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Thermobiology and Clinical Application of Interstitial and Superficial Hyperthermia in Two Groups of Patients

A New Approach for Treating Malignant Tumors

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INTISARI

Maesadjie Tjokronagoro & M. H. Seegenschmiedt – *Termobiologi dan applikasi klinis hypertermia interstitial dan superfisial pada 2 kelompok pasien: Cara baru untuk pengobatan tumor maligna*

Dua kelompok penderita tumor maligna ditherapi dengan kombinasi radiotherapi dan hyperthermia di Strahlentherapeutische Klinik Universitas Erlangen – Nürnberg, Republik Federal Jerman, dari periode Oktober 1987 sampai Juli 1988.

Kelompok pertama terdiri dari 8 kasus (4 kasus karsinoma dasar mulut dan 3 kasus karsinoma lidah dan satu kasus sarcoma Ewing) ditherapi dengan radiasi dan hyperthermia interstisial. Hasilnya adalah 7 kasus mengalami remisi komplet (87,5%), sedangkan satu kasus mengalami remisi parsial (12,5%).

Kelompok kedua terdiri dari 6 penderita (5 kasus karsinoma mamma rekuren pada dinding dada dan regio supraclavicularis, dan satu penderita carcinoma parotis) ditherapi dengan kombinasi radiasi elektron 12 megavolt dari pesawat Mevatron 20 Siemens dan hyperthermia superfisial dengan menggunakan pesawat Lund Buchler Hyperthermia System 4010, 915 Mhz/20 W, seminggu sekali. Hasilnya 4 kasus mengalami remisi komplet (66,6%) dan dua kasus mendapat remisi parsial (33,3%).

Sebagai latar belakang hyperthermia diuraikan juga prinsip-prinsip thermobiologi, interaksi hyperthermia dengan radiasi, mekanisme fisiologis, efek hyperthermia terhadap mikrovaskulatur tumor, dan prinsip dasar fisika serta instrumentasi hyperthermia.

Key Words: cancer – hyperthermia – radiation therapy – thermobiology – thermometry

INTRODUCTION AND HISTORICAL REVIEW

The effect of heat in malignant tumors was first reported by Hippocrates. In 1856 Busch described the disappearence of soft tissue sarcoma following high fever in patients with erysipelas. Later Coley induced artificial fever by injecting bacterial toxin, and Westermark used localized hyperthermia to treat gynecological cancer and produced tumor regression. Warren reported on 32 patients

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with advanced cancer, treated with combination of heat induced by pyrogenic substances and X-ray therapy. Twenty nine of these patients showed improvement for 1 to 6 months.

In the beginning of the 1920s hyperthermia was almost abandoned for several decades due to technical problems. But in the past 20 years interest has been rekindled in the clinical application of this modality and numerous papers have indicated that there is a significant advantage to the use of heat combined with irradiation or cytotoxic drugs to enhance the killing of tumor cells (Dewey *et al.*, 1979, 1977; Field & Bleehen, 1979; Stewart & Denekamp, 1977). Significant progress has been made in clinical thermometry by introduction of invasive thermometry sensor in subcutaneus tissue and into tumors, which provide reliable information on the heat distribution within the target tissues.

The instrumentation to deliver effective heat in deep seated tumor is still in progress.

There is also a strong clinical rationale for the use of hyperthermia, since about 30% to 50% of patients with solid tumor have recurrences at primary site. Many of primary treated tumors have regional lymphnode recurrences. Both failure patterns could be improved, if effective radiation sensitizers are developed and applied in conjunction with radiation therapy.

THERMOBIOLOGY OF HYPERTHERMIA

In vitro and in vivo experiments strongly suggest that heat may be more damaging to tumor tissue than normal tissue for several reasons:

1. hypoxic cells may have an increased sensitivity to heat. The are at least as thermosensitive as oxygenated cells (Dewey *et al.*, 1977).
2. metabolically deprived tumor cells with reduced pH are more heat sensitive.
3. heat affects cells in S phase, which are known to be resistant to radiation, and
4. blood flow impairment in tumors due to heat (Dewey *et al.*, 1979, 1977; Le Veen *et al.*, 1980).

Heat in conjunction with radiation causes a greater degree of mitotic delay than radiation alone and this may affect the cell phase distributions within the cell cycle after heat or x-ray exposure. The heat sensitivity of hypoxic cells is increased by low oxygen tension, or nutrient deficiency, or reduced pH. The rapid response of tumors may be affected by physiologic changes associated with lowering of blood flow and oxygen tension produced by hyperthermia (Dewey *et al.*, 1977).

