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HYPERTHERMIA and CANCER: Human Clinical Trial Experience

Volume I

Ned B. Hornback

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DEDICATION

My Father

Charles Austin Hornback who died of lung cancer in November 1981, a diligent, courageous educator with uncompromising principles, a love of life, and a wonderful gift of storytelling.

PREFACE

With the increasing interest in the use of heat in the treatment of cancer, it was felt that information concerning the general aspects of hyperthermia would be of interest to individuals not familiar with the subject. This book is essentially written from a clinical perspective and is limited in the amount of technical material concerning the highly complicated reactions which occur when physical forces interact with biological tissues. A brief review of basic heat physics and physiology of heat is included to familiarize the reader with physiological responses and problems which may occur when the human body is exposed to heat. The chapters on the biological basis of hyperthermia describe most of the important work that has been performed in the laboratory and form the scientific background for the use of hyperthermia.

It will be noted that the use of hyperthermia at this time should be considered an experimental mode of therapy and should be used only by physicians who are interested and involved in new and experimental methods of cancer research and treatment. Since the treatment is experimental it should be used only in the treatment of advanced cancer patients or patients with recurrent cancer who have failed to respond to currently accepted conventional cancer treatment. Because patients selected for hyperthermia treatments have advanced and usually ''incurable'' cancer, survival is poor and long-term complications are unknown. Even the unlikely possibility that hyperthermia may actually increase the metastatic spread of cancer is reason enough for clinicians to proceed very cautiously when utilizing this treatment method.

Many technical problems plague the physician involved with clinical research. Temperature measurement, hyperthermia equipment design, types of tumors to be treated, temperatures to be achieved, time of heat to be applied, local and regional heating vs. systemic hyperthermia, and methods to measure responses are but a few of the many problems that must be solved before clinical hyperthermia will be accepted as a standard modality of cancer therapy.

Ned B. Hornback, M.D.
1983

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Over 1000 articles and other sources of information have been reviewed in the preparation of this manuscript and while all of the scientific articles in the literature have not been cited, it is felt that the text includes a representative sampling on each subject covered to give the reader an overview of the present "state of the art".

Many individuals have worked tirelessly in the preparation of this book and I am deeply indebted to them for their encouragement and support. I asked my good friend and Chief of our Radiobiology Section, Dr. Robert Shupe, to write the two chapters on heat absorption and temperature measuring devices which I greatly appreciate. In addition, Dr. Shupe has extensively reviewed the entire manuscript and has offered many constructive criticisms. I greatly appreciate Carol Marshall, Nurse Coordinator, for her reviews of the manuscript and helpful suggestions; Pat Kramer, Department Librarian, for her help in locating the many references used in the book; Linda Melton for her untiring work in typing and preparing the manuscript; also Jane Robertson and Marsha Rollings who assisted with typing; and Carol Barrett for her help in checking and collating the references. My special thanks and appreciation to Mary Chitwood, our Department Administrator, for her support, encouragement, and review of the manuscript. I would also like to thank and acknowledge Phillip Wilson for the many excellent line drawings in the chapter on Methods of Hyperthermia, and the Medical Illustration Department, Indiana University School of Medicine, for the drawings in the other chapters.

Ned B. Hornback, M.D.

THE AUTHOR

Dr. Ned B. Hornback is Professor and Chairman of the Department of Radiation Oncology at Indiana University School of Medicine, Indianapolis. Dr. Hornback received his B.S. and M.D. degrees from the University of Wisconsin, Madison. He received residency training in Radiology at Indiana University School of Medicine and is Board certified in Radiology. He is also a Fellow of the American College of Radiology. Dr. Hornback practices therapeutic radiology full time and has held academic positions at Indiana University School of Medicine since completion of residency training. He serves on committees of four national cancer study groups and as site visitor for the National Cancer Institute. He is a member of the accreditation committee of the American College of Radiology and the Joint Review Committee on Education in Radiologic Technology.

Dr. Hornback is the author of 31 papers and is writing the third edition of his *Medical Examination in Therapeutic Radiology* book. He has given over 40 major presentations. He is a member of the leading professional societies in the field of Radiation Oncology and is a member of Sigma Xi Scientific and PHI CHI medical fraternities. He is recipient of many honors and service awards. His primary research interest is in hyperthermia as an adjunct to ionizing radiation and chemotherapy in treatment of advanced malignancies.

