was only 2°C.

Spontaneous tumours in dog in vivo

Temperature distributions were measured by withdrawing a multithermocouple probe through the region of interest during treatment of spontaneous tumours (Odontoma, fibrosarcomas, tonsillar carcinoma, melanomas *etc.*) in dog patients. Results were similar in all respects to those obtained in transplanted tumours in the rat (Figs 11, 12).

DISCUSSION

The temperature distributions resulting from insonation of tumours and normal tissues *in vivo* as well as *in vitro*, with plane wave and moving focused ultrasound fields, clearly demonstrate the inefficacy of the former to raise to a uniform level the temperature of any significant volume of even superficial tissue.

In all of the experiments with plane wave fields at different ultrasonic frequencies, transducer dimensions, distances from the surface of the medium, presence or absence of transducer motion *etc.*, whether in biological tissues or in the t-e phantom, the characteristic pattern of resultant temperature distributions was consistently found to be a small, almost punctate, volume of maximum temperature elevation surrounded by volumes of progressively lower temperatures. The depth of the spot of maximum temperature elevation from the surface of the medium was fixed for any particular medium and could not be varied by changing the distance of the transducer. This depth, although it could not be controlled, varied from one medium to another and thus must be related predominantly to the ultrasonic attenuation and heat diffusion characteristics of the medium itself. With plane wave insonation, the occurrence of a small region of high temperature located approximately in the centre of the insonated volume is not surprising and is predictable on the basis of rather simple heat transfer analysis. Mathematical analysis is beyond the scope of this article and it may suffice here to state that since the heat from a hyperthermic volume of tissue must leave the region through its periphery—whether by conduction alone or with perfusion—the peripheral regions will always be cooler than the centre (Fig. 13A). For this reason the energy needs to be deposited preferentially at the surface of a tumour to achieve uniform hyperthermia therein (Fig. 13B). This, of course, is possible by moving the small focal region of a focused beam of ultrasound but not with plane wave sources. Any detailed analysis of the energy deposition from plane wave sources is further complicated by the fact that in almost all instances the tissues lie in their

near field in which the intensity distribution is very inhomogeneous.

Focusing of the energy also enables control of the depth at which hyperthermia is produced, which is not possible with plane wave sources as discussed in a previous paper (Lele, 1980) and seen in the results of the experiments described herein. The ability to deliver the energy precisely, at the surface of the target volume of tissue, permits generation of localized hyperthermia even in irregularly shaped tumours, without subjecting any significant volumes of surrounding normal tissues to unnecessary heat stress. This is specially important if the tumour is located close to a bone or an air-containing organ, *e.g.* the lungs or intestines. The intensity reaching such an organ after passage through the tumour would have decayed only by attenuation in the tumour when plane wave energy is used for insonation since, in practice, the insonated tissues almost always are located in the near field of the transducer where the beam is collimated. With a focused beam it will additionally be attenuated by beam divergence. Furthermore, with a focused beam, the angle of incidence and the amplitude of excitation of the transducer can be controlled at every point in its trajectory and thus the safety of critical target areas and surrounding tissues can be ensured. This is not possible with plane wave insonation systems. In superficial tumours this would be of special concern, since many of these tumours lie directly over the bone or air, as in the case of metastatic breast cancer or cancer in the head and neck region. In these cases the possibility of excessive heating of deeper tissues by energy reflected from underlying bone (Fig. 6A) must also be borne in mind. It is interesting to note that Marmor *et al.* (1979*b*) found that the temperature near the bone in one of their patients was significantly higher than that in the tumour itself.

The measurement and specification of temperature in the non-uniform spatial distribution of the hyperthermia from plane wave sources present special practical and conceptual problems not encountered in the spatially uniform hyperthermia produced by focused ultrasound. In the absence of a non-invasive technique with sufficient resolution, the region of maximum temperature, generally restricted to a few millimeters in each of three dimensions, can be located only by careful and thorough scanning of the volume of tissue in small steps in each of the three planes with an implanted thermometric device. Such scanning might prove inadvisable or impracticable in many patients because of the location of the tumour and patient movement. Temperature measured at an arbitratily located point is likely to be lower than the peak temperature reached in the tumour. This could lead to local thermal pain or damage in the region of higher temperatures, as reported by Marmor *et al.* (1978; 1979*a*, *b*) in their animal and human patients. The occurrence of this injury is predictable on the basis of temperature - duration relationships for thermal damage (Lele, 1977). Even if temperatures at a number of points within the tumour were determined, because of the non-uniformity of temperature distribution it would be impossible to correlate them with effects on tumour growth or regression. This lack of uniformity may contribute, to a large extent, to the lack of close agreement between the results obtained in cell cultures and those that have been obtained in tumours on the effects of hyperthermia on neoplastic cells. The fact that the use of plane wave sources results in hyperthermia which is maximum near the centre and falls off towards the periphery should be of considerable concern. A threshold tumoricidal temperature (or heat dose) in the centre of a tumour would subject the proliferating tumour tissue at the periphery to a lower temperature (or heat dose) which at best would be ineffective, and at worst may stimulate tumour growth. On the other hand, with steered

