Hyperthermia In Cancer Therapy

Edited by
F. Kristian Storm

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Edited by
F. Kristian Storm, M.D.
Associate Professor of Surgery
Division of Oncology
UCLA School of Medicine
Los Angeles, California

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Contributors

Luigi Aloe, M.D.
Regina Elena Institute for Cancer Research
Rome, Italy

E. Ronald Atkinson, Ph.D.
American Hospital Supply Corporation
Evanston, Illinois

Haim I. Bicher, M.D., Ph.D.
Department of Therapeutic Biology
Henry Ford Hospital
Detroit, Michigan

Joan M. Bull, M.D.
Division of Cancer Treatment, Medical Branch
National Cancer Institute
Bethesda, Maryland

Stuart K. Calderwood, Ph.D.
Cancer Research Unit
University Department of Clinical Biochemistry
Royal Victoria Infirmary
Newcastle-Upon-Tyne, England

Renato Cavaliere, M.D.
Regina Elena Institute for Cancer Research
Rome, Italy

Thomas C. Cetas, Ph.D.
Department of Radiology, Radiation Oncology Division
Department of Electrical Engineering
University of Arizona Health Sciences Center
Tucson, Arizona

Chung-Kwang Chou, Ph.D.
Bioelectromagnetics Research Laboratory
School of Medicine
University of Washington
Seattle, Washington

Douglas A. Christensen, Ph.D.
Department of Electrical Engineering and Bioengineering
University of Utah
Salt Lake City, Utah

Stephen F. Cleary, Ph.D.
Department of Biophysics
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

John A. Dickson, M.D., Ph.D.
Cancer Research Unit
University Department of Clinical Biochemistry
Royal Victoria Infirmary
Newcastle-Upon-Tyne, England

Franco Di Filippo, M.D.
Regina Elena Institute for Cancer Research
Rome, Italy

Robert S. Elliott, Ph.D.
Department of Electrical Sciences and Engineering
University of California at Los Angeles
Los Angeles, California

Eugene W. Gerner, Ph.D.
Department of Radiology, Radiation Oncology Division
University of Arizona Health Sciences Center
Tucson, Arizona

Leo E. Gerweck, Ph.D.
Department of Radiation Medicine
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Beppino C. Giovanella, Ph.D.
The Stehlin Foundation for Cancer Research
Houston, Texas

Arthur W. Guy, Ph.D.
Bioelectromagnetics Research Laboratory
School of Medicine
University of Washington
Seattle, Washington

William H. Harrison, B.A.
Department of Electrical Sciences and Engineering
University of California at Los Angeles
Los Angeles, California

Kurt J. Henle, Ph.D.
Medical Research Service
Veterans Administration Medical Center
Little Rock, Arkansas

Fred W. Hetzel, Ph.D.
Department of Therapeutic Radiology
Henry Ford Hospital
Detroit, Michigan

Rakesh K. Jain, Ph.D.
Department of Chemical Engineering
Carnegie-Mellon University
Pittsburgh, Pennsylvania

Padmakar P. Lele, M.D., Ph.D.
Department of Mechanical Engineering
Massachusetts Institute of Technology
Cambridge, Massachusetts

Michael R. Manning, M.D.
Department of Radiology, Radiation Oncology Division
University of Arizona Health Sciences Center
Tucson, Arizona

Bruno Mondovi, M.D.
Institute of Applied Biochemistry
University of Rome
Rome, Italy

Giorgio Monticelli, M.D.
1st Orthopedic Clinic
University of Rome
Rome, Italy

Guido Moricca, M.D.
Regina Elena Institute for Cancer Research
Rome, Italy

Donald L. Morton, M.D.
Department of Surgery, Division of Oncology
University of California at Los Angeles
Los Angeles, California

Pier Giorgio Natali, M.D.
Regina Elena Institute for Cancer Research
Rome, Italy

Jens Overgaard, M.D.
The Institute of Cancer Research, Radiumstationen
Aarhus, Denmark

Leon C. Parks, M.D.
Department of Surgery
University of Mississippi Medical Center
Jackson, Mississippi

Alessandro Rossi-Fanelli, M.D.
Institute of Biological Chemistry
University of Rome
Rome, Italy

Taljit S. Sandhu, Ph.D.
Department of Therapeutic Radiology
Henry Ford Hospital
Detroit, Michigan

