[CANCER RESEARCH (SUPPL.) 44, 4906s–4907s, October 1984]

# Conference Summary[1]

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Five years ago, the American Cancer Society sponsored a workshop on hyperthermia similar to the one held in Tucson (13). It may be useful to compare the state of knowledge that existed at that time with that described in the various articles in this supplement. One area where progress, if that is the appropriate word, has undoubtedly occurred is in the number of papers published. Without question, more articles on various aspects of hyperthermia have appeared within the last 5 years than in the 50 years before the 1979 meeting. Whether or not our understanding of thermal biology or our ability to control cancer with heat has made similar advances is, unfortunately, far from clear.

The main question in cellular thermal biology is, just as it was 5 years ago, "What are the molecular events that cause a mammalian cell to die after it has been exposed to mildly elevated temperatures (8)?" Our knowledge in this respect is really not greatly advanced. We are certainly more aware of the complexity of events that lead to the demise of the cell. Much attention has been drawn to the role that energy metabolism before heat exposure plays (9, 15), and considerable work has been done to catalogue the damage that heat does to plasma membranes (3, 11). This former research is of importance because it may point to ways of improving the killing of some human tumor cells *in vivo* by manipulating glucose metabolism; the latter work is interesting not only because it may describe the initial heat-inflicted lesion but also because it may lead to ways of killing nutrition-deprived tumor cells *in vivo*.

Another area where advances have been made is in our appreciation of the importance of thermotolerance and its possible relationship to inherent heat sensitivity; much effort is being expended in clarifying its relationship to the heat shock proteins. The importance of thermotolerance in the clinic is also becoming more and more recognized; its effect on heat-induced X-ray sensitization (4), as well as on drug response (11), makes it an important phenomenon that affects all aspects of hyperthermia.

The correlation between levels of some heat shock proteins to thermotolerance and thermal resistance is an area that has developed in the last years. If, as Li (12) suggests, the $M_r$ 70,000 heat shock protein can be used as an indicator of thermotolerance and resistance, then a major effort should be made to obtain monoclonal antibodies against this protein, so that these can be used diagnostically. The availability of such an antibody might lead to the development of an assay for the thermosensitivity of tumors.

The response of cells to many anticancer drugs is modified by the temperature at time of exposure and by the temperature history of the cells (6). Surprisingly, little work has been done in the former area. While the number of known drugs with cytotoxic action that is increased at elevated temperatures has increased somewhat, work on basic mechanisms has lagged. There are, of course, exceptions to this statement (14). Some results are becoming available on the importance of thermotolerance in modification cytotoxicity of drug exposure. This is shown, for example, by studies involving different drug killing by different rates of heating (10).

Much interesting and potentially useful work has been done in the last 5 years in describing the differential effects of heat on blood flow in tumors and normal tissue (18). These experiments have all been done with rodent systems, so that some doubt remains as to their relevance to the clinic. Data on human tumors are badly needed, although in their absence, experiments on tumors in outbred animals would certainly be useful. Should it develop that human tumors behave qualitatively as do the rodent tumors, then surely modulation of blood flow is an area where tumor-specific heat effects can be orchestrated.

Without question, if one subject can be said to have dominated this meeting, it is the difficulty of achieving "adequate" temperature distributions within human tumors with noninvasive heating techniques. Five years ago, we were much more sanguine in our view of the difficulties involved in treating arbitrarily located lesions (13); but, in the proceedings of this meeting, we read over and over again that uniform heating of any tumor is not an easy task and that heating of some lesions appears to be impossible with currently available equipment. We are beginning to appreciate the fact that it is the lowest tumor temperature that very probably determines tumor response to hyperthermic treatment, although how much of the tumor has been heated appropriately must be of equal importance. Hence, knowledge of the existence of cold spots becomes essential. Blood flow is the chief culprit as far as tumors at or near body surfaces are concerned. For deep-seated lesions, the additional difficulty of depositing energy where desired (without excessively heating normal tissue) becomes equally important.

Another serious problem is that techniques of temperature measurements have not advanced to the point where noninvasive methods are more than theoretical concepts. Thus, for these deep-seated lesions, it is still very difficult to obtain temperatures at more than a few isolated points. Theoretical modeling may help in relating temperature measurements at isolated points to tumor temperature distributions (17). The optical measurement devices that have been developed in the last few years do make it an easier task to measure temperatures in electromagnetic fields. In addition, multiple sensor thermocouples and multiple optical sensing elements are now becoming commercially available. Therefore, temperature measurements, in superficial tumors at least, are becoming much more sophisticated; this in turn should establish the possibility of relating measurements at a number of points to predicting temperature distributions throughout the tissue of interest.

