Correspondence


The recent article by J. Overgaard (2) describes striking ultrastructural changes in murine mammary carcinoma cells undergoing cytolysis after exposure to hyperthermia in vivo. The author suggests that these changes are characteristic of cell death induced by increased activity of lysosomal hydrolases in the more acidic intra- and extracellular milieu of the tumor.

We state with great satisfaction that Dr. Overgaard has confirmed by his excellent ultrastructural investigations our previous findings on the therapeutic consequences of the close correlation among heat, lysosomal activity, and acid milieu of the tumor.

Since the early 1960's, we have been working on the theoretical and practical fundamentals of the Cancer Multistep Therapy (CMT) concept. The guiding principles and technical essentials of CMT procedure and evaluation are in our comprehensive book (3) and in a review (4). A series of recent papers published since then show our attempts to develop further and simplify the CMT concept. These articles will not be considered in this correspondence.

A brief definition of the CMT concept follows. The CMT is characterized by the combination of certain weak agents on particularly sensitive systems of the tumor cell. The 2 main steps are: (a) a marked increase in tumor cell glycolysis by controlled long-term infusion of glucose into the blood stream until steady-state conditions are reached in the tumor (optimized tumor hyperacidification), and (b) a temporary increase in body temperature to, e.g., 40°, generated by the stimulated metabolism due to the glucose infusion and supplemented by local hyperthermia in the tumor region by high-frequency diathermy. This double attack fortifies especially systems of the tumor cell. The 2 main steps will not be considered in this correspondence.

Chart 1 in Dr. Overgaard's paper (Ref. 2, p. 986) is a nearly perfect illustration of our therapy concept, although it does not consider increased tumor cell glycolysis by glucose infusion. The specific inactivation of tumor cells by heat and the relative unresponsiveness of normal cells to hyperthermia have been studied in this laboratory (Ref. 3, pp. 117, 190, 194, 215, 226) as a precondition for application of hyperthermia in the CMT concept. The increased acidity of tumor cells, its further stimulation, and its therapeutic exploitation have also been investigated extensively (Ref. 3, pp. 129, 197, 199, 511, 532, 705), as has the importance of lysosomal cytolytic mechanisms (Ref. 3, pp. 320, 358, 470). On the basis of theory and experiment, we proposed the idea of the lysosomal cytolysis chain reaction (Ref. 3, pp. 591).

We can therefore state that Dr. Overgaard's findings that "a high lysosomal activity may be of primary importance in the tumor cell injury in vivo," that "damage to the lysosomal membrane is observed in tumor cells early after heat treatment," and that "a more acid intra- and extracellular milieu may intensify the activity of the lysosomal acid hydrolases" are in full agreement with our thoughts (Ref. 3, pp. 384, 407, 433, 470, 517).

Finally, the statement that "the malignant cells that give rise to regrowth of the tumor are situated mainly in the peripheral areas" (2) was also predicted on the basis of theoretical considerations (Ref. 3, pp. 375, 684). As a consequence, we introduced an immunological step into the framework of the CMT concept (Ref. 1; Ref. 3, pp. 565, 603). These remarks demonstrate the necessity of mutual and continuous communication among scientific groups working in the same field.

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The comments by Dr. von Ardenne and Dr. Krüger deal with the important observation that the environment may influence the hyperthermic tumor cell response. Current studies have shown that factors characteristic for the tumor cell environment, such as low oxygen tension, insufficient nutrition, high acidity, and nonproliferating cell status, all tend to increase the hyperthermic sensitivity (2, 4). Probably, the pH is the most important of these factors. It seems that moderate hyperthermia (41-43°) may be of importance.

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in future cancer treatment, since it especially favors destruction of tumor cells situated in the central core of solid tumors. In general, these cells are less sensitive to other modalities such as radiation and chemotherapy and are the potential source for local treatment failure and tumor recurrence. Clinical application of hyperthermia may, therefore, be most successful if the treatment is combined with other modalities, among which radiation therapy for a number of reasons seems most favorable (4).

The paper in question (1) is one in a series of studies involving the pathology of heat damage, which has been a subject of interest for our group for more than 40 years (3, 4). The ultrastructural observations demonstrated basic pathophysiological mechanisms occurring in a solid tumor following a moderate hyperthermic treatment. The hypothesis discussed in this paper (1) was based on the electron microscopic observations indicating that a primary cytoplasmic destruction dominated by an increase in number, size, and activity of the lysosomes occurs in tumor cells following hyperthermic treatment. However, direct damage to the lysosomal membrane was not found to be a primary effect, but seemed to be a secondary result of the general cytoplasmic destruction.

This is in contrast to the Cancer Multistep Therapy (CMT) concept formulated by Dr. von Ardenne (5). The CMT concept is rather complex and involves a number of steps in a postulated manipulation of tumor cells and, especially, their lysosomes. In Ref. 5 it is stated that "the structural proteins of the lysosomal membranes form the main target in the concept of the multiphase therapy of cancer," and it is postulated that the effect of hyperthermia and the induced hyperacidity is due to damage to "essential structural proteins of cancer cell membranes." However, hyperthermia is only one among a number of different modalities used in the concept.

I also hypothesized that the lysosomal activity may be further intensified by an increased lactic acid accumulation in the heated tumors. This was mainly based on reports by other authors which showed that hyperthermia changes the metabolism in malignant cells to a relatively higher anaerobic glycolysis following a selective inhibition of the respiration (see Refs. 2 to 4).

These endogenous changes in cell metabolism are also in disagreement with the CMT concept. Dr. von Ardenne notes that an increase in tumor acidity "only results from the increase in the blood glucose concentration over a prolonged period of time," e.g., following a 30-hr period of glucose infusion (5).

The above-mentioned differences are major and principal divergences between the theory of Dr. von Ardenne (5) and the hypothesis described in my publication (1). Therefore, I do not feel that the present observations or hypothesis have in any way adopted the principle of the CMT, and I do fully recognize Dr. von Ardenne’s priority to that concept.

The postulated hypothesis for the destructive mechanism of hyperthermia in solid tumors was, in fact, unaltered from what we had discussed in previous papers on this subject (3, 4). The observation that lysosomes and changes in pH play an important role for the cytoplasmic destruction of the cells is not surprising, since such mechanisms are involved in many pathological cell processes.

I appreciate the fact that Dr. von Andenne called my attention to an English explanation of his CMT concept, of which I was not aware, and which may have a place among the references in the discussed publication. A general discussion of Dr. von Ardenne’s work was, however, included in one of the references (Ref. 9, cited in Ref. 1).

I agree with Dr. von Ardenne’s final remarks. I feel that many scientists would be appreciative if the massive and interesting work of Dr. von Ardenne could in the future be published in the same international journals as most other hyperthermic studies. This would undoubtedly stimulate international communication and be beneficial for future hyperthermic research.

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