Francesco Saverio Santori, M.D.
1st Orthopedic Clinic
University of Rome
Rome, Italy

Sudhir A. Shah, M.D.
Cancer Research Unit
University Department of Clinical Biochemistry
Royal Victoria Infirmary
Newcastle-Upon-Tyne, England

George V. Smith, M.D.
Department of Surgery
University of Mississippi Medical Center
Jackson, Mississippi

Chang W. Song, Ph.D.
Department of Therapeutic Radiology,
Section of Radiobiology
University of Minnesota
Minneapolis, Minnesota

F. Kristian Storm, M.D.
Department of Surgery, Division of Oncology
University of California at Los Angeles
Los Angeles, California

Antonio Varanese, M.D.
Regina Elena Institute for Cancer Research
Rome, Italy

Foreword

Hyperthermia at temperatures above 41°C has been used sporadically as an agent for cancer therapy since the early 1900s. Although there were encouraging results, there was not enough consistency to encourage continued and sustained efforts in applying hyperthermia either by itself or combined with radiation or other agents. During the last few years, however, results from studies of cell cultures and animals, as well as from a few preliminary clinical trials, have provided some enthusiasm for systematically investigating the potential use of hyperthermia in cancer therapy.

Results in vitro have provided a rationale for considering the use of hyperthermia in cancer therapy. First, hyperthermia at temperatures above 41°C kills mammalian cells and sensitizes them to ionizing radiation, with the degree of killing and radiosensitization varying greatly with only a 0.5°C change in temperature. Therefore, with inadequate temperature control and measurement in clinical studies in the past, consistent results could not have been expected. Second, hyperthermia selectively kills and radiosensitizes cells that are relatively resistant to ionizing radiation; these populations are those in the process of synthesizing DNA and those existing in the hypoxic compartment of tumors. These hypoxic cells are probably also at a low pH and under nutrient or energy deprivation, all of which sensitize cells to hyperthermia. Therefore, the action of hyperthermia by itself or interacting with ionizing radiation should selectively kill those tumor cells surviving a dose of radiation. This same rationale has been offered for considering the use of high linear energy transfer (LET) radiation and electronic affinic compounds in radiation therapy. Third, hyperthermia has been shown to eliminate or reduce recovery from sublethal and potentially lethal radiation damage; this may have a selective effect on tumor cells, especially those existing in the G_0 compartment. Finally, the toxicity of electron affinic compounds for hypoxic cells and the toxicity of several chemotherapeutic agents can be enhanced greatly by hyperthermia. Thus, basic studies of cell cultures indicate that there are reasons to believe that hyperthermia may enhance the therapeutic efficacy of radiation and chemotherapeutic agents used in clinical practice. Furthermore, since the toxic effects of radiation, radiosensitizers, or chemotherapeutic agents are greatly enhanced by hyperthermia, and since heat and radiation act in a complementary way (e.g., killing of hypoxic and S-phase cells), the combined modality approach appears to offer the greatest potential for use of hyperthermia.

Studies in animals and humans during the last few years have indicated that there may be some merit to the rationale proposed above. For example, hyperthermia has been shown to have a selective effect on the radiation response of chronically hypoxic tumor cells and, under certain conditions, can improve the therapeutic ratio (i.e., the radiation response of the tumor relative to that of normal tissue). As predicted from studies of cell cultures, however, variations in the sequence between administration of hyperthermia and radiation may alter greatly the effectiveness of hyperthermia for improving the therapeutic ratio. Beneficial clinical results are still largely anecdotal but do suggest that careful clinical studies need to be carried out in which variations in sequencing are considered as the temperature profiles in tumors and normal tissues are monitored. Also, physiologic changes, such as changes in oxygen tension and pH, occur from hyperthermic treatment and should be considered in relation to the effectiveness of hyperthermic treatments. Preliminary data from animal and human studies indicate that hyperthermia may indeed enhance the effectiveness of radiation and chemotherapy, but these data also indicate that various parameters must be monitored and carefully evaluated to determine the reasons for both successes and failures.