When it comes to assessing the results of clinical studies of localized heating, I will not repeat the careful analysis done by Stewart (19). But I do want to reiterate that it has become clearly established that the response rate of tumors, whether measured as percentage of total or of partial regressions, is clearly increased when heat is added to radiation therapy. Thus, in this sense at least, heat certainly has efficacy. This finding certainly constitutes a major advance. While most studies seem to indicate that these improved responses occur at little additional normal tissue toxicity, this is an area that still needs more careful study. As was pointed out in the discussion of the final session of this conference (7), we have only looked at short-term normal tissue

[1] Presented at the Workshop Conference on Hyperthermia in Cancer Treatment, March 19 to 21, 1984, Tucson, AZ.

damage. Whether or not long-term effects of radiation damage are accentuated by heat, only time will tell. If, however, animal data are of any help here, the suggestion would be that damage from heat alone appears quickly, and as is very likely, long-term damage from heat will not turn out to be a serious problem.

The difficulty that is associated with localized heating of deep-seated lesions by noninvasive means suggests several approaches. The first is to concentrate on those tumors that can be heated with interstitial devices. The number of such tumors is not inconsequential. Unfortunately (or fortunately, depending on one's point of view), as pointed out by Aristizabal (1), radioactive implants in some sites can yield tumor responses approaching 80 to 90% even in the absence of heating. Thus, for such tumors, it becomes extremely difficult, if not impossible, to demonstrate that the addition of heat improves response rates even further. For Phase III studies, we must choose implant sites that historically yield relatively poor response rates, ideally 20 to 40%. If such sites or tumor types can be identified, then meaningful Phase III trials comparing brachytherapy alone with brachytherapy plus heat could be initiated as soon as protocols are written and approved, and results can be obtained in a relatively short time. Other approaches might combine hyperthermia with biological modifications to improve tumor responses. Dr. Robins (16), already discussed the systemic use of lidocaine; this agent, the physiological and toxic effects of which have been well studied, behaves like a heat dose-modifying factor, reducing the temperature (or duration of treatment) required to achieve a given level of cytotoxic effect. Another approach that appears promising is to attempt to increase the absorption of electromagnetic (or possibly ultrasound) energy into the tumors. Surgical implantation of ferromagnetic "seeds" has already been discussed (2). Even much simpler techniques, such as the injection into the tumor of hypertonic saline, might have beneficial effects.[2] Finally, thermotolerance might be used to protect critical normal tissue as discussed by Fajardo (5).

Whole-body heating is relatively easily accomplished without the physics problems associated with local or regional heating. There are, on the other hand, biological limitations. It is generally agreed that temperatures of 42° or higher have associated with them unacceptable toxicity risks. Although whole-body heating of patients has been carried out since about 1970, no randomized studies have been performed to establish the efficacy of the technique. Yet it would seem that such studies are relatively easy to set up, and a comparison of heating of patients to 38° *versus* 41.8°, for example, would go far to settle this question. Such trials should be established as soon as possible. Perhaps more difficult would be randomized studies comparing heat plus drug with drug given at normothermic temperatures, because of the difficulty of drug selection and scheduling. Nevertheless, such trials also are feasible and should be carried out at least for one or 2 drugs (chosen, perhaps, on the basis of efficacy in culture and in animal model systems, as well as for activity in the clinic). With the equipment described at this meeting by Robins (16), such studies might not be excessively expensive and go far toward proving or disproving the value of whole-body thermochemotherapy. Even more difficult, although again not impossible, would be a meaningful clinical study comprising whole-body heating and localized radiotherapy with radiotherapy only.

Again, to emphasize what I have put forth, the dominant subjects discussed at this conference were: (*a*) thermotolerance, its relation to heat response, and response of heat and radiation (or drug); and (*b*) the difficulties associated with heating tumors and determining temperature distributions of deep-seated tumors and adjacent normal tissues. Thermotolerance affects almost all cellular responses, but its adverse effects on tumor responses can be overcome by careful fractionation, once we know more about the kinetics of tolerance induction and decay in human tumors. Whether or not the problem of heating arbitrary tumor volumes to desired temperature distribution can also be solved is a different matter. It would appear that, in some situations, we are already pushing heating techniques to the limits of physical laws. Therefore, it may be up to biologists and physiologists to provide the intratumor environment that will either facilitate heating or increase response at low temperatures or both.

It is natural in a workshop such as this to concentrate on problems. Nevertheless, the tone of the conference was, on the whole, quite positive. Hyperthermia offers so many avenues for potentially improving cancer treatment, and only relatively few of these have been explored in the clinic. In particular, drug delivery and drug efficacy can potentially be improved substantially via the judicious use of localized heat. Perhaps the American Cancer Society will sponsor another meeting on hyperthermia 5 years from now. Hopefully, then we will hear about proven clinical efficacy not only of heat and X-irradiation but also of heat and chemotherapy.

[2] R. L. Jirtle and W. T. Joines, private communication.

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*Cancer Res* 1984;44:4906s-4907s.