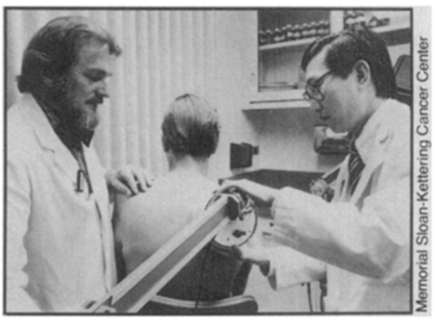
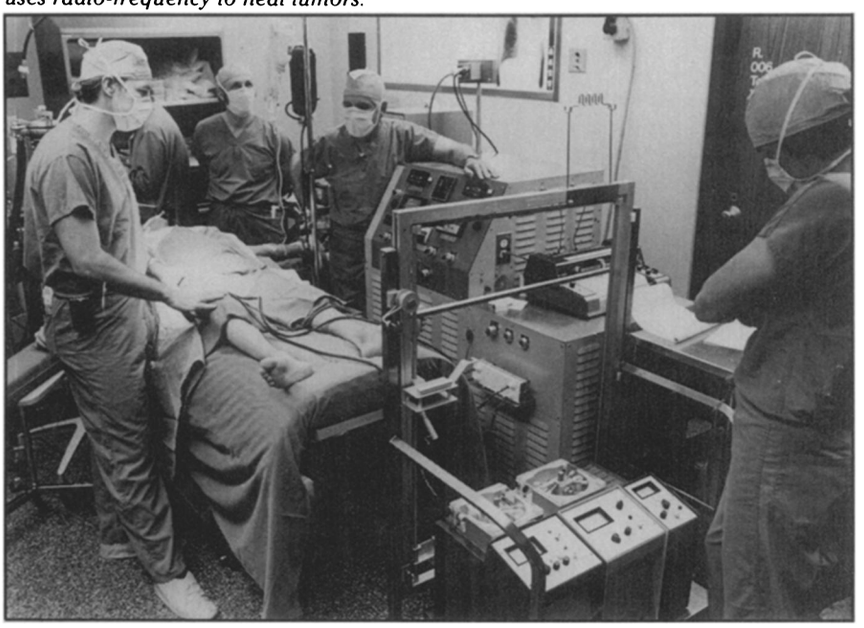
HYPERTHERMIA
Hot Stuff in Cancer Treatment

Doctors are using heat to attack cancer cells. Prognosis? Guardedly optimistic.

BY JOANNE SILBERNER



Howard Frazier (at left below) at M.D. Anderson Hospital administers whole-body heat. Right: at Sloan-Kettering, Jae Ho Kim uses radio-frequency to heat tumors.



Last June Michael Salcman, a neurosurgeon at the University of Maryland, implanted an antenna in the brain of a 28-year-old European businessman with glioblastoma multiforme, a lethal brain tumor that usually leaves its victim dead within 24 months of diagnosis. Salcman removed as much of the cancer as he could, then inserted an antenna and a tiny thermometer directly into the remaining tumor and sewed up the man's head with the antenna still in it. Two times during the next 48 hours Salcman sent microwaves directly into the tumor, heating it to 45°C (113°F). The patient was awake and reported no pain, says Salcman, who has recently repeated the operation on a 30-year-old woman.

"There appear to be indications of a decrease in tumor size," says George Samaras, the biophysicist who developed the technique with Salcman, "but we'll have to wait six months to a year to really tell."

The procedure is one of many ways researchers are manipulating hyperthermia — high levels of heat — to attack cancer cells. In the search for a safe and effective cancer treatment, medical researchers have developed an entire arsenal of weapons. Heat, delivered directly, by antenna, or beamed through the skin on microwaves, ultrasound, or via magnetic induction, is rumbling up over the horizon as a new form of firepower.

While initial results look promising, investigators are quick to caution that the technique is not yet ready for full deployment. Salcman, for example, implanted the antenna only after chemotherapy and radiation failed to shrink the tumor.

