editorials

Heat as Cancer Therapy

Recent clinical reports of hyperthermic tumor regression revitalize an old interest in heat as an anticancer therapy. The clinical observations are supported by experimental data demonstrating that hyperthermia as a single modality kills tumor cells in animal models and in vitro. While the mechanism of injury is imperfectly understood, it is clear that heat induces selective lethal injury to malignant cells, and that this effect is critically dependent on temperature and time of heat exposure. Giovanella et al[1] found that temperatures from 37 to 40 C had little effect on the viability and subsequent ability to metastasize of L1210 leukemia cells, whereas temperatures higher than 41 C killed the tumor cells. Palzer and Heidelberger[2] further defined a critical temperature-time relationship in the 41.0 to 43.0 C temperature range using HeLa cells. Overgaard and Overgaard[3] showed that temperatures of 41.5 to 43.5 C destroyed mouse mammary-tumor implants without injuring adjacent normal tissue.

Hyperthermic therapy is of great potential clinical relevance because it increases the therapeutic index between normal host tissue and malignant cells when combined with conventional radiotherapy and chemotherapy. Ben-Hur et al[4] showed a synergistic effect of heat and radiotherapy on the destruction of cultures of Chinese hamster cells. To explain the synergism of heat with radiotherapy, Hahn[5] demonstrated that heat is lethal to cells in conditions of cell hypoxia and limited nutrients—the conditions under which tumor cells are least sensitive to radiation injury and the very circumstances that often exist in large tumors.

In 1967, Cavaliere et al[6] reported striking tumor regression in 15 of 22 patients with sarcomas and melanomas of the extremity treated with heated perfused blood. Using perfusion temperatures of 41.5 to 45 C, Hall and associates[7] obtained substantial tumor regression in 26 of 32 patients with carcinomas of the urinary bladder, with complete tumor regression in four patients. Recently, Stehlin et al[8] described a marked increase in survival in patients with stage I to III melanoma of the extremity after hyperthermic perfusion with the alkylating agent phenylalanine mustard. This claim is notable because phenylalanine mustard is ineffective when perfused under normothermic conditions and because it is not a useful systemic chemotherapeutic agent for melanoma. Unfortunately, the use of historical controls and a tendency to select patients with a good prognosis diminishes the impact of this study.

For the treatment of widely disseminated malignancies, Pettigrew and his associates[9] developed a technique of whole-body hyperthermia using heated anesthetic gases. They described partial tumor regressions in 25 of 38 patients with a variety of advanced malignancies who were treated with 41.8 C heat alone, and in all of 13 patients who were in addition given systemic chemotherapy. While none of the regressions were complete, the study demonstrates that whole-body hyperthermia is feasible and may be an effective adjuvant with chemotherapy.

LeVeen et al (p 2198) present a unique method of selectively elevating tumor temperature that in preliminary trial achieved destruction of these tumors without significantly altering body temperature or damaging normal tissues. The clinical results, matched with the ingenuity and comparative simplicity of their technique, may allow a more widespread use of this method than of those developed by Cavaliere et al, Stehlin et al, and Pettigrew and associates. Undoubtedly, their report will stimulate others to attempt to reproduce their results and will inspire the creative to explore other methods of tumor destruction by heat.

Conceptually, the clinical reports are exciting. However, the clinical studies in the literature have lacked controls or have had unacceptable controls. Rationally designed and properly controlled studies are now warranted by the present background of data derived from laboratory studies providing a theoretical basis for hyperthermic therapy and by clinical reports that show the feasibility and efficacy of heat therapy. Emphasis should be given to investigations of the potential of heat to increase the tumor-kill achieved with radiotherapy and chemotherapy, in view of the increasing evidence for the superiority of multimodal therapy over single agents in cancer treatment. Future clinical trials must be designed with precise attention to details of temperature measurement in the tumor and normal tissues and the determination of the effects on all vital functions, as is done in phase I trials of chemotherapeutic agents. Reports of studies that are not conducted on the highest scientific level will be viewed with deserved skepticism by the medical community and will impede the extensive investigations in humans that are needed to define the role of heat in cancer therapy.

