HEAT AS AN ADJUNCT TO THE TREATMENT OF CANCER

Experimental Studies

GEORGE CRILE, JR., M.D.
Department of General Surgery

MANY cancers are more susceptible to destruction by heat than are the tissues they grow in. Heat acts synergistically, or at least additively, with radiation so that the combined effects of the two are greater than the effect of either one alone. These observations were reported half a century ago,[1,2] but for the past 20 years little has been published on the effects of heat on cancer.

Our interest in the effects of heat started in June, 1960, when, unaware of previously published studies, we noticed the regression of a mouse tumor that had been exposed to a temperature of 42 C. (107.6 F.) for two hours. The effect was reproducible. When we implanted S91 melanomas on the feet of DBA_1 mice we were able to destroy some of the resulting tumors by immersing the tumor-bearing feet for 30 minutes in water at 44 C. This temperature is only 111.2 F. or the temperature of a comfortably hot bath. In most cases there was no damage to the normal tissues of the feet. All of the animals that appeared to be cured 21 days after treatment lived longer than 90 days without recurrence.

The S91 melanoma is a moderately radioresistant tumor whose progressive growth is not controlled by radiation in doses up to 1000 r. But when this tumor was heated for 30 minutes at 44 C. and immediately treated with 1000 r there was complete regression in 20 of 25 mice. Twenty control mice, whose tumor-bearing feet were immersed in water at 37 C., showed progressive growth of their tumors, and 75 per cent of the animals were dead in 31 days. It appeared that heat selectively killed many tumors without damaging surrounding tissues, and that it acted synergistically with radiation.

Materials and Methods

The literature for the past 15 years was searched for information on the effects of heat on tumor growth without finding any major studies on this subject. Further studies then were made on the effects of heat on tumors, but since there was difficulty in obtaining an adequate supply of DBA_1 mice, we used female Swiss mice three to four weeks old, and a transplantable tumor, sarcoma 180* (S180) that grows rapidly but does not metastasize.

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**Obtained from Arthur D. Little & Associates, Boston, Massachusetts.*

The tumor strain was maintained by injection into the flanks of the mice. The resulting tumors were excised, minced, suspended in an equal amount of Hank's solution, and the tumor fragments were injected with a 20-gauge needle into the web of a hind foot. Tumors usually appeared within three days, and within eight days were about 1 cm. in diameter. Spontaneous regressions never occurred within the first three weeks, but thereafter did occur in 9 per cent of 120 mice, usually associated with ulceration of the tumor or with its being eaten by the mouse.

A week after implantation, when the tumors were about 1 cm. in diameter, the tumor-bearing feet were immersed in a water bath at the desired temperature. To hold the tumor in the bath, the mouse was restrained with adhesive tape in stocks made of a piece of sheet lead, 5 cm. by 13 cm. by 0.1 cm., with a slot 5 cm. long and 0.3 cm. wide through which the tumor-bearing foot was passed. A rubber washer, 1 cm. thick and slit on one side so that it could be opened, was applied on the leg above the tumor to hold the tumor down into the water *(Fig. 1)*. The mice were then placed on a test tube rack, with their tumor-bearing feet

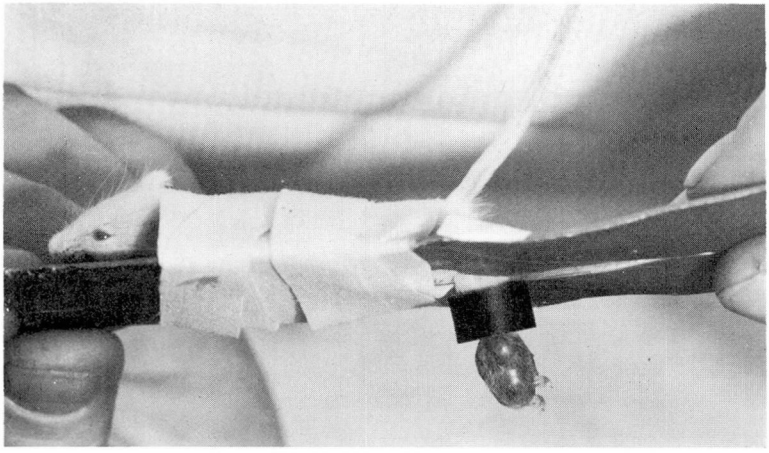

Fig. 1. Mouse restrained on sheet lead with tumor-bearing foot protruding through slot in the lead.

in the water *(Fig. 2)*. Radiation, given by a 200-kv. machine, was applied with the mouse's foot toward the radiation source and the lead shielding the body. Using this system, the following observations were made.