HYPERTHERMIA AND CANCER: HUMAN CLINICAL TRIAL EXPERIENCE

Ned. B. Hornback, M.D.

Volume I

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Chapter 1

HISTORICAL ASPECTS OF HYPERTHERMIA

I. USE OF CLINICAL HYPERTHERMIA FOR CANCER TREATMENT IN ANCIENT TIMES

Hyperthermia, or elevation of temperature above levels that are not normally found in our bodies, has been used to treat a variety of illnesses for hundreds of years. Cauterization has been used as a therapeutic agent for cancer since the year 2000 B.C.[1] Records dating back to Homer's era (800 B.C.) describe the healing qualities of hot steam baths in the treatment of many illnesses. Hippocrates[2] felt that heat was beneficial in "tumors" of the skin and stated, "Those diseases that medicines do not cure are cured by the knife. Those that the knife does not cure are cured by fire, and those that fire does not cure must be considered incurable." It is presumed that cautery was used in the treatment of advanced malignant surface tumors in the early times. Hippocrates did not always feel heat was beneficial and warned his students, "Heat produces the following harmful results in those who use it too frequently: softening of the flesh, impotence of the muscles, dullness of the intelligence, hemorrhages, fainting, and death ensuing in certain of these cases." He further stated, "It is better to give no treatment in cases of hidden cancer as treatment causes speedy death, but to omit treatment is to prolong life."

From this statement, one might speculate as to whether Hippocrates had observed that low-level hyperthermia increased the growth rate of tumors, a caveat expressed by a few scientists in later times. From Hippocrates' words, it is evident that even in early times a controversy existed as to whether hyperthermia should be used in cancer therapy.

Even George Bernard Shaw,[3] the famous British playwright, offers his advice on the treatment of cancer by hyperthermia in a quotation which appeared in his play, *Doctor's Dilemma,* "No man is allowed to put his mother into the stove because he desires to know how long an adult woman will survive at a temperature of 500°F, no matter how important and interesting that particular addition to the store of human knowledge may be. If he pleads, 'What! Not even if I have a chance of finding out how to cure cancer by doing it?' Society still says not even then." Since Shaw included only "mothers" in his quotation, it is assumed that he would not object to the use of other relatives, such as mothers-in-law, brothers-in-law, and an occasional recalcitrant child.

II. EARLY MEDICAL WRITINGS ON RELATIONSHIP BETWEEN FEVER AND CANCER

One of the earliest reports appearing in the medicinal literature concerning the possible beneficial effects of hyperthermia on cancer occurred in 1866 in an article written by Busch.[4] In this essay, Busch described a patient with a histologically proven sarcoma of the face which completely disappeared after two episodes of an erysipelas infection. This infection was accompanied by an extreme febrile illness and the patient was reported alive and well without any evidence of tumor 2 years later.

Following Busch's observation, several authors reported similar experiences with the spontaneous regression of primary tumors as well as metastatic tumors following attacks of erysipelas or other bacterial infections which produced a severe febrile response.[5-7]

Vidal[7] described tumor regression in four different patients who developed febrile responses as a result of trauma. The most marked response was noted to occur when the trauma-induced fever was prolonged and elevated above 40°C.

Fehleisen[6] felt that the streptococcal bacteria which was responsible for the erysipelas infection had some property that exerted an antagonistic influence upon the malignant cells. Vidal,[7] however, felt that the elevated temperature of the fever was responsible for remission of the tumor since tumor regression was seen in his cases in the absence of a bacterial infection.

In 1887, Bruns[8] reported an interesting case history of a patient who was terminally ill with multiple wide-spread superficial malignant melanomas who experienced an attack of erysipelas and developed a fever of over 40°C for several days. Shortly thereafter, all tumors completely regressed and the patient was reported alive and free of all disease 8 years later.

Allison[9] described an extremely bizarre event whereby a patient with a carcinoma of the lip was struck by lightning which resulted in complete disappearance of the tumor from the lip.

The earliest concerted effort in the U.S. to use the febrile response from infectious agents to treat malignant tumors was reported in 1893 by Dr. William Coley.[10] Coley began his febrile-producing experiments in April of 1891 after he had observed the curative action of an accidental erysipelas infection in a patient with recurrent, inoperable round-cell sarcoma seen at the New York Cancer Hospital in 1884. This patient was followed by Coley and was alive and well without disease 7 years later.

