International Journal of Hyperthermia

ISSN: 0265-6736 (Print) 1464-5157 (Online) Journal homepage: informahealthcare.com/journals/ihyt20

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*Int. J. Hyperthermia*, December 2005; 21(8): 675–677

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**FORWARD**

# Thermal medicine, heat shock proteins and cancer

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This special issue of the *International Journal of Hyperthermia* represents the proceedings of a workshop entitled 'Thermal medicine, heat shock proteins and cancer'. It was held on 31 March 2005 at the Natcher Centre on the National Institutes of Health campus located in Bethesda, MD. The principal organizer of the workshop was Dr Elizabeth Repasky on behalf of the Society of Thermal Medicine (STM) and it was held in conjunction with the 2005 STM annual meeting.

References to the treatment of human disease, including cancer, with elevated temperatures have been recorded since the dawn of recorded history. A famous aphorism attributed to Hippocrates ends with 'what cannot be cured with fire must be deemed wholly incurable' at ~400 BC. Early methods included hot pokers applied to superficial tumours and treatment with the dung from cattle with bacterial infections, early non-specific immunotherapy, which also caused fevers. There were numerous anecdotal reports in the 19th and early 20th century describing remission of a variety of tumours using both localized and systemic means of inducing hyperthermia. Unfortunately the methods used were mostly uncontrollable providing unpredictable results. With the discovery of radium and x-rays and the advent of radiation therapy, with its attendant dose-response relationships, interest in hyperthermia was substantially diminished. Around 1960–1970 more modern methods of cell and molecular biology were applied to revive interest in hyperthermia and restart research efforts once again.

Almost exactly 30 years prior to this workshop (28–30 April 1975) the first 'International Symposium on Cancer Therapy by Hyperthermia and Radiation' was held, also in Washington, DC. That meeting, which was organized by Morris J. Wisenberg and J. Eugene Robinson, led to a number of conclusions, most of which have stood the test

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ISSN 0265–6736 print/ISSN 1464–5157 online 
DOI: 10.1080/02656730500272856

of time and have formed the basis for much of the work done over the intervening 30 years. The proceedings of that symposium can be summarized as follows:

- Heat shock causes a significant reduction in cellular metabolism.
- Cancer cells are preferentially sensitive to the effects of heat. (This conclusion did not stand the test of time.)
- Ionizing radiation is supra-additively enhanced by heat, probably by the inhibition of DNA repair mechanisms.
- The cytotoxicity of some common chemotherapeutic drugs is also supra-additively enhanced by temperatures as low as 40°C.
- Data was presented quantitatively describing heat induced resistance to subsequent heat shock. This phenomenon is now referred to as thermal tolerance.
- Methods for delivering hyperthermia clinically were crude consisting primarily of systemic application or isolated limb perfusion. Reliable locoregional devices were in their infancy.

Remarkably, most of the conclusions, with one exception, of that meeting stood the test of time and continue to provide a strong rational for clinical use. It is now known that an apparent preferential sensitivity of tumour cells to hyperthermia arises as a result of tumour biology, ischemia, lowered pH, etc., rather an intrinsic sensitivity resulting from the transformation to malignancy. What is perhaps notable by its absence is any mention of the heat shock proteins or the stress response and only a single page was devoted to the possible role of immunology. The heat shock proteins (HSPs) are now known to be central to virtually every aspect of how a cell copes with thermal as well as other stresses. They, and their possible role in immunological responses and the development of possible anti-tumour vaccines, are an exciting focus of these proceedings.

This workshop was primarily intended to be an educational primer to bring individuals from many disciplines up to date on the subject matter presented. As a result, this Special Issue contains 12 articles that cover a wide variety of topics from general background on radiobiology to the cellular and molecular involvement of the HSPs in immunology to the improved methodology that has been developed for clinical hyperthermia delivery.

The mechanisms of how cells respond to changes in their thermal environment are elegantly discussed by Lepock, where he presents compelling evidence for thermal denaturation of proteins as the sensed event to trigger the overall stress response. Central to this hypothesis are the properties of the HSPs as molecular chaperones where he contends that negative regulation by constitutive HSPs is overcome under stressed conditions releasing the transcription factors that ultimately regulate all downstream activity. Three contributions from Calderwood et al., Wang et al. and Chen and Evans describe the rapidly expanding understanding of the involvement of the HSPs in tumour immunity. Once thought to be simply intra-cellular chaperones it is now clear that the HSPs are expressed on the surface of a variety of human tumours, even in the absence of heat stress, and have been detected in the extra-cellular milieu. They are also shown to be involved in lymphocyte trafficking and dendritic cell activation and their interactions with antigen presenting cells (APC) highlight the potential for the development of anti-tumour vaccines. Along these same lines, Ohtsuka and Saito describe the beneficial effects of chemical inducers of molecular chaperones, including HSPs, on mouse survival after tumour implantation and the lifespan of nematodes. Other roles for the HSPs centre on their interaction with telomerases known to exist in tumours (Pandita) and with DNA repair mechanisms. In an opposite approach, Coss suggests that inhibition of the stress response

may be exploited to enhance anti-tumour modalities that kill tumour cells by inducing apoptosis and/or necrosis.

Another area of significant progress over the past 30 years has been the development of methodology for the induction of systemic, locoregional hyperthermia and thermal ablation therapy. Stauffer provides an extensive review of the methodology that has evolved for locoregional heating including electromagnetic and ultrasonic techniques suitable for both external and interstitial and intra-cavitary application. He describes the evolution from the single element simple systems of the 1980s to the multi-element site-specific conformal arrays which provide far greater spatial control than previously available. Since the thermal ablation methods described by Diederich and by Haemmerich and Laeseke involve peak spatial temperatures between 50–90°C, the primary mechanism of tumour cell killing, coagulation necrosis, is significantly different than for the lower temperature ranges. Nevertheless, the edges of thermal ablation temperature profiles fall into the lower temperature ranges and consequently the same limiting factors apply to these methods as apply to the more conventional methods.

Since the early 1980s, conventional wisdom has dictated that temperatures for clinical locoregional hyperthermia treatment should be 43°C and that at most one or perhaps two heat fractions should be given per week. These considerations were based primarily on the hyperthermic biology of rodent tissues and on the premise that, even in combined modality treatment with radiation, heat cytotoxicity and the avoidance of thermal tolerance were the paramount considerations. This view persisted, despite compelling evidence to the contrary that has developed over the past 25 years, which was largely ignored. In the first contribution by Corry and Armour and the last by Dewhirst et al., buttressed by the evidence presented by Song et al. on hyperthermic tumour reoxygenation, this conventional view of clinical treatment design is directly challenged. It is their contention that unrealistic temperature goals coupled with sparse heat fractionation have led to sub-optimal protocol design compromising clinical outcome. Only future experimentation with the 40–42°C temperature range and denser heat fraction can evaluate these concepts.

Since the primary goal of this workshop was educational, to present current concepts of hyperthermic treatment of cancer, it was necessarily somewhat superficial covering many topics while leaving in depth discussions to other forums. Nevertheless, it was ultimately clear that the rational for the application of elevated temperatures to cancer therapy was broader in scope and more compelling than ever.