Observations on the Effects of Heat on Transplantable Tumors in Mice

(1) *Between 42 C. and 47 C. the time of exposure required to destroy S180 implanted on mice's feet can be halved for each degree of Centigrade that the temperature is elevated.*

The destructive effect of heat on tumors began at about 41 C., but at this temperature many hours of constant exposure were required. At 42 C., 120 minutes

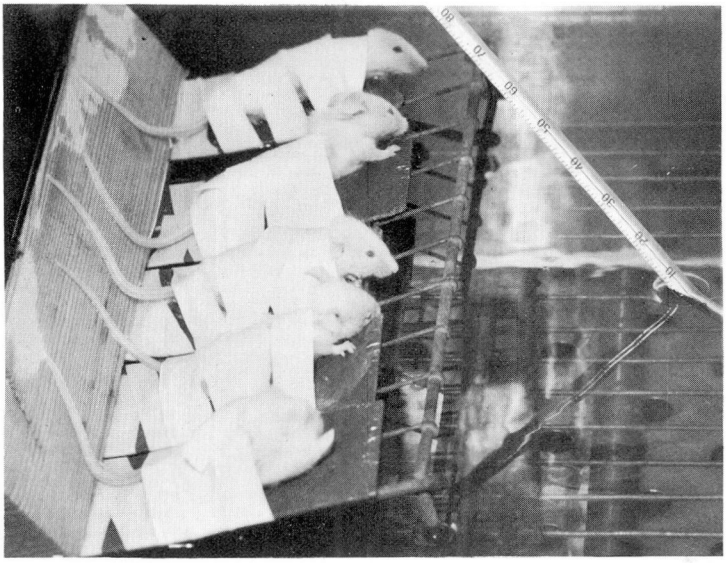

Fig. 2. Method of heating the tumor-bearing feet in a water bath.

was required to destroy S180 in more than 50 per cent of the mice treated; at 43 C., 60 minutes; at 44 C., 30 minutes; at 45 C., 15 minutes; and at 46 C., only seven and one-half minutes. In these tests the tumors were destroyed in 49 of 67 mice. Thus, from 42 C. through 46 C., a similar biologic effect was obtained by doubling the time exposure for each degree that the temperature was reduced. In this range of temperature, the time required to destroy the tumor can be expressed by an exponential curve *(Fig. 3)*. A similar exponential curve *(Fig. 4)*, with longer exposures at each temperature, expresses the exposure to heat that damaged the normal feet of DBA_1 mice to such an extent that the treated feet of half of the mice dropped off within a week of treatment.

Above 46 C., the heat capacity of the skin, and the lag of the tissues in transmitting the heat of the water bath to the center of the tumor, distort the exponential curve. According to the formula that expresses the effects of heat in the range of 42 C. through 46 C., an exposure of less than one minute at 49 C. should suffice to destroy the tumor. But in one minute's exposure of the tumor-bearing foot in a bath at 49 C., there is not time for the heat at the center of the tumor, measured by thermocouple, to reach a temperature higher than 46 C. An exposure of one minute at this temperature does not destroy the tumor. If the time of treatment is prolonged to four or five minutes so that the cells at the center of the tumor are given enough exposure to be destroyed, the exposure of the skin will exceed its threshold of tolerance and it will be scalded. Therefore, exposures at high temperatures in water baths do not effect cures without damaging normal

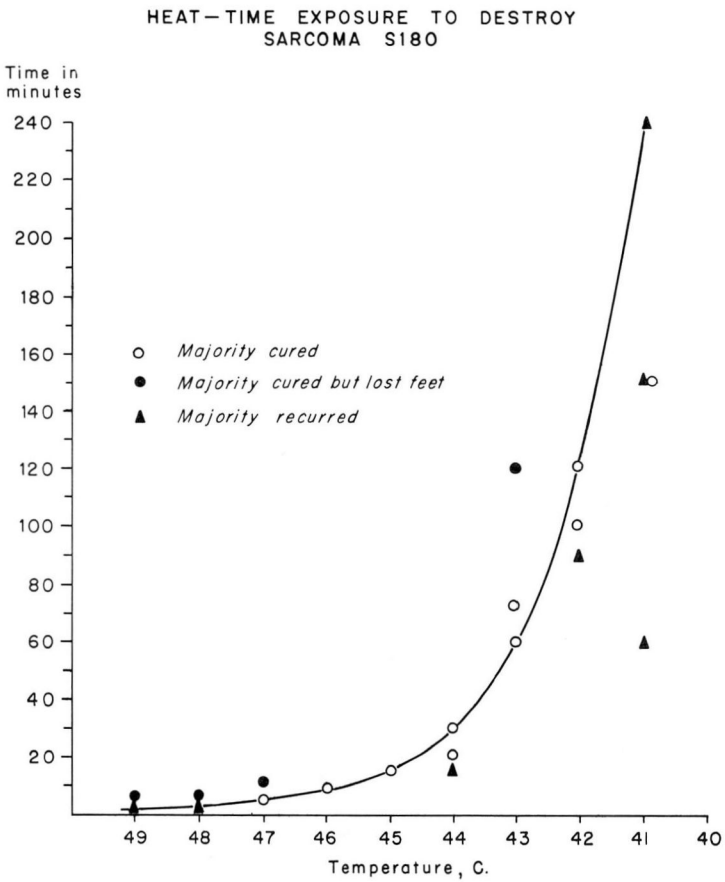

Fig. 3. Exponential curve expressing duration of exposure, in minutes, which is required at various temperatures to destroy the majority of S180 tumors implanted on the feet of Swiss mice. Each dot represents an experiment of from five to eight mice.

