

Dewey W C, Hopwood L E, Sapareto S A & Gerweck L E. Cellular responses to combinations of hyperthermia and radiation. *Radiology* 123:463-74, 1977.

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The effects of hyperthermia complement those of ionizing radiation in that cells resistant to radiation are selectively killed and radiosensitized by heat. These resistant cells synthesize DNA or exist under hypoxic, acidic conditions and would be expected to occur in tumors. [The SCJ® indicates that this paper has been cited in over 305 publications.]

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We wrote the *Classic* manuscript because Ed Epp invited me to review the cell biology of hyperthermia at the annual meeting of the Radiological Society of North America in December 1975. This invitation resulted from the emerging interest in hyperthermia applied to cancer therapy. For this reason, the late J. Eugene Robinson had organized the First International Symposium on Cancer Therapy for Hyperthermia and Radiation in the summer of 1975. At this first symposium, interest was rekindled in the treatment of cancer by hyperthermia, which first occurred in Egypt as long as 5,000 years ago.

Arthur Westra deserves the credit or blame for getting me involved in hyperthermia when in 1969 he worked in my laboratory at Colorado State University as a postdoctoral student. His quantitative studies as a graduate student of the survival of mammalian cells after exposure to heat or heat combined with radiation suggested that we should investigate the effect of heat during the mammalian cell cycle. Indeed, a selective effect of heat on the radioresistant S-phase cells was observed and was associated with the induction of chromosomal aberrations.

We determined from the thermodynamics of hyperthermic cell killing that if the temper-

ature was increased 1° C, the treatment time for an isoeffect must be decreased by a factor of 2. This relationship gives an activation energy of 140 kcal/mole and suggests that protein denaturation is involved in hyperthermic damage. L.E. Gerweck expanded our observations to include selective heat radiosensitization of S-phase cells. S.A. Sapareto and L.E. Hopwood further illustrated the development of thermal resistance as cells were heated over three to four hours, and Gerweck showed that the interaction between heat and radiation depended on the sequence between the two modalities. Subsequent work has supported these findings.¹⁻⁴ From a practical point of view, our thermodynamic analysis has resulted in the definition of a thermal-isoeffect dose,⁵ which is currently being used in biological and clinical studies to specify the amount of heat delivered during treatment.^{3,6}

Our manuscript has been cited by various scientists working in the interdisciplinary field of hyperthermia. The engineers, physicists, and clinicians are interested in the time-temperature relationships discussed, and clinicians and biologists are pursuing the biological concepts involving differences in heat sensitivity during the cell cycle and the selective effect of heat on cells existing under low pH or nutritionally deprived conditions. Furthermore, the phenomenon of thermal tolerance or resistance is bringing the molecular biologists into the field as the induction and role of heat-shock proteins is being investigated. Clinical studies are encouraging as they indicate that by combining heat and radiation, a 50 percent partial and complete response rate for tumors can be increased to 75 to 80 percent. As methods are being improved for delivering heat to tumors, we are attempting to exploit the biological rationale for applying hyperthermia combined with radiation and/or chemotherapy to the treatment of cancer. Without this biological rationale, there is little point in utilizing hyperthermia because energy can be deposited selectively in tumors much more easily from ionizing radiation than from hyperthermia delivered by ultrasound, radiofrequency currents, or microwaves.

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3. Overgaard J, ed. *Hyperthermic oncology 1984. Volume 2. Review lectures, symposium summaries and workshop summaries: proceedings of the 4th International Symposium on Hyperthermic Oncology held at Aarhus, Denmark, 2-6 July 1984*. London: Taylor & Francis, 1985. 385 p.
4. Spiro I J, Deuman D L & Dewey W C. Effect of hyperthermia on CHO DNA polymerases α and β . *Radiat. Res.* 89:134-49, 1982.
5. Sapareto S A & Dewey W C. Thermal dose determination in cancer therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 10:787-800, 1984.
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