In the meantime, the National Cancer Institute is funding nearly $4 million worth of hyperthermia research this year. At least ten major research centers across the country now provide hyperthermia therapy, most on an experimental basis, but at least one offers it as the treatment of choice for certain tumors. Methods of heat application vary from packing patients in hot wax to swaddling them in hot water blankets to beaming ultrasound, radio waves or microwaves at the tumor. All methods make use of the same concept — heat can kill cancer cells.

The idea is not a new one. In 1866, a German physician reported the spontaneous disappearance of a facial tumor in a patient who had come down with erysipelas, a streptococcal infection that causes high fever. His report was soon followed by a description of the disappearance of multiple recurrent melanoma, a quickly spreading often fatal cancer originating in pigment cells, in another patient with erysipelas.

A few years later, New York surgeon William Coley found a healthy man who had been diagnosed with terminal sarcoma, another quickly spreading cancer, whose cancer had disappeared after he contracted erysipelas. To take advantage of the fever effect, Coley developed bacterial fever-producing injections. Some of his "terminal" patients lived another fifty years. But because the toxin's effects were dangerous and not readily reproducible, the technique fell by the wayside.

Since the end of the nineteenth century publications on hyperthermia's effectiveness against cancer have appeared sporadically. In the mid-1960s Italian researcher Renato Cavaliere and University of Wisconsin researchers reported encouraging results — 6 of 22 patients with malignant cancer had regressions after their blood was warmed to over 41.5°C (106.7°F). On the cellular level, researchers reported finding that nutritionally deprived cells are sensitive to heat, and that cells react to heat in much the same way they react to X-rays.

Scientists still aren't ready to say exactly how hyperthermia works. While some believe tumor cells are more sensitive to heat, others feel that poor circulation around tumors causes them to concentrate heat. Well-irrigated areas of the body dissipate the high temperatures. Other not necessarily contradictory possibilities: The lack of oxygen, low pH or insufficient nutrition characteristic of tumor cells make them more vulnerable to heat; protein molecules in tumor cell membranes break down easily in high heat. What is well-established is that for every degree Centigrade above 42.5°, the sensitivity of cells to heat doubles, so that cells at 45.5°C are eight times as sensitive to heat as cells at 42.5°C.

And researchers, manipulating that concept, are getting clinical results.

Six years ago Jae Ho Kim and associates at the Memorial Sloan-Kettering Cancer Center in New York discovered that while poorly oxygenated cells typical of tumors

are three times more resistant to radiation-caused damage than are normal cells, they are more prone to damage by heat. One reason for the efficacious combination may be that during the growth phase when cells are most resistant to X-ray damage, they are most sensitive to heat damage.

When Kim and Eric Hahn tried using hyperthermia alone to clear up tumors, they got only short-term results. But when they tried a combination treatment, their results were more encouraging—of about 40 melanoma cases they treated with radiation and hyperthermia, they report that tumors have disappeared in 80 percent of the cases, this while radiation exposure was cut to two-thirds the normal dose. With radiation alone, they got only a 30 percent response, and only a 15 to 20 percent response with heat.

Hyperthermia's greatest contribution, many researchers believe, may come in combination with the traditional modes of cancer treatment by potentiating the effects of drugs, surgery or, as in Kim's work, radiation.

Peter M. Corry at M.D. Anderson Hospital in Houston is also using radiation with hyperthermia. Of more than 200 patients whose tumors were irradiated and heated with ultrasound or by magnetic induction, tumor size was reduced by at least 50 percent in half of the persons treated, Corry reports. Using an ultrasound transducer strapped over the tumor and pumping water through to keep the skin cool, Corry has gotten tumor temperatures as high as 50°C (122°F).

George Hahn, who reported six years ago that nutritionally deprived cells such as tumor cells are heat-sensitive, and Jane Marmor at Stanford University have also reported some success using hyperthermia and radioactivity. They are currently working with hyperthermia alone to see what its side effects are.

Using six treatments of ultrasound, they have heated tumors to 43°C for 30 minutes and shrunk metastatic tumors with no undue effects to the patients. But though they have gotten tumors to disappear, the disease is still metastatic. "The patient isn't cured," Marmor notes. The researchers will soon put to use a new piece of ultrasound equipment developed by physicist Douglas Pounds. The apparatus will reach deep-seated tumors without broiling intervening tissues by converging multiple beams on the tumor.