Biomolecular mechanisms by which heat kills or inactivates malignant cells are summarized in three major problems:

1. Cellular membrane damage with changes in permeability, composition and fluidity, ultimately leading to the death of cells (Wallach *et al.* dalam Streffer *et al.*, 1978:19–26). Heat effects on membrane fluidity have been in conjunction with the interaction of heat with membrane modifying drugs, *i. e.* alcohol and local anaesthetics (Yatvin 1977). An inverse relation between cholesterol and phospholipid ratio and heat sensitivity was shown in studies with several cell lines (Cress & Gerner, 1980).

2. Damage to the lysosomes of the cellular cytoplasm as suggested by Overgraad. Desintegration of lysosomes and cellular damage by the released digestive enzymes are discussed as the cause of cellular death. Biochemical evidence of increased lysosomal enzyme activity in heated cells was reported by Hume *et al.* (1978) and Overgraad & Overgraad (1972).
3. Thermal damage to protein was suggested by Tomasovic and associates (Tomasovic *et al.*, 1978; Roti Roti & Winward, 1978). They reported an increased, non-specific attachment of non-histone nuclear protein to DNA following heat exposure; however, this phenomenon showed only limited correlation to cell killing and is more likely an important sensitizing mechanism by preventing repair of radiation damage (Dickson & Shah, 1972). Heat produces effects on various proteins such as DNA (Dube *et al.*, 1977; Tomasovic *et al.*, 1978), RNA (Warocquier & Scheerer, 1969), and protein synthesis (Mondovi *et al.*, 1969), and respiration (Mondovi *et al*, 1969). CHO cells exposed to various time of temperature ranging from 41.5° to 46° C are killed at an exponential rate. A marked increase in the cells sensitivity to heat exposure occurs between 42°C and 43°C.

HEAT INTERACTION WITH IRRADIATION

Combination of heat and irradiation is of potential benefit in cancer therapy. The first and most generally observed phenomenon is heat radiosensitization of cells (Dewey *et al.*, 1977; Fayardo *et al*, 1980; Sapareto *et al.*, 1979). In S phase cells are more radiosensitized by heat than are cells in Gl (Sapareto *et al.*, 1978). It is believed that accumulation of non-histone protein which binds to DNA following heat treatment prevents the cells from repairing radiation damage. This hypothesis is supported by several observations. *First,* the interaction between heating and subsequent radiation exposure persists for about 72 hours between subsequent heat exposures. This coincides with the return to a normal DNA to non-histone protein ratio (Clark *et al.*, 1981). *Second,* the observation that inhibition of enzymatic repair of induced thymic damage occurs only when chromatin is heated, but not when only enzyme is heated (Waters & Roti Roti, 1988). *Third,* there is a linear increase both in the amount of non-histone protein attached to DNA and in the inhibition of micrococcal nuclease digestion of chromatin into fundamental nucleosome structure, which suggests that access to the sites between nucleosomal structure is blocked (Waters *et al.*, 1978).

Another factor of possible clinical relevance is the fact that cells in G1 are less sensitive to heat than cells in S phase, whereas S phase cells are normally resistent to radiation. The magnitude of difference between G1 and S phase is reduced if the severity of the heat exponentially decreases (Westra & Dewey, 1971).

PHYSIOLOGIC MECHANISMS OF HYPERTHERMIA IN MICROVASCULATURE OF TUMORS

1. *Effect of hyperthermia in normal tissue microcirculation*

The blood flow of skin overlying the tumor and muscle near the tumor is twice than blood flow in skin and muscle far from the tumor (Song *et al*, 1980).

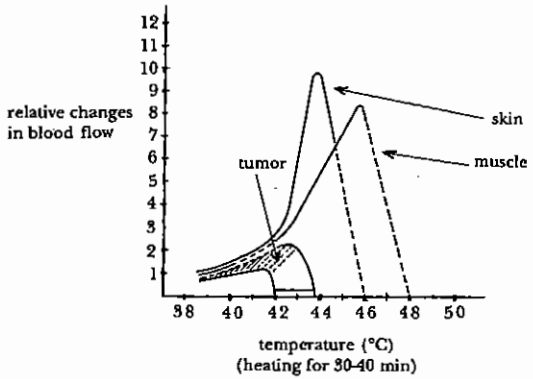

FIGURE 1.– Relative changes in blood flow in the skin and muscle of S.D. rat in various animal tumor at different temperatures. Values in this figure are the relative changes of blood flow as function of temperature, and are not the changes in absolute value of blood flow.