Issues to be resolved or confirmed are: the mechanisms of action for heat killing and heat radiosensitization; the importance of the particular temperature used and its duration; the importance of sequence (heat before radiation or radiation before heat); whether heat and the second agent of radiation or chemotherapy should be separated by a long interval such that the two agents act independently, or by a short interval such that the two agents interact additively or synergistically; the best interval between combined heat and x-ray fractions; how to heat the tumor with precise temperature control; the recognition and possible use of thermal tolerance for heat alone and possibly for heat combined with radiation, especially if tolerance is reduced for tumor cells at low pH; heat effects on the immunologic response and on destroying or spreading metastases; and physiologic changes that are especially important for heat before irradiation and that may involve changes in pH, nutrients, oxygen consumption, blood flow, and oxygen concentration. For example, when heat is delivered before radiation, the frequently observed decrease in oxygen concentration might be expected to increase the hypoxic radioresistant fraction in the tumor. The most important observation to be made, however, is

whether there indeed will be a differential effect between tumor and normal tissue when both are at the same temperature. If there is no differential effect, then the tumor will have to be heated selectively to achieve any therapeutic efficacy. These studies of therapeutic gain or efficacy are most important for fractionated doses and when tumor cure is compared with late effect in normal tissue.

The immediate challenge is to develop and make available heating and thermometry equipment that is essential for conducting definitive experiments in small and large animals and in humans. Then, as basic mechanisms involved in heat inactivation, heat radiosensitization, and heat-drug interactions are understood, results obtained in vitro and in small and large animals, as well as in phase I and II clinical trials, should lead to meaningful phase III trials. It is hoped that phase III clinical trials will demonstrate that hyperthermia, when applied properly, is a beneficial agent for cancer therapy: that it will provide an improvement in the therapeutic index defined as a percentage of a group of treated cancer patients who remain both free of recurrence and free of severe complications over a given period of time.

This volume reviews and addresses the questions and issues mentioned above. The authors hope that its readers will gain an insight into both the problems and the potential benefits associated with hyperthermia in cancer therapy.

William C. Dewey, Ph.D.
Department of Radiology and
Radiation Biology
Colorado State University
Fort Collins, Colorado

Preface

Hyperthermia in Cancer Therapy is a succinct state-of-the-art text on thermal therapy, its history, its current status, and its potential use. No other medical field has required the interaction of such a multitude of experts for its development—mathematicians, engineers, cell biologists, biophysicists, pharmaco-kineticists, radiation therapists, medical oncologists, computer programmers, and oncologic surgeons. To this end, the text contains over 2000 references from many of these specialists.

There will be 750,000 new cases of cancer diagnosed this year in the United States, and 450,000 patients will die of this disease. Of the one in four Americans who will be afflicted by cancer in a lifetime, only one in three will be cured by present methods of therapy that include surgery, radiation therapy, chemotherapy, and immunotherapy. This book was written for all those investigators who have given and who will give a significant portion of their life to the development of hyperthermia as a fifth treatment of cancer. All contributors are recognized national and international authorities. Each author reviews the principles of hyperthermia in his or her own way, and in some instances redundancy has been allowed for comprehension. Indeed, the writing of this book has served to define more clearly those areas of agreement and disagreement as the strategies for treatment for cancer patients improve and evolve.

This book is dedicated to Donald L. Morton, M.D., my teacher, colleague, and friend, who has helped me to understand the many rewards of scientific investigation. This book is dedicated also to my wife, Patty, for her unselfish and continued encouragement, to my parents, Dorothy and Fred Storm, whose love and sacrifices have been my inspiration, and to my young daughters, Sandy, Lori, and Darlene, for their gift of time to complete the necessary editing.

F. Kristian Storm, M.D.

Contents

CHAPTER 1

Background, Principles, and Practice

F. Kristian Storm

EARLY HISTORY

Hyperthermia, from the Greek *hyper*, meaning beyond, above, over, or excessive, and *therme*, heat, has been applied to various ailments, including cancer, since ancient times. The early translations of Ramajama (2000 B.C.), Hippocrates (400 B.C.), and Galen (200 A.D.) record the use of *ferrum candens* (red-hot irons) and chemical caustics in the treatment of small, nonulcerating cancers. After the Renaissance there were numerous case reports of spontaneous tumor regressions in patients with erysipelas, smallpox, influenza, tuberculosis, and malaria. A factor common to all these illnesses was an infectious fever of about 40°C, which lasted for several days.