tissues; whereas, longer treatments at temperatures in the range of 46 C. through 42 C. are effective. Forty-four degrees Centigrade for 30 minutes proved to be the most convenient and effective exposure to destroy the majority of S180 tumors implanted on the feet of Swiss mice.

(2) *The destructive effects of heat are visible immediately after exposure of the tumor.* There is cyanosis of the tumor-bearing part of the foot; the cut surface of the tumor is dark red; and microscopically there is striking dilatation of blood vessels and hemorrhage into the tumor. If the tumor is large in proportion to the size of the mouse (i.e., more than 2 cm. in diameter in a four-week-old Swiss mouse) the mouse dies within from 10 minutes to 24 hours after treatment, perhaps as a result of shock from loss of blood or fluid into the tumor, or perhaps as a result

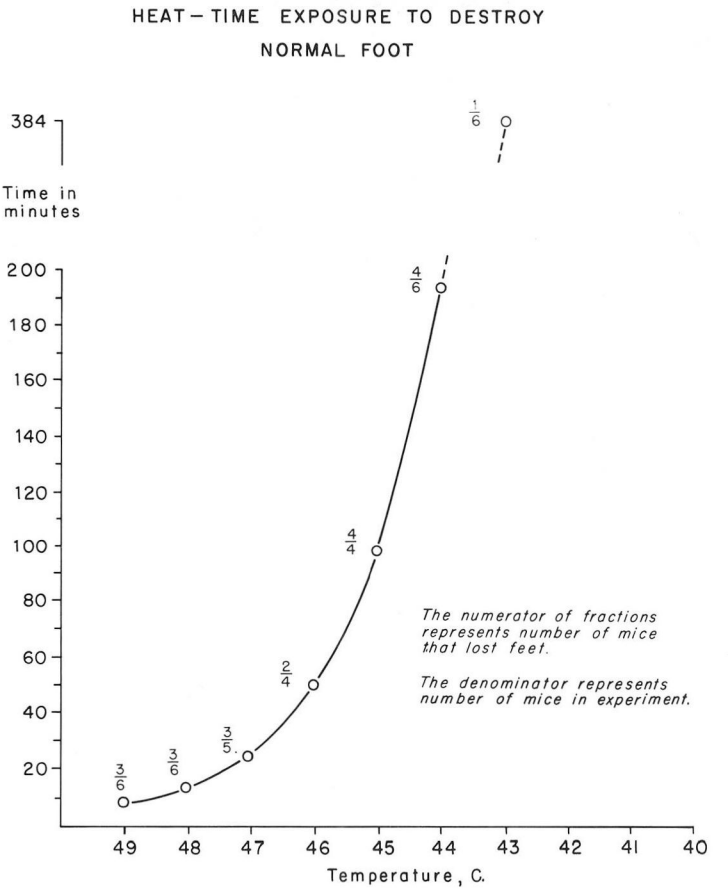

Fig. 4. Exponential curve expressing duration of exposure, in minutes, which is required at various temperatures to destroy the majority of heated feet in DBA_1 mice.

of toxic metabolites from the treated area.

(3) *When the exposure to heat has been in the therapeutic range, the tumor turns black within 24 hours after treatment, and in the next few days becomes a dry scab that falls off about the seventh day, leaving the remainder of the foot intact.* Sometimes the death of the tumor is less abrupt, and it seems to be resorbed and to disappear without death of the overlying skin. When the tumor is more than 1 cm. in diameter and dies suddenly, the mouse may lose its foot in the course of the rapid necrosis of the tumor. Sometimes a mouse chews off its own foot. Usually the tumor sloughs off and leaves the foot scarred but intact *(Fig. 5)*.

(4) *If recurrence takes place, it appears promptly, usually within two weeks.* Late recurrences were not observed in 28 mice that appeared to be cured three weeks

after treatment and were followed for 40 or more days. Ten "cured" mice have been observed for longer than nine months without evidence of recurrence. In this respect the effects of heat differ from those of radiation, in which late recurrences after primary regressions are common.

(5) *At temperatures between 42 C. and 46 C. the time of exposure required to destroy the majority of normal feet is more than twice the time necessary to destroy the majority of S180 tumors implanted on feet.* This relationship provides a relatively broad range of therapeutic exposure in which the tumor is destroyed without irreversible damage to normal tissue. Above this range there is a high incidence of damage to normal tissues.

