George M. Hahn

Hyperthermia and Cancer

Hyperthermia and Cancer

George M. Hahn
Stanford University School of Medicine
Stanford California

PLENUM PRESS ● NEW YORK AND LONDON

Library of Congress Cataloging in Publication Data

Hahn, George M., 1926–
Hyperthermia and cancer.

Includes bibliographical references and index.
1. Cancer–Treatment. 2. Thermotherapy. 3. Heat–Physiological effect. I. Title.
[DNLM: 1. Fever therapy. 2. Neoplasms–Therapy. QZ 266 H148h]
RC271.T5H33 1982 616.99'40632 82-12368
ISBN 0-306-40958-5

A Division of Plenum Publishing Corporation
233 Spring Street, New York, N.Y. 10013

Printed in the United States of America

Hyperthermia and Cancer

Dedicated to the memory of
DAVID HAHN: 1950–1962

Preface

Hyperthermia as a tool for the treatment of malignant disease is rapidly becoming a clinical reality. In this book I am attempting to summarize the known biological and physical underpinnings that have led to this development. I also present a compilation of existing clinical results, limited as these are. My aim is to provide oncologists and other physicians with up-to-date information on this modality, which is both new and old, as well as to make available to biologists, physicists and engineers summaries of currently available information on specific areas of hyperthermic research.

Many people have helped me with this book. Specifically, thanks are due to Drs. William Dewey, Jean Dutreix, Peter Fessenden, Gloria Li, and Jane Marmor. Their suggestions have been invaluable. I hope that not too many errors and omissions have crept into the volume, but in any case, for these I have only myself to blame. I also wish to express my appreciation to David Betten and Marie Graham for their help.

Most of this material was written while I was on sabbatical leave on the shores of Lake Atitlan in Guatemala. There I enjoyed the hospitality of a gracious, friendly, and proud people who deserve better than fate seems to have in store for them.

George M. Hahn

Contents

1

Introduction
Historical and General Comments

Hundreds of years ago, the Greek physician Parmenides said that given the means to induce fevers he would be able to cure all illnesses. Presumably he meant to include cancer, since malignancies were described in early Greek literature. The effects of elevated temperatures on human physiological functions and, in particular, on the healing process have fascinated clinicians and researchers for many years. Hippocrates described in detail many febrile diseases and commented extensively on the beneficial role of fever. A Roman, Celsus, catalogued the clinical symptoms of inflammation and noticed their association with fevers.

Today, the induction of elevated temperatures (hyperthermia), either locally or over the whole body, has become quite feasible. Whether or not this is a realization of Parmenides's wish is somewhat questionable. Fever is a unique form of hyperthermia in that it is not associated with the failure of a thermal regulatory system but rather with a change in the "set point," i.e., the temperature about which regulation is exerted. This is true not only in humans but also in a wide range of animals. The point is perhaps most graphically illustrated in a fascinating set of experiments involving a poikilotherm, the desert iguana, *Disposaurus dorsalis* (Kluger *et al.*, 1973). These animals were placed in a box in which a thermal gradient had been established by heating one end of the container and cooling the opposite end. The "normal" iguanas consistently settled in one temperature zone. This very primitive regulation, their own motion, established the set point for normal lizards. The reptiles were then injected with a known reptilian pathogen (e.g., *Pasteurella hemolytica*). They promptly moved to a warmer zone, thus inducing a "fever." After further injection with appropriate doses of sodium salicylate, which is a well-known antipyretic agent, the iguanas returned to the cooler location. In these experiments, the movement of the animal was a direct, visual demonstration of the change in "set point" of their thermal regulatory system.

Other forms of hyperthermia, such as heat stroke, the clinical syndrome called malignant hyperthermia, or pharmacologically induced hyperthermias, seem to involve the failure of one or more regulatory systems (Stitt, 1979).