The first documented evidence that elevated temperatures might have a selective effect on tumors usually is ascribed to Busch, who in 1866 reported the disappearance of a histologically verified sarcoma of the face after two attacks of erysipelas. Many reports from the late nineteenth and early twentieth centuries describe the regression of primary and secondary tumors after infection with pyrogenic bacteria (Bruns 1887; Coley 1893, 1896; Rohdenburg 1918). In 1896, Coley introduced febrile therapy with "mixed toxins of erysipelas and *B. prodigensus*" for the treatment of malignant tumors and reported a disease-free survival of one to seven years in 3 of 17 inoperable carcinomas and 7 of 17 inoperable sarcomas. Interestingly, these original works stated that for the toxin to be effective a fever of 39°C to 40°C had to be maintained for several days. Nauts, Fowler, and Bogatko (1953) later repeated Coley's work and found 25 of 30 selected patients with soft tissue sarcoma, lymphosarcoma, and carcinoma of the cervix and breast alive and disease-free at 10 years. The earlier results achieved with the original highly pyrogenic agents were never equaled with lesser agents, however, and it has been suggested that the fever itself, rather than the toxin, was the tumoricidal agent. F. Westermark in 1898 placed water-circulating cisterns at 42°C to 44°C into inoperable carcinomas of the uterus for 48 hours and observed palliative shedding of many tumors, although subsequent healing was rare. Also in the 1890s, d'Arsonval, Telsa, and others simultaneously reported upon the healing effects of high frequency currents on deep tissues. Using this information, Nagelschmidt in 1926 coined the term *diathermy*, to deep heat, and the use of electromagnetic heating of tumors rapidly followed.

SELECTIVE THERMOSENSITIVITY

The modern era of hyperthermia investigation has since provided mounting evidence to support a hypothesis that cancer cells are more selectively sensitive to heat than are normal cells. In 1927, N. Westermark heated Flexner-Jobling carcinoma and Jensen's sarcoma in rats using diathermy and found total tumor regression after 180 minutes at 44°C or 90 minutes at 45°C, while normal tissues were not damaged under similar conditions. He was the first to introduce the concepts of dose-time thermal effect and histopathologic examination of treated tumors for evidence of heat-induced necrosis. Stevenson (1919) and Rohdenburg and Prime (1921) also were among the first to investigate the relationship between treatment times and temperature of animal tumors. Crile (1961, 1962) extended the work of Westermark and confirmed a dose-response relationship between heat and tumor cure. Above 42°C, he found that for each 1°C increase in tumor temperature, the exposure time needed for tumor cure in mice could be halved. Crile also discovered the phenomenon of delayed cell killing after hyperthermia; tumors excised immediately after heating were able to grow in recipient animals on transplantation, but tumors removed four hours after heating did not grow when transplanted. In 1961, Crile heated mice feet implanted with sarcoma 180 in a water-bath for various times and temperatures and found that 70 minutes at 43°C "cured" most of the tumors, while only one of six normal feet was lost after 384 minutes at the same temperature. In 1963, Crile found that preheating tumors could make them less sensitive to a further heating dose (thermal tolerance), and that clamping the tumor blood supply increased heat sensitivity. In 1966, Bender and Schramm studied the effects of 30 minutes of heat on human cells in vitro and found that tumor cell lines were killed at 45°C to 46°C, whereas normal cells were killed at one degree higher temperature. In 1967, Cavaliere caused irreversible damage to Novikoff hepatoma cells by incubation at 42°C to 44°C, which did not occur in either normal or regenerating rat liver cells, or in minimal deviation hepatoma 5123. Two years later (1969), co-worker Mondovi reported that the selective inhibitory effect of high temperature on tumor cells was paralleled by a higher sensitivity of these cells to the polyene antibiotic filipin as well as ethanol, and that ethanol inhibition was also enhanced by higher temperature. The effects were tentatively ascribed to an alteration in cell and/or lysosomal membrane permeability. In clinical trials, these investigators performed regional limb perfusions with blood prewarmed to 41.5°C to 43.5°C in 22 patients with large, recurrent, or single metastatic cancers localized to the extremity. All gross tumor disappeared in 10 patients, although three had disease recurrence, five had regression, three failed to respond, and four were not evaluable. The complication rate was high, with six deaths and three immediate amputations; however, 8 of 22 patients had complete massive tumor necrosis. In 1971, Muckel and Dickson treated highly malignant squamous carcinoma VX-2 in rabbit extremities with water-bath hyperthermia at 42°C. After three one-hour applications there was widespread tumor necrosis, subsequently replaced by connective tissue, and survival was prolonged by 18 months in 50% of the treated animals. All control animals died within 10 weeks. In the next year, Overgaard and Overgaard (1972) reported permanent cures of transplantable mouse mammary carcinoma using shortwave-induced hyperthermia in the range of 41.5°C to 43.5°C. A definite relationship could be established between temperature and exposure time. They found that the heat induced distinct histologic changes in the tumor cells but not in stromal or vascular cells within the tumor, or in normal surrounding tissue. They saw rapid, autolytic distintegration of heat-damaged tumor cells, followed by a marked increase in connective tissue stroma and scar formation. Giovanella, Lohman, and Heidelberger in 1970, and Giovanella and associates in 1973, studied the effects of hyperthermia on normal (embryonic) and neoplastic (methyl-cholanthrene sarcoma) mesenchymal cells derived from C57BL/6 mice. They found that 95% of all cultures of tumor-derived and tumor-producing cells died after two hours at 42.5°C, whereas only 43% of all cultured normal and non-tumor-producing cells died under similar conditions. When a cell subline derived from a non-tumor-producing line acquired high tumor-producing ability, it also acquired greater thermosensitivity. These results suggested that the acquisition of malignant potential, both in vivo and in vitro, is accompanied by decreased thermotolerance. In 1976, Mendecki, Friedenthal, and Botstein applied microwave-induced hyperthermia of 43°C for 45 minutes to superficially implanted mammary carcinoma in C3H mice and found that the neoplasm completely disappeared after two treatments. All mice in the treated group survived four months, while all nontreated controls died within 4 weeks. In 1977, Dickson and Shah and Dickson with others reported shortwave heating of VX-2 carcinomas in rabbit extremities at 47°C for 30 minutes. Skin and normal muscle remained 3°C to 4°C below minimal tumor temperature. After one application, 7 of 10 tumors regressed completely. In a similar experiment, Marmor, Hahn, and Hahn (1977) found that shortwave heating of EMT-6 sarcomas in