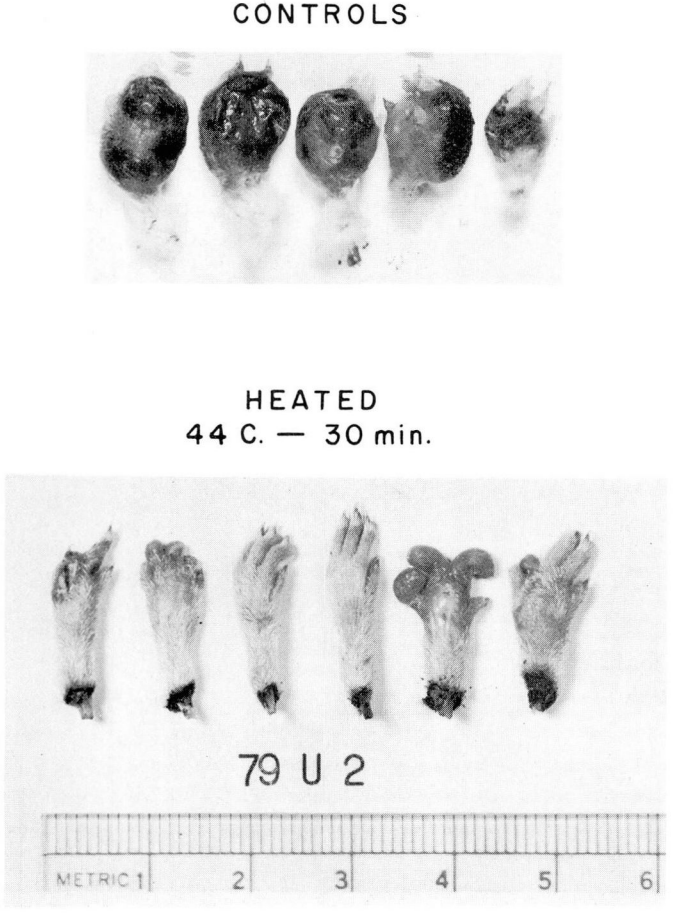

Fig. 5. Feet of mice on which S180 had been implanted. Control mice received no treatment and were photographed soon after the other mice had been treated. Treated mice were exposed to 44 C. for 30 minutes and were photographed one month after treatment.

(6) *Exposure of a tumor to heat for a period of time shorter than that required to destroy it, makes the tumor temporarily resistant to subsequently applied heat.* In each of 12 mice a single exposure of the tumor to 44 C. for 10 minutes, made the tumor so resistant to subsequent treatment that the next day it was undamaged by exposure of 30 minutes at 44 C., a dose that destroyed more than 70 per cent of previously unheated tumors. This acquired resistance to heat appears to be the result of a biologic adaptation of the cells and is associated with the disappearance of all mitotic figures. It could be likened to the transformation of heat-sensitive bacteria into heat-resistant spores. Fractionated treatment, consisting of exposure to 44 C. for 10 minutes daily for five days, slows the growth of a tumor but does not destroy it. The same is true of heating at 42 C. for 90 minutes followed in four days by repetition of the same treatment. In this respect the effects of heat appear to differ from those of radiation. There does not seem to be a cumulative effect of small treatments that ultimately destroys the tumor.

(7) *Conventional anticancer drugs do not seem to enhance the destructive effects of heat on tumors.* For example, 5-fluorouracil, in doses of 25 mg. per kilogram of body weight, injected daily for two days before heat treatment and for three days after, had no additive or synergistic effect. In 26 mice treated at various exposures to heat alone there were 14 recurrences. In 24 mice treated by 5-fluorouracil and identical exposures to heat there were also 14 recurrences. In small pilot experiments Thio-Tepa* injected intraperitoneally during the heat treatment in a dose of 10 mg. per gram of body weight did not alter the incidence of regression, nor did 75 micrograms per kilogram of body weight of actinomycin D, injected for five days before heating S91 melanomas.

Distilled water injected into the tumors before they were heated did not change the effect of heat. This experiment, however, was unsatisfactory because the water often escaped through the needle tract.

Application of a tight rubber band above the tumor during the heat treatment resulted in more frequent loss of the foot, but had no significant effect on the tumor's response to heat. At room temperature, application of a tourniquet above the tumor for half an hour did not cause either necrosis or regression of the tumor.

