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# The Physiological Effects of Hyperthermia[1]

**Haim I. Bicher, M.D., Ph.D.**

**In the application of hyperthermia to control cancer, physiological factors such as pH, $pO_2$, and blood flow must be documented *in vivo* at normal and elevated temperatures for both the tumor and its normal host tissue. The present symposium was arranged to gather recent research done in this area and to expose the problems inherent in these efforts.**

INDEX TERMS: Blood, flow dynamics • Hyperthermia • Oxygen

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HYPERTHERMIA is currently being employed in clinical trials to control cancer. The protocols in these trials employ hyperthermia either as the only treatment modality or in combination with other accepted modalities such as radiation therapy and chemotherapy.

The current interest in hyperthermia is prompted mainly by some very interesting radiobiological observations made at the cellular level. *In vitro* studies (1–4) demonstrate that heat-induced lethal damage to cells in culture follows a quasithreshold exponential response similar in shape to cell survival curves obtained for ionizing radiation exposure or treatment with some cytotoxic agents. Different cell lines exhibit widely different thermal sensitivities (2, 3). Heat survival curves at 45.5°C for aerobic and hypoxic cells using CHO cells show that hypoxic cells are more heat sensitive than well oxygenated cells (5). Similar observations were made by Schulman and Hall (6) for V79 Chinese hamster cells and by Kim *et al.* (7) for HeLa cells. Assuming that the W138VA 13/2 RA cells model the malignant cells of a human tumor and WI38 cells model the associated normal tissue, Kase and Hahn (8) observed that the transformed cells are more readily destroyed by hyperthermia. Others (9–13) have also reported that tumor cells are more thermosensitive than normal cells. Just as in the case of ionizing radiation, the response to hyperthermia is also dependent on the phase of the cell cycle during exposure. However, mid-to-late S-phase cells, which are the most resistant to ionizing radiation, are the most sensitive to hyperthermia (4, 12, 14). Gerweck (15, 16) has clearly demonstrated that the lethal response of CHO cells to hyperthermia (41–44°C) increases as *p*H is reduced from 7.6 to 6.7. Hahn (17) has shown that when cells are heated in a salt solution lacking nutrients instead of in a complete medium, thermal sensitivity increases greatly. Another aspect of hyperthermia which may have a great impact on its success is the resistance of cells to subsequent heat treatments. The phenomenon is termed thermotolerance. From studies with mammalian cells in culture (18, 19) it was observed that there is an increase in $D_0$ of a subsequent hyperthermia survival curve. Thermotolerance is induced during a 3–5 hour incubation period at near physiological temperatures after heating for a short time at temperatures greater than 43°C (20, 21).

*In vitro* studies (7, 10, 22, 23) also have demonstrated that hyperthermia combined with ionizing radiation has a synergistic cell killing effect. The importance of the sequence in which heat and radiation are applied has been studied in detail by Sapareto *et al.* (22). The synergistic effect is most pronounced for radioresistant S-phase cells (22, 24). There are no *in vitro* data indicating differential sensitization of cancer cells as opposed to normal tissue cells.

In the recent literature (26–38), several investigators have achieved local tumor control using hyperthermia either alone or in combination with irradiation. Crile (26) studied the effectiveness of hyperthermia and the dependence of cure on the temperature achieved and the length of the treatment period on mouse sarcoma. He also demonstrated the effectiveness of the combination of heat and radiation in the treatment of cancer of the rectum (27). Hartman and Crile (28) applied hyperthermia in the treatment of human osteogenic sarcoma with good results. Cavaliere *et al.* (29) and Morica *et al.* (30) documented the effect of heat on tumor cells in rats and the sparing of normal tissues. Other investigators (31, 32) had similar data showing normal tissue sparing with the combined modalities. Recent clinical reports (33–38) clearly demonstrate that hyperthermia, particularly in combination with irradiation, can prove to be a very useful modality in the treatment of cancer.

*In vivo* results do not always agree with the *in vitro* observations made under controlled conditions. This is probably due to the interaction of various physiological factors not present in the *in vitro* systems. An interesting example is the conflict between the *in vitro* results of Sapareto *et al.* (23) and the *in vivo* results of Law *et al.* (25)

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[1] From The Department of Therapeutic Radiology, Division of Radiation Biology and Physics (H.I.B., Division Head), Henry Ford Hospital, Detroit, MI 48202. Submitted for publication 5 April 1980; accepted 1 July 1980.

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when combining hyperthermia and irradiation. The *in vitro* results indicate that, with heating time adjusted to achieve the same killing from heat alone at various temperatures, a decrease in temperature increases the relative killing from the interaction of radiation and heat. This is in contradiction to the *in vivo* results (25) which indicate that the opposite should occur.

In order to fully make use of *in vitro* observations made under controlled conditions in the application of hyperthermia to cancer control, the physiological factors such as *p*H, oxygen consumption, nutrients, and blood flow of both tumor and normal host tissue should be measured *in vivo*. Furthermore, these factors should be documented not only at normal temperatures but also under hyperthermic conditions. Under certain conditions a selective destruction of tumor tissue might be possible with normal tissue sparing. For example, several studies (39–42) indicate that *p*H of fluid in human and rodent solid tumors is lower than the normal tissue *p*H of 7.4. Paramount among the other factors which may change and subsequently influence the response of cells or tissues to supranormal temperatures are the vascular changes, blood flow response and the net result of this on tissue oxygenation. The last factor may change the effect of both hyperthermia and radiation therapy when used in combination. Insufficient information is available on the temperature modifications of tumor blood supply, tumor oxygen tension and consumption and respiratory gas exchange by malignant cells *in vivo*.

This symposium on the physiological effects of hyperthermia was arranged in order to assemble recent research on the physiological response of normal and tumor tissue to hyperthermia.

Haim I. Bicher, M.D., Ph.D.
Staff Radiotherapist
Head, Division of Radiobiology and Physics
Henry Ford Hospital
Detroit, MI 48202

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#112 09/30/99