mice for five minutes at 44°C resulted in cure of nearly 50% of the tumors.

SYSTEMIC HYPERTHERMIA

Clinical trials also support the potential usefulness of systemic (total-body) hyperthermia. In 1935, Warren produced systemic hyperthermia in the range of 41.4°C to 43°C in a heating cabinet using a combination of carbon filament lamps and radiofrequency diathermy. He reported an immediate improvement in constitutional symptoms, as well as tumor regression of varying degrees, with remissions from one to six months. Pettigrew and associates in 1974 described treatment of 38 terminal cancer patients who were immersed in molten wax for total-body hyperthermia at 41.8°C for an average of four hours. An objective response—weight gain or pain relief plus measured tumor regression or histologic evidence of necrosis—was seen in 18 of 38 cases. Four patients died from disseminated intravascular coagulation. Larkin, Edwards, and Smith in 1976 reported their experience with total-body hyperthermia applied by a water-circulating suit. Nineteen patients were maintained at 41.5°C to 42°C for two to five hours, with an objective tumor response of about 70%. Complications included one death, transient cardiac arrhythmias in 15%, superficial burns in 15%, and transient respiratory distress in 11% of patients. These complications were attributed to the many hours of anesthesia time initially required to raise and maintain body temperature in these critically ill patients. Since these pioneering efforts, heat therapy techniques have been refined. Bull recently defined the physiologic effects of total-body hyperthermia as a single agent and in combination with chemotherapy, and Parks has achieved a practical reduction in total treatment time by the use of extracorporeal circulation of heated blood.