Because alcohol is an enzymatic poison that causes coagulation of protein at low temperatures we studied its effects on heated tumors. Fifty per cent alcohol, injected into the stomach, in doses of 0.3 ml. was sufficient to make a mouse stagger and lose coordination. When the tumors of 10 intoxicated mice were heated for 20 minutes at 44 C., the tumors were destroyed in three of them; whereas in none of 20 mice that were not given alcohol were the tumors controlled at this exposure. In the mice treated with heat and alcohol the growth of the tumors was retarded significantly as compared with that of the mice treated by heat alone. It is possible that alcohol affects the same enzymatic system that causes tissues to be more suscep-

**Thio-Tepa (N[1], N[1], N[1|1], triethylenethiophosphoramide), Lederle Laboratories.*

tible to destruction by radiation at high oxygen tensions. The field of synergism of chemicals with heat requires further investigation.

(8) *Heat enhances the effect of radiation on tumors, and radiation enhances the effect of heat.* Treatment of S180 for 15 minutes at 44 C. (instead of for the 30 minutes that is required to kill the tumor) did not increase the incidence of regressions above that occurring in untreated control mice. In another experiment, exposures to 1000 r caused regression in 25 per cent of the mice compared to 9 per cent in untreated control animals. Combining heat at 44 C. for 15 minutes with 1000 r given immediately, raised the rate of cure to 75 per cent, and it made no difference whether the tumors were heated first or radiated first. Results of a typical experiment are shown in *Table 1.*

Table 1.—*Results of treatment of sarcoma 180 on feet of Swiss mice followed 75 days*

Type of treatment	Total number of mice	Number of mice		
		Tumor controlled	Lost foot	Died of recurrence
None	8	1 (Late spontaneous regression)	0	7
Heat alone				
44 C. for 15 min.	8	0	0	8
44 C. for 30 min.	19	13	4	2
Radiation alone				
500 r	4	1 (Late spontaneous regression)	0	3
1000 r	16	5	1	10
1500 r	4	0	1	3
Heat and radiation				
44 C. for 15 min. + 500 r	12	5	0	7
44 C. for 15 min. + 1000 r	12	8	1	3

Another type of tumor, the S91 melanoma, in DBA_1 mice is more resistant either to heat or to radiation than is S180, yet as mentioned in section 1 this type of tumor also was controlled by combining heat and radiation *(Fig. 6).* It was difficult to cure the melanoma by either heat alone or radiation alone without using exposures that caused irreversible damage to normal tissues. The reason for the effectiveness of combined therapy in controlling the tumor without damage to the feet may be that the peak of the reaction to heat and the peak of the reac-

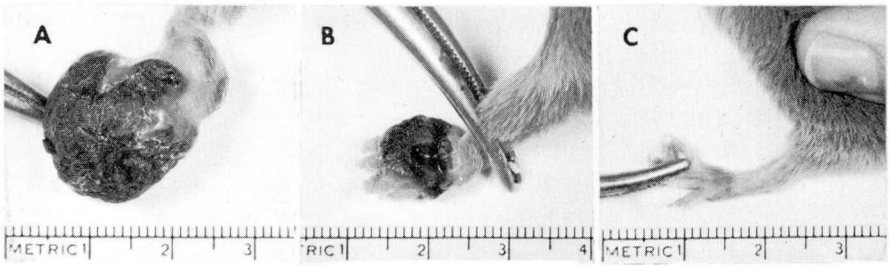

Fig. 6. A = heat alone; B = radiation alone; C = heat and radiation (same doses as in A and B). Synergistic effect of heat and radiation shown by complete control of S91 melanoma in DBA_1 mouse. Neither treatment given alone controlled the tumor.

tion to radiation occur at different times, the heat effect being immediate and the radiation effect being delayed; or it may be that a synergistic effect is exerted selectively on the tumor as compared with the normal tissues.

(9) *It is unlikely that immunologic mechanisms are responsible for the disappearance of heated tumors.* The effect is too prompt for an immunologic reaction and, furthermore, after a tumor on one foot has been controlled by heat, challenge of the contralateral foot by injection of new tumor cells usually is followed by growth of tumor. Twenty-six mice whose tumors had been destroyed by heat, from one to two months earlier, were challenged by reinjection of the same tumor strain on the opposite feet. In 22 the tumor grew progressively and killed 20 of the mice within 33 days.

(10) *Tumor cells in vitro withstand more heat than they do in vivo.* Minced tumor cells suspended in Hank's solution and heated in a sealed tuberculin syringe at 45 C. for 15 minutes (an exposure that would destroy S180 in vivo) were still viable and produced tumors in all of 11 mice. However, the first appearance of the tumors was retarded and in the beginning they grew more slowly than usual. In another experiment, when minced tumor was heated to 49 C. for six minutes and was injected into 9 mice, the tumors did not appear for 14 days, compared with three days for tumors arising from unheated cells. Twenty-one days after the heated cells were injected all the mice had tumors.

In one pilot experiment involving 36 mice, tumors from heated cells that had been separated from one another, by passage through a cytosieve, appeared five days earlier than those from tumors that were merely minced. The opposite was true when the cells were not heated, the tumors arising from minced tumor appearing four days earlier than those arising from tumor cells passed through a cytosieve.