Over the next few years, Coley treated several advanced cancer patients with attenuated fluid cultures of *Streptococcus erysipelatosis*. The first case was a patient with a recurrent sarcoma involving the neck and tonsil who was treated with boullion cultures of erysipelas injected directly into the wound. Coley reported this patient was alive and free of disease 3 years later.

Coley's first article, which was written in the *American Journal of Medical Science* in 1893, was a detailed history of the treatment and responses of his first ten patients treated with bacterial toxins. He noted that tumor responses were better when the more virulent strains of the bacteria were used. He found that most tumors regressed under treatment regardless of histological type, with sarcomas responding better than carcinomas. During the treatment sessions, temperatures of 104°F (40°C) to 104.5°F (40.2°C) for 24 to 36 hr were attempted but not achieved in every case. Coley had an interesting theory as to the reason why the toxins he used to treat cancer resulted in the regression of tumors. He felt that a microparasitic organism was responsible for the development of cancer and theorized that the streptococcal bacteria produced toxins which destroyed these cancer-causing organisms. In this same article, Coley cited a paper inscribed "Tumeurs Malignes et Maladies Infectieuses" (*Annales de L'Institut Pasteur,* October, 1892) written by Professor Spranck. In this article, Spranck described 26 cases of malignant tumors, 8 of which were sarcomas and 18 carcinomas, into which he had subcutaneously injected the toxic by-products of erysipelas. All cases of the sarcoma improved and one case with the highest fever had complete disappearance of the primary. The highest temperature reached in these patients was 103°F (39.4°C). To quote Sir William Osler,[11] "In science, the credit goes to the man who convinces the world, not to the man to whom the idea first occurs." As evidenced by Coley's original article, he was not the first to produce fever for cancer therapy by injecting bacterial products into tumors, but he certainly received the most publicity because of the many articles he wrote and the considerable controversy he created on the subject of hyperthermia and cancer treatment.[12-14]

Despite Coley's numerous successful reports with the use of these toxins, his results could not be consistently duplicated by others, and some physicians who used these toxins were unable to obtain any response. At about the same time as Coley's experiments, X-rays were discovered (1895), and shortly thereafter, X-ray therapy was introduced as a treatment method for cancer. A great deal of excitement was generated over the discovery of radiation as a treatment for cancer and this revelation tended to decrease the interest in fever therapy and hyperthermia as a treatment for cancer. Coley persisted in his work and was disappointed that others could not duplicate his work. He felt that one of the major problems he and others encountered when using toxins to treat cancer was the inconsistency of the toxins produced and the failure to develop a reliably standard strain of bacterial cultures. Because of his varied results and failure of others to confirm his work, Coley's work with toxin therapy soon fell into disrepute and later made the American Cancer Society's infamous list of unproven methods of cancer therapy, along with Laetrile®, Krebiozen®, vitamin therapy, and other "dubious" cancer treatment methods.

Coley's daughter, H. C. Nauts, has extensively reviewed long-term follow-up of patients treated with Coley's toxins.[15,16] According to Nauts' review of her father's work in which some patients were followed for 35 years, she noted that if the fever had averaged between 38.5 and 40°C, the 5-year survival rate was 60% in the inoperable cases. If the fever reached an average of 38.5°C or less, the 5-year survival rate dropped to 28%, and the highest cure rates obtained were in patients who received febrile treatments for 4 to 6 months. Nauts has theorized a relationship exists between hyperthermia and the prevention of cancer and that the low incidence of cancer of the penis, skin, and breast in Japanese was most likely due to the frequent use of hot baths. (Temperature of these baths normally runs from 42 to 48°C, with rectal temperatures reaching as high as 39°C.)