The question of heating intervening tissues brings up the question of whole-body hyperthermia — when trying to get at a tumor, why heat healthy tissue as well? Some researchers suggest that heating the whole body will permit them to reach tiny cancer colonies as well as their parent tumors. "Cancer is a systemic disease," says O. Howard Frazier, a surgeon at M.D. Anderson Hospital, "that's why we lose patients. In lung cancer you can take out a lung but two or three years later the cancer will appear somewhere else."

Frazier is using a modified heart-lung machine hooked up to the large femoral artery and vein in the thigh, which allows him to raise and lower blood temperature quickly. "We can control the patient's temperature to within one-tenth of a degree," he says.

But whole-body hyperthermia presents a problem — the body cannot tolerate the high temperatures to which a tumor alone can be brought. Frazier is experimenting with jumping the temperature during treatment from 41.5°C to 43°C for short periods of time. "My hope is that with their poor blood supply system, tumors will be unable to get rid of the heat the way the rest of the patient's body does. Therefore, the internal temperature of the tumor will stay at this higher temperature much longer, damaging the cancer cells," he says.

Marmor/Medical World News

Jane Marmor at Stanford treated right tumor with X-rays plus heat, left with X-rays alone. Top: before treatment. Middle: during. Bottom: Four months later, X-ray treated nodule reappears.

For the past three and a half years at the National Cancer Institute, Joan Bull, now at the University of Texas at Houston, has been wrapping her patients in plastic water-circulating blankets for four hours, raising their temperatures to 41.8°C. This whole-body treatment puts a good deal of stress on patients. "You must choose patients carefully," she says. "They must have adequate cardiovascular systems." The heat treatment in combination with carefully-worked-out chemotherapy "seems to be useful" in treating melanoma, she says.

As a middle ground between whole-body heating and direct tumor heating, there's regional hyperthermia. Surgeon John S. Stehlin and cell biologist Beppino C. Giovanella at St. Joseph Hospital in Houston, who have been working with hyperthermia since the 1960's and have been called the fathers of hyperthermia, claim impressive results in treating recurrent melanomas of the arms or legs.

Using a treatment devised with Giovanella, Stehlin has treated hundreds of patients and has kept 77 percent of them alive for five years with drug therapy and regional hyperthermia; on drug therapy alone, this figure is only 22 percent. The first patient treated in 1967 is still alive.

Stehlin cuts into an artery in an arm or leg and sends in heated blood for about two hours. "The rest of the body is barely warmer than usual," explains Giovanella. "Sometimes the legs swell, but it's only temporary," he says.

Haim Bicher, who heads the recently opened hyperthermia unit at the Henry Ford Hospital in Detroit, has found another way of getting at an internal tumor — by placing antennas in the throat, rectum, vagina, bladder or uterus. Bicher reports a 60 percent response in 30 patients with this technique. He's already gotten the same success rate in 105 patients using externally applied heat at 45°C. "We can treat anything we can reach," he says.

And there's more. Kristian Storm at the University of California in Los Angeles has treated 175 patients with radiowaves, with positive results. At the University of Arizona, at the Roswell Park Memorial Institute in Buffalo, at the National Cancer Institute, at Indiana University and at the University of New Mexico, researchers are working on hyperthermia.

With some of the initial positive results, one would expect the researchers to be extolling hyperthermia's virtues, but they're not. One researcher estimates it will be five to ten years before the answers are in. Among the concerns: Equipment for both heat delivery and heat monitoring is not sophisticated enough for them to be able to quantify doses; they don't know if there are any long-term negative effects. Most researchers are using hyperthermia only on patients for whom all other therapies have failed.

The drawbacks exist. There are occasional skin burns. Direct hyperthermia to an individual tumor will not cure a cancer that has spread. There are limits to how much whole body heat can be tolerated, and some people can't tolerate it at all. But as technology catches up, the researchers are continuing in their efforts to develop hyperthermia into a major weapon against cancer. □