These results suggest that heated tumors or their hosts make some substance that is toxic to the tumor and destroys it. Experiments on 24 mice whose tumors were heated in vivo support this hypothesis. When the tumor-bearing feet were exposed to 44 C. for 40 minutes, and tumor cells were transplanted immediately

after heating, the cells grew as well as those of unheated tumors. But when the tumor was left intact on the living mouse for four hours after heating, and then was transplanted, the time of appearance of tumors was delayed for two or three weeks beyond the time of appearance of those that were transplanted immediately, and in two of the twelve mice no tumors appeared.

(11) *The growth of tumors may be temporarily slowed by heat even when the tumors are not killed.* Tumors that are heated sublethally at first shrink and then for a few days grow more slowly than usual. Mitotic figures disappear from the tumor, and often there are cellular changes that pathologists describe as similar to those seen after radiation. Later the tumor may resume its usual rate of growth or may grow more rapidly than unheated tumors.

(12) *There are differences between normal and malignant tissues in their tolerances to heat, and there are also differences between various types of tumor and between various types of normal tissue.*

S180, which grows rapidly, is extremely sensitive to destruction by heat; the S91 melanoma, which grows slowly, is moderately sensitive to heat; and the carcinosarcoma in C57, which grows almost as rapidly as the S180 and much more rapidly than the melanoma, is so resistant that we have not yet been able to control it permanently either by heat alone or by radiation alone without damage to the foot.

Not only tumors, but tissues vary in their sensitivity to heat. The tail of the mouse is more easily destroyed by heat than is the foot. Results of pilot experiments designed to test the tolerance of mucous membranes of the mouth and rectum suggest that they may be more tolerant of heat than is the skin. Perhaps the higher the normal temperature of the tissue the higher is its tolerance to heat.

The Use of Heat in the Treatment of Cancer by Other Investigators

At this point in our studies, we came upon the work of Warren[3] who in 1935 reported on induced systemic hyperthermia as an adjunct to roentgentherapy in the treatment of patients with advanced cancers. We then reviewed the literature of the 1920s and 1930s and found a number of excellent studies on the biologic effects of heat and radiation, among which were Rohdenburg and Prime's[4] classic paper, published in 1921, and Westermark's[5] work with rat tumors in 1927. Our studies had confirmed the results of these earlier investigations. Similar results have been reported by Selawry, Goldstein, and McCormick[6] working with cancer cells in tissue culture. Since Selawry, Carlson, and Moore's[7] review summarizes observations made on the biologic effects of heat and radiation up to 1958, and since Westermark[4] reports in detail the many successful applications of heat to the treatment of human tumors, I shall not cite the old literature in detail. It can be summarized by saying that 50 years ago exposure to temperatures between 41 C. and 49 C. was extensively and apparently successfully used in the treatment

of cancer both in man and in laboratory animals. From the reports that have been published and from our own observations the following conclusions can be drawn:

(1) The destructive effect of heat does not depend on temperature alone, but on the duration of exposure at a critical temperature.

Some cancers in animals and in man are more susceptible to destruction by prolonged exposures to temperatures between 41 C. and 50 C. than are the normal tissues around them.

(2) Heat and radiation act synergistically, or at least additively, to effect destruction both of normal and of malignant tissues.

Effect of Heat on Spontaneous Tumors in Animals

The effects of heat on spontaneous tumors in several animals besides mice were studied. Three illustrative case reports are presented.

Case 1. A pet female rabbit several years old was brought to us with a tumor of the ear, 1.5 cm. in diameter and 1.5 cm. thick. A biopsy specimen showed an anaplastic histiocytic tumor with many inclusion bodies. The ear was immersed in a water bath at 47 C. for 15 minutes. Three days later the tumor fell off. A week after treatment, a biopsy specimen of the remaining ulcer showed no tumor. There was no damage to the ear, and healing was complete within two weeks. Four months after treatment, there was no recurrence. Pathologists believe that this was a tumor of viral origin.

Case 2. A 17-year-old female mongrel dog was brought to us by F. A. Coy, D.V.M., with an osteogenic carcinoma, the size of a golf ball on the tip of the lower jaw. During the previous year it had recurred five times after curettage and exposure to 1400 r. The diagnosis was confirmed histologically.

Under intratracheal anesthesia the dog's mouth was held open with a gag and the tumor-bearing jaw was immersed in water at from 48 to 49 C. for one hour. During treatment, the temperature of the center of the tumor, measured by thermocouple, was 44 to 46 C. After the treatment the tumor was cyanotic, and three days later sloughed off, leaving the jaw intact. A week after treatment a biopsy specimen of the jaw showed no tumor. The dog incurred no damage except a second-degree burn of the chin, which re-epithelized rapidly. The mucous membrane of the mouth was not damaged.