It is similar to an inflammatory process near the tumor. There is a significant increase in the blood flow in skin and muscle both near and far from the tumor upon heating to 43°C for 1 hour (Song *et al*, 1980). The blood flow of normal tissue surrounding the tumor will returned to normal levels within 2 hours after cessation of heating.

2. *Effect of hyperthermia on tumor microcirculation*

Hyperthermia at modest temperature (up to 40°C) has been shown to have no effect on tumor microcirculation (Gullino *et al.*, 1965; Song, 1978), and no significant increase in tumor microcirculation blood flow occurred (Bicher *et al.*, 1980; Emami *et al.*, 1980; Vaupel *et al.*, 1980). It was found that there is a significant decrease in tumor blood flow microcirculation during the course of hyperthermia at temperature levels in the range of 42°C to 45°C (Bicher *et al.*, 1980; Eddy, 1980; Vaupel *et al.*, 1980).

A pathologic study by Emami and colleagues confirmed the physiologic findings described above: no specific changes in microvasculature were observed with temperature up to 40.5°C. However, at 42°C blood vessels became dilated and were packed with red cells and stasis occurred. At therapeutic temperature, massive haemorrhage, coagulative necrosis and rupture of blood vessels were evident. This study has shown that the vascular damage became increasingly severe if the tumor is left in situ after termination of hyperthermia (Emami *et al.*, 1980). This phenomenon correlates well with delayed cell death that has been observed by Song, and Fayardo and colleagues (Song *et al.*, 1980; Fayardo *et al.*, 1980).

3. *Role of blood flow tumor microcirculation in combined use of hyperthermia and other modalities*

These are indications that hypoxic cell fraction in a tumor increases as a result of vascular damage, despite the fact that heat induced death previously decreases hypoxic cells. Song and coworkers found that the proportion of hypoxic cells in SKC tumors was about 45%; it is increased to about 95% at 5 hours

after heating to 43.5°C for 30 minutes. The proportion of hypoxic cells started to decrease after this period, probably because of cell death as well as reoxygenation of hypoxic cells, but the proportion of hypoxic cells 48 to 72 hours after heating was still greater than that in the unheated tumor. In contrast, partially hypoxic normal tissues may be better oxygenated by an increase in blood flow, causing an increase in radiosensitivity. This thermal enhancement is the strongest argument for the potential benefit of hyperthermia. These facts also strongly suggest that the therapeutic gain may be greater if radiation therapy is applied before hyperthermia rather than vice versa.

EFFECT OF HYPERTHERMIA ON INTRATUMOR pH

The pH of arterial blood flow is 7.4 and that of venous blood flow and interstitial fluid is about 7.35. Intracellular pH usually ranges between 6.0 and 7.4 in different cells, averaging about 7.10. Recent studies have shown that there is no significant difference between the intracellular pH of normal cell lines and that of their malignant counterpart (Jahde *et al.*, 1982).

Hyperthermia triggers an immediate and significant decrease of the pH in tumors (Bicher *et al.*, 1980; Song *et al.*, 1980). The pH in SKC tumor of mice decreased from 7.05 to 6.67 when tumors were heated at 43.5°C for 30 minutes. When heat was terminated, the pH rose to 6.78, but decreased to 6.5 to 6.6 in tumors (Song *et al.*, 1980). The lowering of tumor pH caused by hyperthermia is a result of an increase in the acidic metabolites. So acidic condition not only enhances heat killing but also inhibits repair of thermal damage (Song *et al.*, 1980), and development of thermotolerance (Goldin & Leeper, 1981; Overgraad *et al.*, 1972).

The reason for decreased pH in tumors is an increase of lactic acid contents in mouse tumor, as well as β-hydroxy butiric acid (Streffer *et al.*, 1981).

BASIC PRINCIPLES OF PHYSICS AND INSTRUMENTATION

Instrumentation in clinical hyperthermia is concentrated in three major problems:
1. power deposition
2. thermometry
3. treatment planning
4. safety.