THERMORADIOTHERAPY

As attention has focused increasingly on local cancer therapy, hyperthermia has been combined with radiation therapy, both external beam and interstitial, in an effort to produce a synergistic and augmented response. Several investigators have concluded that hypoxic cells may be at least as sensitive to hyperthermia as oxygenated cells, forming the rationale for combined therapy, since hypoxic cells seem to be more radioresistant. Ben-Hur, Elkin, and Bronk (1974), however, suggested that the primary effect of hyperthermia was to inhibit cellular recovery from sublethal radiation damage. Connor and co-workers (1977) found that if tumor cells were exposed to hyperthermia followed by 600 rad, there was a greater than 3-log increase in cell kill at 43°C compared to 37°C. He suggested that clinical doses for local and regional treatment using radiation plus hyperthermia would lie in the range of 200 to 600 rad per fraction. Manning and colleagues (1982) have performed phase I studies that suggest that effective thermal doses may be in the range of 43°C to 45°C, combined with high doses of radiation, or an equivalent of 4000 rad in four weeks. Kim, Kim, and Hahn (1975) and Kim and colleagues in 1977 reported their experience with hyperthermia and radiation for cutaneous cancers in man. With fractionated doses to 800 to 2400 rad followed by 43.5°C surface heating by water bath or microwaves, 7 of 10 patients showed significant prolonged benefits by combination therapy when compared to radiation alone. Hornback and colleagues (1979) have treated 70 patients with advanced malignancies with a combination of microwaves (434 MHz, extrapolated to produce 41°C at 7 to 8 cm from phantom models) and standard radiation therapy fractions and total doses. There were no complications to combined therapy, and no patient developed symptomatic or unusually sensitive skin reactions in or around the treatment area. Of 21 patients who received a full course of therapy, 16 (80%) had complete regression of all local tumor, and nine of these remained free of disease for 9 to 14 months.

THERMOCHEMOTHERAPY

The combination of hyperthermia and chemotherapy has been under investigation ever since the realization that heat may alter tumor cell membrane permeability and enhance uptake of chemotherapeutic agents. In 1970, Giovanella, Lohman, and Heidelberger found that temperatures from 37°C to 40°C had little effect on L1210 leukemia cells, but a lethal effect could be achieved between 41°C and 42°C, such that a 4-log kill was observed at 42°C in three hours. Moreover, a 100-fold kill enhancement was observed with the addition of dihydroxybutylaldehyde, with no increase in toxicity. DL-glyceraldehyde, melphalan, and sodium oxamate were also more active in combination with heat. In vitro data from Hahn and co-workers (Hahn 1974; Hahn, Braun, and Har-Kedar 1975; Hahn and Pounds 1976) suggested benefit using hyperthermia with Adriamycin, bleomycin, the nitrosoureas, cisplatin, and possibly other drugs. In 1976, Goss and Parsons reported on four human fibroblast strains and seven melanoma cell lines exposed to various concen-

trations of melphalan alone and in combination with heat at 42°C for four hours. They found that sensitivity to melphalan was usually accompanied by sensitivity to heat, and that combined treatment was not only synergistic but increased the differential between fibroblast and melanoma lines. Reporting clinical trials in limb perfusion, Stehlin and colleagues (1975) found an increased response from 35% to 80% by the addition of heat of 40.5°C to 41.5°C to melphalan perfusion for regionally metastatic melanoma.

IMMUNE CORRELATES

Several investigators have suggested that tumor regression after hyperthermia may be, in part, due to some augmentation of the immune system. Few studies are available and much data is needed. Crile (1963) showed that tumor cell killing in vivo occurred after development of a host inflammatory reaction and that heat could be potentiated by serotonin, a chemical mediator of inflammation. Heat has been shown also to have increased effectiveness against the more immunogenic tumors (Dickson 1978; Dickson and Shah 1980), and the effects of heat may be enhanced by immunostimulation (Szmigielski and Janiak 1978; Dickson and Shah 1980) or reduced by immunosuppression (Dickson and Shah 1980). Goldenberg and Langner (1971) found growth inhibition of GW-77 human colonic tumors growing in hamster cheek pouches after shortwave diathermy heating, as well as growth inhibition of contralateral, presumably normothermic cheek pouch tumors. Marmor, Hahn, and Hahn (1977) found that EMT-6 sarcomas implanted in mice were highly sensitive to cure by radiofrequency heating. Cell kill as assessed by cloning efficiency of treated and immediately excised tumors, however, was insufficient to account for the in vivo cure rate. This led the authors to suggest that delayed killing might be the result of destruction of tumor blood vessels and possibly of stimulation of a tumor-directed immune response.