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Restless Legs Syndrome

Except for *Current Medical Information and Terminology*,[1] standard reference sources (eg, a popular textbook of medicine) are unlikely to reward a seeker of information about restless legs syndrome. In like manner, writings on the subject in medical periodicals are comparatively few.

When a practicing physician, uninformed about the malady, is confronted for the first time by a patient who complains of the syndrome, the physician may be mystified. Characteristically, an afflicted person is likely to tell the attending physician that the symptoms are difficult to describe. They are usually most bothersome at night when the patient goes to bed. He may say that his legs feel funny, or heavy (or light) and fidgety. Or, he may resort to saying what the symptoms do *not* feel like (itching, crawling sensation, warmth, coldness, and so on to the limit of the patient's vocabulary) and will conclude with, "Doctor, unless you've had it, you can't know what it feels like."

In the current issue of *Archives of Neurology* (33:368-370, 1976), other dimensions are added to the syndrome by Boghen and Peyronnard who describe its occurrence in a family in which 18 members were affected over a span of five generations and in which ten patients had myoclonus. The authors noted that, although the familial incidence of the syndrome has been observed by other writers, neither its hereditary character nor the frequent prominence of myoclonus has been emphasized.

Boghen and Peyronnard were first consulted by a 57-year-old man whose case report can be condensed as follows.

> The patient complained of involuntary jerks of the lower extremities that prevented him from falling asleep at night and awakened him after the onset of sleep. To obtain relief, he would get up and walk around for approximately ten minutes. Following this, he would be comfortable for 20 minutes or so, after which the symptoms would recur. The same movements occasionally occurred during the day when he was sitting or going for a drive, and were aggravated by fatigue. The movements never occurred while he was standing. The condition began with excessive restlessness in classrooms when he was 7 years old and had since varied in intensity. Symptoms had become more severe in the preceding year, following a bilateral iliac endarterectomy for intermittent claudication. . . . Observation showed two types of abnormal motor activity of the legs during the relaxation period preceding the patient's sleep. One type consisted of abrupt asymmetric myoclonic jerks ranging from a brisk dorsiflexion of the foot to a triple flexion of the limb, which resembled a withdrawal reflex. These were vigorous, often accompanied by contraction of the abdominal muscles and an expiratory grunt, and occasionally extended to the left upper extremity. The other kind of motor activity consisted of seemingly voluntary fidgeting movements for more than a few distressing moments when increasing "tension" in the legs became intolerable. He had no control over the myoclonic jerks.
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> Simultaneous electromyographic recording showed multiple aperiodic bursts of polyclonic motor discharges involving both anterior tibialis and gastrocnemius muscles, lasting from less than one to more than eight seconds. They occurred at a frequency of 4 to 12 per minute, with no accompanying electroencephalographic changes. The bursts disappeared within 15 minutes after the subject entered phase 1 sleep.

Following encounter with the initial patient (whose symptoms, incidentally, were not relieved by administration of any one of various pharmaceutical agents), Boghen and Peyronnard were able to identify a number of members of the patient's family in whom a similar syndrome had occurred. Clinical data available in 15 patients showed that some patients had myoclonus without sensory symptoms, and study of the family pedigree indicated a pattern of transmission most consistent with an autosomal dominant trait.

Returning to one of the thoughts that started this editorial, namely that the symptoms of restless legs syndrome are difficult for a patient to describe and for a physician to comprehend, Boghen and Peyronnard characterize the syndrome as "deep, ill-defined, disagreeable sensations in the legs and an irresistible urge to move them." Frankel et al[2] use the words "severe, hard-to-describe dysesthesia (rather than paresthesia or actual pain) that is felt deep within the lower extremities." Ekbom[3] writes of "disagreeable creeping sensations deep inside the legs, mostly between the knee and ankle . . . felt on both sides symmetrically." The foregoing quotations may raise the question whether the authors themselves had the syndrome and therefore had less difficulty with description. Further to compound an uninitiated physician's difficulty is the fact that he can offer little or nothing by way of treatment that the patient has not already found out for himself by experience.

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