1. *Power deposition*

The physical agents employed for power deposition in local clinical hyperthermia are:

a. Electromagnetic irradiation at very high and microwaves frequencies (300 to 2450 Megahertz).

b. Electric and magnetic fields at radiofrequencies (0.1 to 27 Megahertz) and

c. Ultrasound waves with frequency ranging from 0.3 to 3 Megahertz.

The temperature versus time plot during the very first stage of heating is a typically straight line. During this early time interval (typically 20 to 30 seconds) the constant rate of temperature rise is directly proportional to the absorbed power

density (Watts/cm^3) at the point of interest. In muscle tissue an absorbed power density of 0.060 Watts/cm^3 will produce an initial rate of temperature increase of 1° C per minute.

For superficial local tumors microwave heating with external applicators would be sufficient. The field size would be large enough to cover the tumor and normal tissue surrounding it. The applicator usually has sizes of 8 x 8 cm, 10 x 8 cm, 12 x 10 cm and 6 x 12 cm.

For deep-seated tumors below the surface of the skin, microwave local heating with external or interstitiae antennae would be possible. Coaxial antennae operating at frequencies of 300 to 1000 Megahertz are applied. Antennae are placed in plastic catheters inserted into tumors similar to the use of irridium wire for brachytherapy.

For tumors adjacent to viscera, such as gastrointestinal tumors (esophagus, rectum) or in gynecology (vagina, cervix, uterus) and genitourinary (prostate, bladder) intracavitary microwave could be used.

Local deep heating with radiofrequency electric fields or with conductive or resistive heating is under development.

2. *Thermometry*

Temperature measurement of tumor and tissue surrounding it is absolutely necessary to obtain during treatment, because of its critical importance and truly reliable method of thermal treatment verification (recommended accuracy and precision of 0.1° C). Invasive thermometers fall into 3 categories:

a. electrically conducting
b. minimally conducting and
c. non-conducting or optically conducting probes.

Standard thermistor and thermocouple sensor with metallic leads are conducting probes. For thermistor, the sensor is a semiconductor, which resistence decreases with increasing temperature. For thermocouple the temperature sensor is a binietal.

Minimally conducting probes are highly resistive thermistor white carbon impregnated plastic shield. Non-conducting optical probes employ sensors composed of Gallium arsenide and mixture of pure earth phosphorus.

CASE STUDIES

In the Department of Radiation Therapy, University of Erlangen-Nürnberg, Federal Republic of Germany, during October 1987 to July 1988 there have been two groups of patients, treated with combined radiation and hyperthermia, using LUND BUCHLER Hyperthermia System, 4 010, 915 Mhz/20 W. The first group consists of 8 patients, and was treated with radiation combined with interstitial hyperthermia. The 8 patients consist of 4 cases of carcinoma of the floor of the mouth, 3 cases of tongue carcinoma, and 1 case of Ewing sarcoma. Two cases with 16 antennae, and the other less than that, but minimal 13 antennae. Two cases received 1 time interstitial hyperthermia and 6 cases received 2 times interstitial hyperthermia with interval at least 1 week. Optimal time for heating ranged between 45 to 65 minutes at 42°C.

The results of these two combined modality treatment approaches are: 7 cases have complete remission (87.5%) and 1 case has partial remission (12.5%). Complication noted in the group with complete remission: 3 cases showed a soft tissue necrosis, and one of them needed a graft.

The second group consisted of 6 patients treated with combined modality, radiation therapy and external (superficial) hyperthermia, using LUND BUCHLER hyperthermia system 4 010 915 Mhz/20 W. For coupling hot water was used. Extensive thermometry was performed both superficially and interstitially inserted into plastic tubes below the surface in the center and margins of the tumor. The heating time ranged between 45 to 65 minutes at 43° C. Five patients had breast cancer recurrence in the chest wall and some others in the supraclavicular region. One case had cancer of the parotid gland. Radiation therapy was applied with electron beam 12 Mev from Mevatron 20 with doses ranging from 35 Gy to 50 Gy. Two cases received 5 series of superficial hyperthermia and 1 case received 10 series of hyperthermia with an interval of one week.

The results of this combined modality treatment are: 4 cases have complete remission (66.6%) and 2 cases have partial remission (33.4%). In the group showing complete remission, 1 case has 6 months following treatment recurrence outside the field. Two cases developed small blisters which healed within days.