In 1971, Miller and Nicholson[17] reviewed 52 patients' records with "reticular" sarcoma of the bone who received Coley's toxins either alone or in combination with surgery and/or radiotherapy. All but two patients received high-dose, localized radiation therapy and some patients were followed for as long as 44 years. The overall absolute 5-year survival rate was 64%. The authors, in their review of Coley's material, noted several factors which influenced survival rates. Among those were (1) the stage and extent of disease when the patients were first treated; (2) the timing and dosage of radiation used; (3) the site, dosage, frequency, and duration of the bacterial toxin injections (i.v. or intratumoral injections were more effective than if the toxins were given intramuscularally); and (4) the temperature achieved during the febrile response. (A temperature of at least 101 to 104°F [38.3 to 40°C] with 12 to 15 injections in 3 weeks and 3 to 6 courses over 6 to 12 months was necessary for a good response.) The authors concluded that Coley's toxins were effective in increasing survival rates over those seen in patients with tumors of similar histology who did not receive the toxins. Two particular strains of bacteria were found to be more effective than other strains. These were *Streptococcus pyrogens* and *Serratia marcescens.*

Konteschweller[18] reviewed various products that had been used as pyrogens up until 1918 to determine if any specific group of pyrobens produced a more favorable response. Specific pyrogens reviewed included typhoid vaccines, milk, colloidal selenium, tuberculin, "nucleinate of soda", as well as various bacterial vaccines, antidiphtheria serum, peptones, pollens, and gelatin. Konteschweller felt that there was little difference in mode of action and white blood cell response between bacterial vaccines and colloidal preparations. Following injection of a pyrogen, there was a marked leukopenia which appeared to peak at 1 hr. This was followed by a leukocytosis which occurred at a maximum of 6 hr. The white count began reverting to pretreatment levels and was completely normal by 48 hr.

Soon after Coley's and others' reports on the beneficial effects of fever therapy on malignant tumors appeared in the literature, several investigators began studying the effects of heat against malignant tumors in the laboratory. As early as 1903, Loeb[19] and Jensen,[20] working independently, observed the thermal sensitivity of several different types of malignant tumors.

III. EARLY LABORATORY WORK WITH MALIGNANT CELLS AND HEAT

Lambert,[21] in 1912, was one of the first investigators to compare heat sensitivity of malignant cells to that of normal cells. Using hanging drop cultures, he found that mouse sarcoma cells could survive 43°C for only 3 hr whereas mouse normal proliferating connective tissue cells derived from the aorta could survive for 6 hr at the same temperature. Lambert concluded that connective tissue cells were more resistant to heat damage than malignant cells and that the mouse sarcoma cells were preferentially destroyed over normal cells at temperatures from 42 to 47°C.

Using a different approach, Gosset et al.[22] studied the biological effects of high-frequency electromagnetic radiation emitted by vacuum tube oscillator on tumor-bearing geranium plants. These authors noted that when the plants' tumors were exposed to radio frequencies of 150 MHz for 3 hr, the tumors underwent necrosis after the first exposure day. Sixteen plants were used as controls and tumors without treatment rapidly grew to great size and recurred after excision. No details were reported as to the apparatus used, techniques followed, or temperature measurements taken; however, Gosset felt that increased temperature was not a factor in the regression of the tumors but the tumors regressed because of the specificity of the radio frequency beam.

IV. EARLY LABORATORY STUDIES USING HEAT OR HEAT AND X-RAY ON ANIMAL TUMORS

Although the clinical use of heat in cancer therapy began soon after the turn of the century, it was not until 1921 that reports began emerging from the medical literature concerning experiments studying the effects of heat or combination radiation/heat on neoplasms in animals. Rohdenburg and Prime[23] studied Crocker 189 tumors and spontaneously developing mammary tumors at various temperatures ranging from 42 to 46°C. An enormous number of animals (3248 mice) were used in these experiments where the effect of heat combined with sublethal doses of irradiation was studied. In general, these authors reported that when heat was added to sublethal doses of radiation, regression of malignant tumor growth was noted. The authors concluded that there was a definite synergistic effect when X-ray and heat treatments were combined, as the combination treatment results far exceeded the summation of the effect when the two treatment modalities were used individually. This was especially true at temperatures above 42°C. They also noted that when heat and radiation were applied in sublethal doses, it made little difference which was applied first, as there was a marked lethal effect with the combination. These authors reported the important relationship between the length of time the treatment was given and the temperature reached during the treatment. Lower temperatures (41°C) produced the same result as higher temperatures (46°C), but to be as effective, the lower temperature had to be applied for longer periods of time. In their article, they described the detailed histological effects of heat on malignant tissues. Within 24 hr after exposing rat sarcomas or carcinomas to 20 min of diathermy, an intense congestion of all small blood vessels occurred and within 72 hr, tumor cell outlines became obscure, tissues stained poorly, and karyorrhexis developed. Between 72 and 144 hr, massive coagulation necrosis and areas of liquefaction occurred, and at the 7th day, tumor replacement by fibrosis began.

