INTRODUCTION

The use of hyperthermia for the treatment of cancer by physicians in the modern era began with the observation by Busch\(^5\) in 1866 that a facial sarcoma in one of his patients regressed and resolved completely following two sustained febrile episodes of erysipelas, a streptococcal infection. Two years after the high fevers, the patient remained tumor-free. In 1893, Coley\(^8\) induced systemic hyperthermia in cancer patients, using injections of erysipelas initially and a mixed bacterial toxin later.\(^9\) These experiments followed his observation of the complete disappearance of a recurrent sarcoma in a patient who also developed an intercurrent streptococcal infection with prolonged high fever and was found to be completely tumor-free seven years later. His first ten cancer patients were treated with toxin-induced hyperthermia that ranged from 38 to 40.2\(^\circ\)C.\(^8\) With Coley's studies, hyperthermia first became a part of the oncologist's armamentarium for the treatment of cancer.\(^10\)

In 1898, Westermark conducted hot water through metallic tubes placed in proximity to the uterus in patients with endometrial carcinoma. He was able to produce selective necrosis in the tumor without damage to normal uterine tissue.\(^46\) In 1935, Warren devised a heating cabinet with which he produced whole body hyperthermia in patients with disseminated cancer.\(^45\) His studies followed observations of sarcoma resorption following systemic hyperthermia in a patient with both systemic and cutaneous metastases. Patients in his series were treated with systemic hyperthermia at 41.5\(^\circ\)C for five hours with encouraging results.

Shortwave and microwave diathermy have been used for more than forty years in departments of physical medicine and rehabilitation to produce deep heating of muscle masses for the relief of spasm, for the reduction of tissue inflammation and to increase circulation locally in various areas of the body.\(^24\) Schliephake\(^32\) in Germany described the use of shortwave therapy in physical medicine in 1938. Soon after the introduction of radar during World War II, Krusen\(^20\) utilized microwave diathermy for deep heating of localized areas. Since then, microwave heating has remained a standard technique in the field of...
physical medicine. During the last fifteen years, microwave energy has become the most widely utilized modality for producing localized adjuvant hyperthermia in the treatment of cancer.

RATIONALE

Biochemical and clinical studies by Cavaliere and his associates\textsuperscript{6,7} beginning in 1967 demonstrated convincingly that there is a selective vulnerability of cancer cells to hyperthermia, as compared with their tissues of origin. In vitro and in vivo studies have also confirmed the differential thermal sensitivity between cancer cells and their tissues of origin.\textsuperscript{15,18} This differential sensitivity can be utilized therapeutically in cancer patients by heating the neoplastic tissue to a tumoricidal level that can be tolerated by the host tissue in which it is growing.\textsuperscript{18} The difference of thermal sensitivity between normal and neoplastic cells varies with individual histological types,\textsuperscript{18,26} and determines the "therapeutic range" for treatment with hyperthermia in a specific tissue or organ.

It has also been established that hyperthermia produces sensitization of mammalian cells to ionizing radiation.\textsuperscript{18} Hypoxic tumor cells are relatively radioresistant, but are sensitive to hyperthermia. The rationale for the increasing clinical use of hyperthermia in combination with ionizing radiation during the past fifteen years has been based in large part upon its radiosensitizing capability.\textsuperscript{26} The increase in the thermal enhancement ratio (TER) is defined as the ratio of the effect of the combined therapeutic regimen compared with the effect of the radiotherapy alone. It has been demonstrated that the TER obtained when hyperthermia is added to ionizing radiation treatment is approximately 1.5 for a number of tumors.\textsuperscript{18,26}

Another factor that has strong influence on cell survival is its position in the cell cycle at the time of exposure to radiotherapy. Cancer cells are significantly more radioresistant in the late S phase.\textsuperscript{18} The influence of cell cycle position on the hyperthermic response indicates that there is a peak in hyperthermia resistance from late G\textsubscript{1} phase to early S phase, whereas cells in late S phase are extremely sensitive to hyperthermia. It is clear that the combination of hyperthermia with radiation therapy is likely to be more effective for killing cancer cells than is either agent alone.

BIOLOGICAL EFFECTS

In addition to its antineoplastic effects, hyperthermia has a marked effect on local blood flow in the thermal field. It induces vasodilatation in tissues with moderate levels of temperature elevation (40-43°C).\textsuperscript{34} As long as the blood