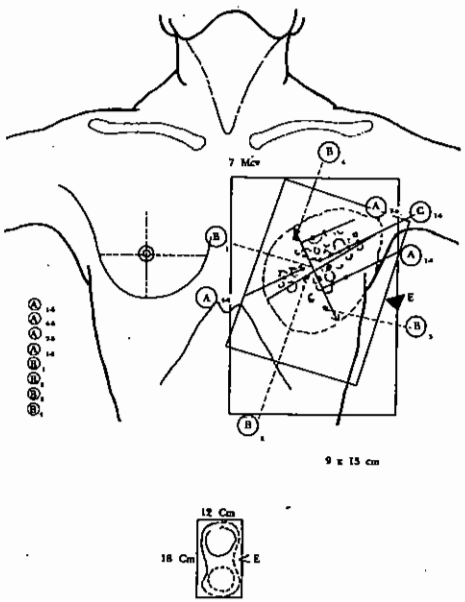

FIGURE 2. – Treatment planning of chest wall from a patient with breast cancer recurrence, using combination electron radiation and hyperthermia. The larger area is field for electron beam, and smaller field is for hyperthermia probe. A, B, and C are sites of thermometric sensor.

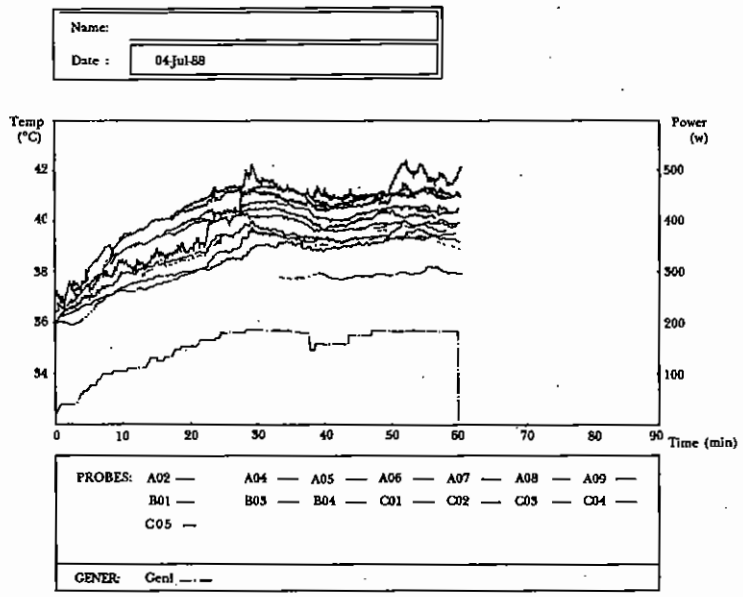

FIGURE 3. – Temperature in the target area as recorded by computer. Heat at several points of sites inside the tumor, below the tumor and superficial on the skin are measured by thermometric sensor, than curves are displayed in computer screen monitor.

HYPERTHERMIA TREATMENT LOG.

NAME: DATE: 1.7.88 RX I : HTX 3
RX SITE: MODE: PT I :
FILE NAME: DISK NO.: PRE RT/POST RT

TIME	PWR F	PWR R	CTRL	TUMOR MAX	MIN	SKIN MAX	B/P	PR/T			
PRE HTX	910		37,7	33,0	37,3	37,9	37,9	35,0	35,1	38,8	38,
5 MIN	1250		39,0	40,8	38,9	39,5	39,2	39,3	39,7	40,5	39,
10 MIN	1320		39,2	41,9	39,4	40,3	39,9	39,9	40,6	41,5	40,0
20 MIN	1630		39,9	42,7	40,0	41,0	40,4	41,4	41,0	43,3	
30 MIN	1690		40,3	42,0	39,6	40,8	40,2	41,7	40,3	42,4	42,0
40 MIN	1670		42,1	41,4	41,2	41,4	39,1	39,7	41,6	44,4	43,8
50 MIN	1720		39,5	40,0	40,2	41,6	39,9	41,3	41,0	42,1	42,6
60 MIN	1540		40,5	39,7	40,1	40,7	39,7	40,5	40,6	41,9	42,2
65 MIN	1560		40,4	39,5	39,8	40,5	39,4	40,1	40,2	41,5	42,3
AVG TEMP											

HTX COMMENT: ADM. BY:

FIGURE 4. – Hyperthermia treatment log used for recording important data, including power, temperature in tumor, skin, etc.