In 1927, Westermark[24] studied the effects of heat produced by diathermy on rat tumors bearing Flexner-Jobling carcinoma and Jensen sarcomas. Regression of tumor occurred after 180 min at 44°C and 90 min at 45°C, while normal tissues (including skin) were not damaged under the same conditions which were lethal to tumors. Westermark reported that the differential heat sensitivity between cancer cells and normal cells diminished above 42°C and expressed his concern with the inhomogeneous heating patterns that occurred when diathermy was used for heat production.

In 1928, Schereschewsky[25] reported on the action of high frequency currents upon transplanted mouse sarcomas and noted that tumor growth was inhibited with complete disappearance of the tumor in a few cases. In Schereschewsky's experiments, he used variable frequencies from 8.3 to 135 MHz and noted a greater effect on the tumors at frequencies from 66 to 68 MHz than at other frequencies. In his original paper, he felt the lethal action of short-wave diathermy was due to specific wave frequency damage and was not related to the heat produced. In a later publication (1933), he again used variable frequencies of 8 to 135 MHz and measured the rectal temperature as well as the tumor temperature of the exposed mice and concluded that the "curative effects" of the high frequency fields were due to the heating produced rather than any specific frequency effect.

Rapid regression of tumors following heat therapy was also reported by Rohdenburg and Prime,[23] as well as by Pflomm,[26] who treated Jensen rat sarcomas with short-wave treatments of 4.5 length. Pflomm was one of the first authors to describe the effects of marked hyperthermia which occurred in tumor capillaries when heat was applied to the tumor. Hill,[27] in 1934, also reported regression of Jensen sarcomas injected into mice when the tumors were subjected to heat plus sublethal doses of radiation.

In 1937, Jares and Warren[28] injected Wood's sarcoma tumors in over 3000 mice and treated them with various combinations of heat and X-ray. When heat was given prior to radiation, a 49.5% cure rate was obtained as compared to 22.3% cure when the heat was given following radiation. These authors noted that a time interval of 12 to 24 hr between heat and radiation reduced the synergistic effects of combined therapy. The influence of timing the heat and radiation as well as the delay between the two modalities of therapy has been extensively studied by many researchers since that time and will be discussed in greater detail in the chapter on the biological basis of hyperthermia.

Not all of the early work supported the premise that heat potentiates the effects of radiation. Taylor,[29] in 1936, using Jensen rat sarcomas and Walker rat carcinomas as tumor models, injected the tumors into flanks of the animals (rats) and treated some animals with ultrashort radio waves followed by radium and compared them with animals treated with radium alone. No temperature measurements were made in the 245 animals studied; however, Taylor found that heat did not change the growth rate of the tumor unless necrosis was produced and heat did not potentiate the effects of the radium applied later. This is one of the few articles which appeared in the early literature that did not find that heat potentiated the effects of irradiation. Since no temperature measurements were made, nor was there any detailed information concerning the treatment schedules, the time of heat application, etc. it is difficult to evaluate Taylor's work as to why he did not find that heat potentiated the effects of ionizing radiation that others have so consistently found.

V. EARLY CLINICAL STUDIES USING HEAT OTHER THAN FEVER TO TREAT CANCER PATIENTS

Introduction of hyperthermia into human clinical studies other than by fever-produced heat began appearing in the literature at the end of the 18th century. Westermark,[30] in 1898, reported the long-term remission of patients with inoperable carcinoma of the cervix treated with hot baths and local heat applications. No information was available concerning the tumor temperature reached during therapy or the duration of responses obtained.

In 1889, Byrne[31,32] described the use of cautery in the treatment of both operable and inoperable carcinomas of the cervix. Byrne noted the rapid disappearance of most pelvic and perineal pain following cautery of the tumor. When cautery was used in conjunction with surgery, it was unusual for recurrences to be seen in the scar tissue. Even in those patients who developed recurrence or metastasis, a long delay in reactivation of the disease was noted in most cases.

Strauss[33] began using surgical diathermy in the treatment of cancer of the rectum and sigmoid colon as early as 1913. By 1928, Strauss was so impressed by his results, he began