One month after treatment, a biopsy specimen of the jaw showed recurrence, and the dog was given a second hot-water bath treatment of one hour at 49 C. Again there was sloughing, and a week later a biopsy specimen of the cleanly granulating jaw showed no tumor. Eight weeks after the last treatment, there was a second recurrence that was treated by a combination of heat by microwave diathermy and 1000 r of cobalt-60* teletherapy. This resulted in necrosis of the tumor and slough of the tip of the jaw. The dog died two weeks after the last treatment with quadriplegia of unknown origin. Microscopic examination showed viable tumor still present at the periphery of the treated field.

**The radioactive material was obtained on authorization of the United States Atomic Energy Commission.*

Case 3. A female boxer dog had a proved mast-cell tumor of the ankle that had recurred three times in a year after local excisions and was the size of a golf ball *(Fig. 7A)*. Mast-cell tumors in the dog are similar in their clinical behavior to reticulum-cell sarcomas in man. The dog also had a huge tumor of the shoulder.

The pad of the dog's foot was protected with a plastic boot, and to facilitate conduction of heat, the tumor-bearing part of the foreleg was shaved. The leg up to mid-thigh then was immersed in water at 49 C. for one hour, digital pressure being maintained on the femoral artery most of the time to diminish the cooling effect of blood flow. The temperature of the center of the tumor, measured by thermocouple, ranged between 42 C. and 45 C.

After treatment, the skin over the tumor was slightly cyanotic. Two days later the tumor was softer and smaller than before treament. By the fourth day, the tumor had disappeared and the underlying bone was easily palpable. Ten days after treatment the tumor had vanished, leaving a small concavity. There was superficial damage to the outer layer of the shaved skin over the tumor and breakdown of the thin epithelium of the former surgical scars. All areas healed promptly *(Fig. 7B)*. Six weeks after treatment the tumor recurred and was treated again, this time by a combination of heat and radiation; and again it disappeared. The dog died three weeks after treatment, as a result of its other tumor. Sections of the ankle showed no viable tumor.

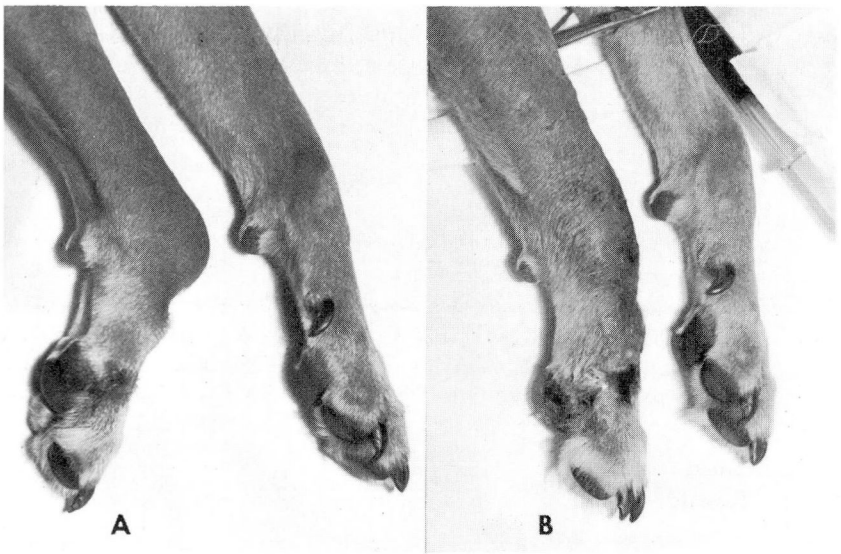

Fig. 7. A, Mast-cell tumor of dog's ankle before treatment. B, Dog's ankle one week after immersion in water bath at 49 C. for one hour.

Tests of Heat Sensitivity of Human Cancer

Metastatic cancer of the breast. In three patients with extensive intracutaneous

metastasis of breast cancer, proved by biopsy, a small area of the involved skin was treated by moist hot packs or hot water, the exposures ranging from 24 hours at 42 C. to one-half hour at 48 C. In each case there was striking regression of cancer in the heated area. The induration and nodularity of the skin vanished within seven days. In the patient treated at 42 C. for 24 hours there was a small superficial second-degree burn in the heated area.

In each of the three patients, in spite of disappearances of gross tumor, microscopic cancer was still evident in biopsy specimens.

Metastatic cancer of the stomach. Intracutaneous metastases of a cancer of the stomach were heated in the same way as the breast cancers but showed no regression of the skin nodules following exposure sufficient to cause a small superficial blister.

Recurrent cancer of the colon. The heat sensitivity of a fungating pelvic radioresistant recurrence of a sigmoid cancer was studied by observing the reaction of the tumor to irrigation with hot water. Under anesthesia, 250 gm. of necrotic tumor that filled the rectum, vagina , and ischiorectal space was scooped out and a mushroom catheter was inserted in the cavity. The cavity was then irrigated with water at 50 C. for 20 minutes, during which time the vagina and skin were cooled by a spray of cold water. Radiation of 1000 r was administered by cobalt-60 teletherapy immediately after the heat. Two weeks after the treatment there was no damage to the normal tissues and there were no visible fungations. Cancer was still present microscopically deep in the fibrous tissue but the fungating part of the tumor had been destroyed. A month later it recurred.