SELECTIVE TUMOR HEATING

Most studies to date have dealt with moderate hyperthermia in the range of 42°C to 43°C alone, or in combination with radiation or chemotherapy, based upon the evidence of selective thermal sensitivity of tumor cells. Lethal temperature/exposure time relationships have been established for many cell lines, and for each degree above 42°C the time for tumor destruction seems to be approximately halved (Dickson and Shah 1977; Dickson et al. 1977; Overgaard and Overgaard 1972). Storm and colleagues (1980a) have found similar dose/time relationships in human tumors. Several investigators, however, have shown that at temperatures approaching 45°C the differential susceptibility between malignant cells and normal cells decreases, and host tolerance becomes the prime consideration (Hardy et al. 1965). In 1927, Nils Westermark succeeded in achieving marked regression of rodent tumors at 45°C to 50°C using radiofrequency without the attendant destruction of surrounding tissues, and said that such experimental tumors could not derive any great influence through their circulation, "their thermoregulation being apparently bad." His was the first suggestion that reduced blood flow in tumors might allow selective tumor heating to very high temperatures without normal tissue injury. Hahn, Braun, and Har-Kedar reached a similar conclusion in 1975. Therapeutic hyperthermia in higher temperature ranges seemed feasible with the realization that some solid tumors might act as heat reservoirs to retain heat because of their abnormal vascularity and relatively poor blood flow. Natadze (1959) found that adrenalin, histamine, and actylcholine had no effect on tumor blood flow, and Gullino and Grantham (1961) found that experimental hepatomas had a 20-fold smaller blood supply than host liver. Shibata and MacLean (1965) evaluated cancers in man and found the blood supply to be poorer in all tumors studied. LeVeen and co-workers (1976) subsequently found that tumor blood flow was only 2% to 15% that of surrounding tissue using isotope dilution techniques and reaffirmed the theory that tumors retain more heat than normal tissue because of differential blood flow. Storm and colleagues (1979a, 1980a) recently suggested that while ambient blood flow may differ in tumor and normal tissue, the inability to regulate and augment flow in response to hyperthermia may be the determining factor in achieving selective tumor heating.

ELECTROMAGNETIC HYPERTHERMIA

Hyperthermia has been applied by various means, including fluid immersion, irrigation, regional perfusion, and electromagnetic waves. It is the latter, in the form of microwaves or radiofrequency waves, that appears to be the most practical and efficient for producing localized hyperthermia. All these forms of electromagnetic energy seem to cause tissue heating by a similar mechanism. Energy is transferred into tissue by a field interaction that causes oscillation of ions in

the tissue, or changes in the magnetic orientation of molecules, which is locally converted into heat. The energy of a microwave or shortwave quantum is only about 10^{-5} eV and therefore is insufficient to produce ionization or excitation (Milroy and Michaelson 1971). The biological effects of electromagnetic waves seem to be primarily, and possibly solely, due to heat production. The absorption and penetration characteristics of electromagnetic waves are dependent, however, on tissue composition and interfaces (viz., skin/muscle/fat/bone). Moreover, the depth of penetration often is limited and is frequency-dependent (Guy 1975). Satisfactory heating is limited presently to depths of 2 to 3 cm with commercially available diathermy apparatus. In an attempt to overcome limited penetration, several investigators have designed specialized equipment in the 915-MHz and 2450-MHz microwave bands; however, even with surface cooling, documented temperatures of only 42°C to 44°C have been possible at only 2- to 3-cm depths, with a continuously decreasing thermal gradient with increasing depths. Microwave phase array is being investigated in several centers to obviate this problem. For these reasons, clinical trials using microwaves have so far been limited to superficial cancers. LeVeen and co-workers (1976) applied standard radiofrequency diathermy techniques at 13.56 MHz to 21 patients and achieved tumor temperatures over 46°C in three cases, 8°C to 10°C higher than adjacent normal tissue. Tumor necrosis or substantial regression of cancer was reported in all cases. They also found, however, that energy was best transmitted to surgically exposed tumors to avoid the undesirable heating of skin and subcutaneous tissue, which occasionally resulted in burns.

More recently, Storm and colleagues (1979a, 1979b, 1980a, 1980b, in press) and Storm and Morton (1979) developed a noninvasive circumferential electrode that creates a magnetic field whose field lines are coaxial with the body portion being treated, thereby producing deep internal hyperthermia without attendant surface tissue injury. Using this method, the field is not focused, and selective tumor heating is dependent upon the inability of tumors to dissipate heat. Alternately, Lele and Hahn have indicated independently that it may be possible to produce safe and effective deep hyperthermia with focused narrow-beam ultrasound (acoustic waves), although the exact location of the tumor must be known.