ABSTRACT

Two groups of patients were treated with combined modality radiation and hyperthermia at the Strahlentherapeutische Klinik, Universität Erlangen-Nürnberg, Federal Republic of Germany, from October 1987 to July 1988. The first group of 8 patients (4 cases of carcinoma of the floor of the mouth, 3 cases of tongue carcinoma, 1 case of Ewing sarcoma) was treated with combination radiation and interstitial hyperthermia. 7 cases have complete remission (87.5%), whereas 1 case has partial remission (12.5%). The second group of 6 patients (5 breast cancer recurrences in the chest wall and supraclavicular region, 1 case with cancer of the parotid gland) were treated with combined radiation of electron beam 12 Mev by Siemens Mevatron 20 and superficial hyperthermia using Lund Buchler hyperthermia system 4010, 915 MHZ/20 W, once a week. 4 cases have complete remission (66.6%) and two cases have partial remission (33.3%). As a background of hyperthermia we also describe the principles of thermobiology, heat interaction with irradiation, physiologic mechanisms, and effects of hyperthermia on microvasculature of tumors as well as basic principles of physics and instrumentation of hyperthermia.

KEPUSTAKAAN

Bicher, H. I., Hetzel, F. W., & Sondh, T. S. 1980 Effect of hyperthermia on normal and tumor microenvironment. *Radiology* 137:523-64.

Busch, W. 1866 Über den Einfluss welchen heftigere Erysipelas zuweilen auf organisierte Neubildungen Amiben. *Verh. Naturh. Preuss. Rheinl.* 23:28-37.

Coley, W. B. 1983 The treatment of malignant tumors by repeated inocculations of erysipelas – with a report of 10 original cases. *Am. J. Med. Sci.* 105:487-99.

Clark, E. P., Dewey, W. C., & Lett, J. T. 1981 Recovery of CHO cells from hyperthermia potentiation to x-rays: Repair of DNA and chromatin. *Radiation Res.* 85:302-14.

Crees, A. E., & Gerner, E. W. 1980 Cholesterol inversely reflects the thermal sensitivity of mammalian cells in culture. *Nature* 283:677-86.

Dewey, W. C., Highfield, D. P., & Freeman, M. L. 1979 Cell biology of hyperthermia and radiation, *dalam* S. Okada (ed.): *6th Int. Congr. Radiat. Res.* pp. 832-43, Tokyo.

_____, Hopwood, L. E., & Sappareto, S. A. 1977 Cellular response to combination of hyperthermia and radiation. *Radiology* 123:463-74.

Dickson, J. A., & Shah, D. M. 1972 The effect of hyperthermia (43°C) on the biochemistry and growth of a malignant cell line. *Eur. J. Cancer* 8:561-71.

Dube, K. D., Seal, G., & Loeb, L. A. 1977 Differential heat sensitivity of mammalian DNA polymerase. *Biochem. Biophys. Res. Comm.* 76:483-95.

Eddy, H. A. 1980 Alterations in tumor microvasculature during hyperthermia. *Radiology* 137:515-21.

Emami, B., Nussbaum, G. H., & Ten Haken, R. K. 1980 Physiological effect of hyperthermia: Response of capillary blood flow and structure: Local tumor heating. *Radiology* 137:805-16.

Fayardo, L. F., Egbert, B., & Marmar, J. 1980 Effects of hyperthermia on malignant tumors. *Cancer* 45:613-23.

Field, S. B., & Bleehen, N. M. 1979 Hyperthermia as the treatment of cancer. *Cancer Treatment Rev.* 6:63-94.

Goldin, E. M., & Leeper, D. B. 1981 The effect of reduced pH on the induction of thermotolerance. *Radiology* 141:505-17.

Gullino, P. M., Grantham, G. H., & Smith, S. H. 1965 Modification on the acid base status of the internal millieu to tumors. *J. Natl. Cancer Institute* 34:857-68.

Hume, S. P., Rogers, M. A., & Field, S. B. 1978 Heat induced thermal resistance and its relationship to lysosome response. *Int. J. Radiat. Oncol. Biol. Phys.* 34:503-16.

Jahde, E., Rajewski, M. F., & Baumgartl, H. 1982 pH distribution in transplanted neural tumors and normal tissues of BDIX rats as measured with pH microelectrodes. *Cancer Res.* 42:1505-14.