There is one important point that I have not discussed so far. When talking about hyperthermia, what range of temperatures is meant? Before answering this question it is necessary to look at the range of core body temperatures of various animals, as measured under nonpathogenic situations. For humans, the "normal" body temperature has been reported to vary from 35.1 to 37.7°C, while camels seem to show the widest variation in temperature, 34 to 40°C. All other mammals fall somewhere in this range. Obviously, during fevers temperatures may rise to higher values; the maximum in man seems to be about 41.5 to 42°C before severe central nervous system symptoms are encountered. Birds tend to be at higher temperatures; their normal range starts at 37°C, with the highest temperature, a surprising 43.3°C, reported for the abert towhee (Swan, 1974). By hyperthermia I mean temperatures above those encountered under either pathogenic or normal situations. For mammalian cells, temperatures of 42°C or higher may then be regarded as hyperthermic. Obviously a different range needs to be established for avian cells, with hyperthermic temperatures beginning at about 43.5°C. Unicellular organisms can withstand or adapt to much higher temperatures. The eukaryotes capable of withstanding the highest temperatures are the thermophilic fungi. For these there may be an absolute temperature limit slightly above 60°C (Tansey and Brock, 1972). Prokaryotes can exist right up to the boiling point of water. For example, members of the genus *Sulfolobus* have been found in springs whose normal temperature is 97°C, where these organisms reproduce, apparently happily, in water whose pH is 2.4! Brock (1978) has presented an interesting argument for the inability of eukaryotes to evolve members capable of growing at temperatures above about 60°C. Functionally, the thermophilic fungi are quite similar to those prokaryotic heterotrophs that are able to grow at high temperatures. Both are aerobes and can grow on media containing single compounds. Enzymes and other macromolecules of both types of organisms are equally heat stable. Cellular functions such as active transport (and presumably the establishment of pH gradients) occur in both types of organisms at high temperatures; hence, the plasma membrane for both prokaryotes and eukaryotes must be heat stable. The critical difference between prokaryotes and eukaryotes that allows the former to grow at higher temperatures, Brock argues, is therefore neither at the plasma membrane level nor at the macromolecular level but at an intermediate level of organization. All eukaryotes have membranous intracellular organelles (e.g.,

nuclei and mitochondria). It is argued, and it seems to me to be a reasonable argument, that the inability of eukaryotes to grow at high temperatures resides in their inability to retain the integrity of these intracellular membranes. These membranes differ from plasma membranes in that the former must allow for the passage, by diffusion, of large macromolecules. To be able to do this, they must of necessity be relatively leaky and hence not heat labile. Thus, the argument goes, it would be impossible for eukaryotes to construct intracellular membranes that are both thermally stable and functional. I have given considerable space to this argument because of the possible role of membranes in determining the heat death of mammalian cells.

In this book I will deal only peripherally with the effect of fevers on cancer, because I plan to concentrate on the application of externally induced hyperthermias against tumors. That is not to say that fever may not have beneficial effects for some cancer patients. One need only to read the literature of Busch (1866), Fehleisen (1883), and others, particularly Coley (1893), to convince onesself that tumor regression and extension of life span may well be associated with the deliberate or accidental exposure of patients to fever-inducing illnesses or with the injection of pyrogenic bacterial toxins to induce fevers. Much of this literature has been reviewed by Selawry *et al.* (1957; 1958). Pertinent to assessing the role of fever may also be the frequently quoted observation that the rate of cancer incidence is lower in countries whose population is affected by endemic malaria (Dietzel, 1975). However, there are obvious limitations to the role pyrogen-induced fevers can play. The maximum temperature inducible in humans without incurring risks of severe toxic effects is about 42°C. However, as I will show in subsequent chapters, the optimum temperature for treatment of tumors may be much higher. Fevers of necessity raise the temperature in all parts of the body. Yet differential heating of specific malignant tissue is almost surely desirable in those patients suffering from localized or partially localized disease. Finally, after an induction of a fever, cooling is not accomplished very quickly or reproducibly. As a result, it is difficult to speak with any precision of the temperature–time profile resulting from the administration of the pyrogen. Reproducible temperature–time profiles may be of great importance if hyperthermia treatments are to be standardized.

The current expectation that heat should have a useful role in the clinical management of cancer is based not just on the historical anecdotes discussed but on results from recent biological experiments, on the development of equipment designed and capable of heating arbitrary volumes of human tissue, and on preliminary clinical trials. My plan in this monograph is to describe first the existing experimental evidence that

indicates that tumor cells *in situ* should be more sensitive to hyperthermia than normal tissue. This evidence includes the possibility that at least some neoplastic cells are inherently more sensitive to heat than their normal counterparts, although the data supporting this optimistic view are opposed by almost as many negative results. Much more conclusive evidence exists that indicates that the milieu of at least a large fraction of cells in solid tumors makes these particularly heat sensitive. Cells in a poor nutritional environment and cells at low pH appear to be easily inactivated by exposures to temperatures that do not impair the proliferative ability of the cells in a more favorable environment. Many tumors have low blood flow rates; cells away from capillaries may therefore be in precisely the states identified with increased heat sensitivity. I will then proceed to discuss the potential of hyperthermia in conjunction with radiation therapy and chemotherapy. In the case of the interaction of hyperthermia and X irradiation, the evidence is incontrovertible: cells become much more radiation sensitive if exposed to elevated temperatures either shortly before, during, or immediately after irradiation. At present, the question of whether normal tissue is equally sensitized remains unanswered. The interactions of drugs and hyperthermia in cell inactivation present a complicated picture; either appreciable sensitization or protection by hyperthermia can be seen, depending upon the drug and the time sequence of exposure. Unfortunately, only a very limited body of data is available. This field, which deserves much more attention than it has been receiving, offers considerable potential for improving the treatment of patients. In my opinion, most of the benefit to be derived from hyperthermia depends critically on the ability to induce and measure locally elevated temperatures. The physiology of tumors, particularly the inability of many neoplasms to exchange blood rapidly with their normal surroundings, makes it highly desirable to accomplish heating *via* the local deposition of energy. For this reason I shall devote considerable space to describing the means of doing so, either by ultrasound or by electromagnetic techniques. The final chapter will be devoted to a summary of the somewhat limited clinical experience available today.