A major unknown factor in hyperthermia is dosimetry, the ability to quantitate absorbed heat. Without it, standardization and comparison of treatments is impossible. The measurement has been particularly elusive in electromagnetic hyperthermia. For microwave frequencies, only 40% of incident energy is absorbed, and even this value is extremely variable, depending on relative water concentrations and the presence of interfaces. Because of these many variables, microwave energy absorption can in no way be assessed on the basis of power output of the microwave generator. Several investigators have attempted to overcome this problem using reflectometers and field-strength meters with feedback loops; however, no reliable system has yet been reported in this frequency range. Ultrasonic energy absorption has been readily measured. Storm suggests that radiofrequency absorption may be monitored with greater than 95% accuracy employing specialized equipment in certain circumstances (magnetic-loop induction) (see chapter 14).

TEMPERATURE MEASUREMENT

Temperature measurement, an essential prerequisite to hyperthermic treatments in humans, presents another obstacle to heat therapy. The most reliable and accurate measuring devices seem to be thermocouples and thermistors. Unfortunately, the metal in these instruments distorts the electromagnetic field from radiofrequency and microwave applicators, which in turn causes independent heating of the thermometer and surrounding tissue, resulting in erroneous readings. Christensen, Cetas, and Bowman have been experimenting to allow temperature recording with relative or completely nonconducting materials, and research is currently underway at several centers with liquid crystal, solid crystal, and viscometric thermometers.

HYPERTHERMIA TREATMENT SCHEDULES

Another unresolved area in hyperthermic therapy involves treatment scheduling. Palzer and Heidelberger (1973) studied quantitative killing of HeLa cells in vitro by a cloning assay and found that the cells could not only recover from hyperthermic damage, but that this phenomenon appeared to be cell cycle phase dependent. Cells seemed to be more sensitive to heat during late-S or early G_2 phases by sevenfold, compared to other phases of the cell cycle. Bhuyan and colleagues (1977) found that CHO cells were most sensitive to hyperthermia in the mid- and late-S phase and that G_1 and G_2 cells were the least sensitive. Gerner and co-workers (1976) studied HeLa cells at temperatures from 41°C to 45°C and again found that cell killing increased exponentially with time at ele-

vated temperatures. Surviving cells, however, seemed to develop a transient state of thermotolerance that only began to abate as the cells divided, and was completely lost to progeny of previously heated cells. This study suggested that temporally spaced thermal doses may allow transiently induced thermal resistance to subside for more effective therapy. The import of their studies bears upon scheduling in all clinical trials.

UNRESOLVED QUESTIONS

This brief historical introduction is intended to highlight some of the areas of hyperthermia that have come under intense investigation. It should be evident that hyperthermia is a rapidly evolving field with a multitude of unresolved questions. Hyperthermia clearly is an effective tumoricidal agent; but how should it best be used, and when, and with what other therapies? What techniques will prove most efficacious for a particular tumor, and what is the optimum treatment schedule? How does hyperthermia work, and will it work in all tumors and in all patients?

Do metastases selectively grow in specific organs because of the ambient hospitable temperature (e.g., skin 33°C, lung 35°C, liver 38°C), and if so, is the hyperthermia treatment result more dependent upon the *relative* change in temperature rather than on the absolute temperature achieved? (Storm, in press).

Does in situ thermal tumor destruction augment the immune response? Can the understanding of thermal cell kill kinetics eventually provide a guide to treatment with a prediction of response? And finally, do as yet unrecognized hazards exist, and if so, how might they be remedied? Pragmatically speaking, the answers to these questions will not come from individual achievement, but rather from the cumulative effort of all who are committed to the cure of cancer, including physicians and biological and physical scientists.

The resolve to develop hyperthermia as a potentially fifth form of cancer therapy must be tempered by judgment and logic. It has been said repeatedly that "if cancer were easy to cure, it would have been cured a long time ago." The development of hyperthermia as a clinical tool will depend on rigorously controlled scientific investigation. At this time, human hyperthermic therapy must be considered experimental and should not be used in lieu of proved methods of cancer treatment.

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