Cancer of the rectum. The heat sensitivity of a large, low-lying rectal carcinoma has been tested. It was a typical adenocarcinoma grade 3 with raised edges and a central crater involving two thirds of the circumference of the bowel. Its location indicated treatment by abdominoperineal resection. In view of the reported advantages of preoperative radiation in the treatment of rectal cancers, it was decided to treat the tumor preoperatively by a combination of radiation and heat.

The heat was applied by water at 50 C. With the patient under caudal anesthesia in the Kraske position a large Bakelite proctoscope was inserted in the rectum and through this a Foley catheter was passed beyond the tumor into the colon. The bag was then inflated and the catheter was pulled down until the bag rested snugly against the tumor, thus isolating the tumor and the rectum from the rest of the colon. The isolated tumor-bearing segment of the rectum then was filled with water at 50 C. and was replenished with hot water so that the temperature was kept constantly between 50 C. and 51 C. for 15 minutes. Biopsies were performed immediately before and immediately after the treatment; there was no histologic change as the result of the heat treatment. Immediately after the heat treament, 1000 r of cobalt-60 teletherapy was administered.

The next day there was tenderness of the anus and a profuse dark-brown dis-

charge. On the second day after treatment, the lower part of the tumor was inspected through a proctoscope, and showed sloughing necrotic tumor, but no trace of viable tumor for biopsy. A week after the heat and radiation treatment, abdominoperineal resection was done. There was no evidence of metastasis and nothing unusual about the external appearance of the bowel.

When the removed rectum was opened, the rolled edge of the upper part of the tumor against which the Foley bag had rested looked the same as the rolled edge of any untreated rectal cancer. However, the crater of the tumor, which had not been shielded from the hot water by the bag, was covered with an adherent brown slough, and the rolled edge of the lower two thirds of the tumor had vanished so that the soft, normal-looking mucosa ended abruptly in the slough-covered crater.

The only damage to the rectal mucosa was in a strip 8 mm. wide and 4 cm. long located at the level of the center of the tumor where there was superficial loss of mucosa, resembling a burn. Although the mucosa of the rest of the rectum had been exposed to the same amount of heat as the tumor, it appeared normal.

Histologically the thermal injury in the strip of damaged mucosa was limited to the mucosa. The rest of the heat-treated mucosa was indistinguishable from the untreated mucosa above the Foley bag. Histologic examination of the various heat-treated parts of the tumor showed only an occasional tumor cell deep in the fibrous tissue; whereas, the untreated part was typical of rectal cancer.

These observations and those reported in the first part of the century,[4,5] suggest that some cancers in man have a spectrum of heat sensitivity similar to that of cancers in mice and rats. It is therefore likely that heat could be used as a valuable adjunct to the treatment of cancer, especially when it is employed in conjunction with radiation.

Conclusions

The results of studies reported in the first 30 years of the century have been confirmed by our own observations, and suggest the following conclusions.

1. Some cancers, in both man and animals, are more susceptible to destruction by heat than are the tissues they grow in.

2. Heat acts synergistically with radiation in controlling the growth of many cancers.

3. The mechanism by which heat kills cells is poorly understood and deserves further study.

4. The uses of heat as an adjunct to the treatment of human cancers should be explored.

References

1. Müller, C.: Die Krebskrankheit und ihre Behandlung mit Röntgenstrahlen un hochfrequenter Elektrizität resp. Diathermie. Strahlentherapie **2**: 170-191, 1913.

2. Doyen, E.: Traitement local des cancers accessibles par l'action de la chaleur au dessus de 55°. Rev. de thérap. méd.-chir., Par. **77**: 577, 1910.

3. Warren, S. L.: Preliminary study of effect of artificial fever upon hopeless tumor cases. Am. J. Roentgenol. **33**: 75-87, 1935.

4. Rohdenburg, G. L., and Prime, F.: Effect of combined radiation and heat on neoplasms. Arch. Surg. **2**: 116-129, 1921.

5. Westermark, N.: Effect of heat upon rat-tumors. Skandin. Arch. f. Physiol. **52**: 257-322, 1927.

6. Selawry, O. S.; Goldstein, M. N., and McCormick, T.: Hyperthermia in tissue-cultured cells of malignant origin. Cancer Res. **17**: 785-791, 1957.

7. Selawry, O. S.; Carlson, J. C., and Moore, G. E.: Tumor response to ionizing rays at elevated temperatures; review and discussion. Am. J. Roentgenol. **80**: 833-839, 1958.