Le Veen, H. H. O., Brien, P., & Wallace, K. M. 1980 Radiofrequency thermometry for cancer. *J. SC Med. Assoc.* 76:5-14.

Mondovi, B., Argo, A. F., & Rottilio, G. 1969 The biochemical mechanism of selective heat sensitivity of cancer cells. I. Studies on nucleic acid and protein synthesis. *Eur. J. Cancer. Clin. Oncol.* 5:137-49.

———, Strom, R., & Rottilio, G. 1969 The biochemical mechanism of selective heat sensitivity to cancer cells. I. Studies on cellular respiration. *Eur. J. Cancer Clin. Oncol.* 5:129-36.

Overgraad, K., & Overgraad, J. 1972 Investigation on the possibility of a thermic tumor therapy. I. Short wave treatment of a transplanted isologous mouse mammary carcinoma. *Eur. J. Cancer Clin. Oncol.* 8:65-78.

Overgraad, J., & Nielson, O. S. 1980 The role of tissue environment factors on the kinetic and morphology of tumor cells exposed to hyperthermia. *Ann. Ny. Acad. Sci.* 335:254-67.

Roti Roti, J. L., & Winward, R. T. 1978 The effects of hyperthermia on the protein to DNA ratio of isolated Hela cell chromatin. *Radiat. Res.* 74:159-68.

Saparetto, S. A., Raapharst, G. P., & Dewey, W. C. 1979 Cell killing and the sequencing of hyperthermia and radiation. *Int. J. Radiat. Oncol. Biol. Phys.* 5:343-54.

———, Hopwood, L. E., & Dewey, W. C. 1978 Combined effect of X-irradiation and hyperthermia on CHO cell for various temperatures and orders of application. *Radiat. Res.* 73:221-32.

Song, C. W. 1978 Effect of hyperthermia on vascular function of normal tissue and exprimental tumors. *J. Natl. Cancer Inst.* 60:711-18.

———, Kang, M. S., & Rhee, J. G. 1980 Vascular damage and delayed cell death in tumors after hyperthermia. *Brit. J. Cancer* 41:309-12.

Streffer, C., Beuningen, D. van, & Dietzel, F. (eds) 1978 *Cancer Therapy by Hiperthermia and Radiation.* Urban & Schwarzenberg, Munich.

———, Hengstebach, S., & Tamlevicius, P. 1981 Glucose metabolism in mouse tumor and liver with and without hyperthermia. *Henry Ford Hosp. Lead J.* 29:41-49.

Stewart, F. A., & Denekamp, J. 1977 Sensitisation of mouse skin to X-irradiation by moderate heating. *Radiology* 123:195-206.

Tomasovic, S. P., Turner, S. N., & Dewey, W. C. 1978 Effect of hyperthermia on non-histone protein isolated with DNA. *Radiat. Res.* 73:535-47.

Vaupel, P., Ostheimer, K., & Muller, Kliesler, W. 1980 Circulatory and metabolic responses of malignant tumors during localized hyperthermia. *J. Cancer Res. Clin. Oncol.* 98:13-24.

Warocquier, R., & Scheerer, K. 1969 RNA metabolism in mammalian cells at elevated temperature. *Eur. J. Biochem.* 10:362-71.

Warren, S. L. 1935 Preliminary study of the effect of artificial fever upon hopeless tumor cases. *Am. J. Röntgenol.* 33:75-81.

Waters, R. L., & Roti Roti, J. L. 1988 Nucleosome structure in chromatin from heated cells. *Radiat. Res.* 84:504-13.

Waters, R.L., Roti Roti, J. L., & Winward, R. T. 1978 Production and excision of 5'6' dihydroxy dihydrothymine type products in the DNA of praeheated cells. *Int. J. Radiat. Oncol. Biol. Phys.* 34:381-92.

Westra, A., & Dewey, W. C. 1971 Variation to sensitivity to heat shock during the cell cycle of Chinese hamster cells in vitro. *Int. J. Radiat. Oncol. Biol. Phys.* 19:467-75.

Westermark, F. 1898 Über die Behandlung des ulcererend Cervix Carcinoms mitle Konstanter Warme. *Zentralbl Gynäkol.* 22:1335-47.

Yatvin, M. B. 1977 The influence of membrane lipid composition and protein on hyperthermia death of cells. *Int. J. Radiat. Oncol. Biol. Phys.* 32:513-22.