The literature that I have cited in these chapters is largely limited to works dealing with mammalian systems. I have attempted to quote most of the pertinent results, but the number of papers published that deal with hyperthermia is enormous, and they appear in journals covering many disciplines. Therefore I have undoubtedly omitted many potential references. I apologize to the investigators involved and assure them that no slight is intended.

When it comes to experiments not dealing with mammalian systems, I have selected only those results specifically relevant to points not cov-

ered sufficiently by mammalian data. This by no means implies that work on other organisms has not been done or is less interesting. In fact, two books have appeared within the last few years that deal with areas not covered here. A volume by Alexandrov (1977) primarily describes work on plants and plant cells and makes available to Western readers the vast Soviet literature on the effects of both heat and cold. While the book is not exactly easy to read, I cite it here because it points out clearly how dangerous specialization and parochialism can be. Had mammalian cell biologists been aware of the data described by Alexandrov, many of the recent experimental results obtained with mamalian cells could have been anticipated. Heat-induced heat resistance (thermotolerance) and the effects of ethanol and deuterium oxide on heat sensitivity, to cite only a few examples, were all known to the plant physiologists. The second book is that of Brock (1978); I have already quoted extensively from that work. This delightfully written volume presents a wealth of material on the ways unicellular organisms have evolved to deal with high-temperature environments. Very likely some of the material presented there is also relevant to more complicated biological structures such as mammalian cells.

While the orientation of my book is clinical, I have attempted to include in it much of the currently available information on heat effects as they relate to mammalian cellular and tumor biology. My aim is to attract not only clinicians, but also radiobiologists, tumor biologists, and cell biologists in general. The study of hyperthermia is one of the most fascinating areas of cellular biology active today. It involves many disciplines, from membrane biophysics to histology and morphology. Much of the work that I will discuss originated in my laboratory. This has its advantages and disadvantages. The advantages, e.g., close familiarity with the work and acute awareness of experimental limitations, are obvious. The disadvantages are perhaps less visible. It is impossible to work in a field for many years and not form specific prejudices. I am sure some of these will appear throughout the exposition, and I make no apologies for them. Of course, I do try to present a balanced view, even on subjects where my own inclinations lead me to adopt a particular point of view. For example, I think that damage to membraneous structures is the most likely lesion leading to heat-induced cell death. At the same time I point out in the text that this is far from being a closed subject, and that other "targets," such as chromosomes, may well have equal or greater importance. It must be remembered that only within the last ten years have effects of hyperthermia on cells and tissues been investigated in a systematic way. Very likely, as new knowledge is accumulated, new prejudices will replace the old.

2

Mammalian Cell Survival Responses after Exposure to Elevated Temperatures

2.1. INTRODUCTION

Current concepts of cancer treatment focus on the killing of neoplastic cells. In the case of surgery this is accomplished by excision and physical removal of the cancerous tissue. Radiation and drug treatments require the inactivation *in situ* of the vast majority of individual malignant cells. This must be done without damaging normal tissue to the point where its function is permanently compromised. For many normal tissues such as bone marrow, skin, and the lining of the gastrointestinal tract, functional level is largely determined by the number of stem cells that have maintained reproductive integrity at the end of the radiation or drug treatment. For all of these reasons, the survival kinetics of malignant and normal cells exposed to heat are of considerable importance. Experiments are much easier to perform on cultured cells than on cells *in vivo*, although of course the contribution to cancer research of such investigations depends on their ability to predict behavior of cell populations *in vivo*. Historically, in research on heat effects the tissue culture studies enjoy a rather unique position. It is largely the results of such studies that have fanned the current clinical interest, not the reverse, as tended to be the case with radiotherapy and chemotherapy.

Most of the data that I present in this chapter come from experiments directed toward answering the following critical question: Are malignant cells in tumors frequently or perhaps even invariably more heat sensitive than are cells of surrounding normal tissue? There are at least two possibilities whose realization could lead to an affirmative answer. It is conceivable that the process of malignant transformation itself could involve a step that would cause cells to become more heat sensitive. Many tem-