focused ultrasound, even under sub-optimal conditions, the temperature would always be higher at the proliferating margins of the tumour than at the centre, which is often necrotic in tumours of clinically relevant sizes.

Thus, detailed and accurate measurement of temperature distributions, induced in tissues by a given mode for production of hyperthermia, cannot be overemphasized. Since these measurements cannot be conducted in patients due to unavailability of non-invasive temperature measuring devices with adequate spatial resolution and sensitivity, the studies must necessarily be conducted in experimental tumours or animals, excised tissues or t-e phantoms. The best experimental substitute for a spontaneous tumour in man would appear to be a spontaneous tumour in animal and, possibly, the second best a transplanted tumour—both *in vivo*. However, the comparison of the results obtained *in vivo* with those obtained *post mortem* in the brain and in tumours in this study indicate that the distribution of temperature in a zone of hyperthermia itself does not change when perfusion ceases—only the spatial rate of the fall-off of temperature to normothermic values is slightly lowered. The effects of perfusion can be computed mathematically and added to the temperature distributions measured *in vitro*. Thus preliminary studies, conducted in large cuts of meat carefully selected for uniformity of grain, can yield useful data on temperature distributions resulting from any device to induce hyperthermia. In the presence of blood flow, the power requirements for induction and maintenance of the level of hyperthermia are higher and the pattern of temperature distribution may show slight displacements. These too can be estimated from comparison of the results obtained *in vivo* and *post mortem*. The use of a t-e phantom can yield misleading results unless the phantom is truely tissue-equivalent both in its acoustic and heat transfer characteristics.

CONCLUSIONS

Insonation with plane wave ultrasound results in spatially non-uniform hyperthermia which is characterized by the existence of a small, almost punctate, region of maximum temperature rise the depth of which appears to be dependent on the acoustic and heat transfer properties of the medium and cannot be altered by spatial manipulation of the plane wave ultrasonic source. The existence of an ultrasound reflecting structure below the target may lead to the generation of a second region of hyperthermia at depth. The region of maximum temperature elevation cannot be easily located, except by thorough scanning of the region in all 3 orthogonal planes, because of the smallness of its size and is likely to be missed by temperature measuring procedures practicable under clinical conditions. This may explain the occurrence of burns observed by various investigators in animal and human tumour treatments using plane wave ultrasound. Furthermore, the resultant non-uniformity of temperature distributions within the tumour renders impossible any precise correlation of the temperature and duration of hyperthermia (either alone or in combination with radiation or chemotherapy) with resultant effects on tumours. Thus, plane wave ultrasound is not optimal even for therapy of superficial lesions.

All these problems and difficulties are obviated by use of focused ultrasound which enables precise tailoring of the heat dose to individual tumours. Spatially uniform levels of hyperthermia, restricted to the tumour, located superficially or at depth, can be achieved with equipment presently available.

The best model for evaluation of devices for production of local hyperthermia appears to be a large, non-necrotic transplanted tumour in the flank of the rat *in vivo*. This can be overlaid by muscles of dog *in vivo* to simulate deeply situated tumours when necessary. Selected cuts of meat *in vitro*, appear to

be satisfactory for preliminary studies. A phantom which is truly tissue-equivalent for evaluation of ultrasonic hyperthermia is not yet available.

This research was supported in part by USPHS Grants CA 16111 and CA 26232. It is a pleasure to acknowledge the assistance of Mr K. E. Greene in procurement of tissue samples, Mr R. C. Greenwald, III in the taming of the computer and Mr Eric Buckman in many of the scans. The considerate generosity of Dr Ralph de Vere White, Urology Service, Boston University School of Medicine, in supplying specimens of the renal adenocarcinoma transplanted in the flank of the rat is gratefully acknowledged.

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