Ultrasound Destroys Cancerous Tumors

by Joseph Neglia

While the Bristol Meyers symposium last October at the University of Chicago attracted over 400 cancer researchers to compare notes on their search for the ultimate causes of cancer, researchers at the University of Pennsylvania and elsewhere were pursuing a different strategy for ultimately controlling the disease.

Rather than focusing on virology and genetics, these researchers are attempting to kill tumors while they are still inside the patient, noninvasively, using nothing more complex than carefully applied and focused heat.

The idea is simple. When tumors are heated, they tend to die, just as ordinary tissue. The difference is that tumor cells tend to die a little faster than normal cells at these elevated temperatures. This phenomenon is commonly known as hyperthermia.

W. Busch, the German researcher who first noticed this phenomenon quickly realized its potential as a cancer treatment. Instead of attempting the difficult procedure of removing tumors, he researched the idea of heating them. Physicians have been developing various techniques for heating tumors ever since.

Artificial hyperthermia's beginnings were entirely empirical: in 1886, Busch noticed a quick regression of a number of highly malignant tumors in the face of a woman after she had successfully fought off a streptococcus infection and the high fever that accompanies it. Busch suspected a connection between the fever and the regression of the cancer and thus began widespread investigation into the effects of heat on cancer.

Meanwhile, experimentation also advanced rapidly in the United States. William Coley, a New York surgeon, developed bacterial injections that deliberately induced severe fever in his patients, thus artificially inducing the high temperatures supposedly needed to kill tumors. Some of his experiments with otherwise hopeless cancer patients were unexpectedly successful; some of these "terminal" patients lived for another fifty years. Others, however, were not as lucky. The toxins they were injected with were just that – toxic. Rather than getting a controlled fever, these patients were inflicted with more harmful effects, which shortened their lives considerably. Being unpredictable, Coley's method was dropped.

But the observation that tumors do not react well to elevated temperatures, remained. Solid a priori explanations of the phenomenon of hyperthermia still do not exist. Why are tumor cells more sensitive to heat than normal cells? The theories differ.

One of these simply assumes that the poor blood circulation inside tumors cannot dissipate heat fast enough to keep temperatures within limits necessary for survival. Another, more comprehensive theory concerns nutrition; because the tumor cells are already low in oxygen and poorly nourished, they would naturally react unfavorably to further "inconveniences" such as excessive heat.

Recently, researchers have been more successful in light of new observations and new techniques. For example, it has been noted that while heated tumors generally regress, this condition is temporary, lasting about one year at most. Only when used in conjunction with some of the traditional methods of cancer treatment does hyperthermia display its real power in destroying cancer. One research team at the Sloan-Kettering Cancer Center in New York City found tha when they used radiation therapy alone, they obtained a 30 percent rate of tumor regression. With heat alone, the regression rate dropped to 20 percent. But when these two

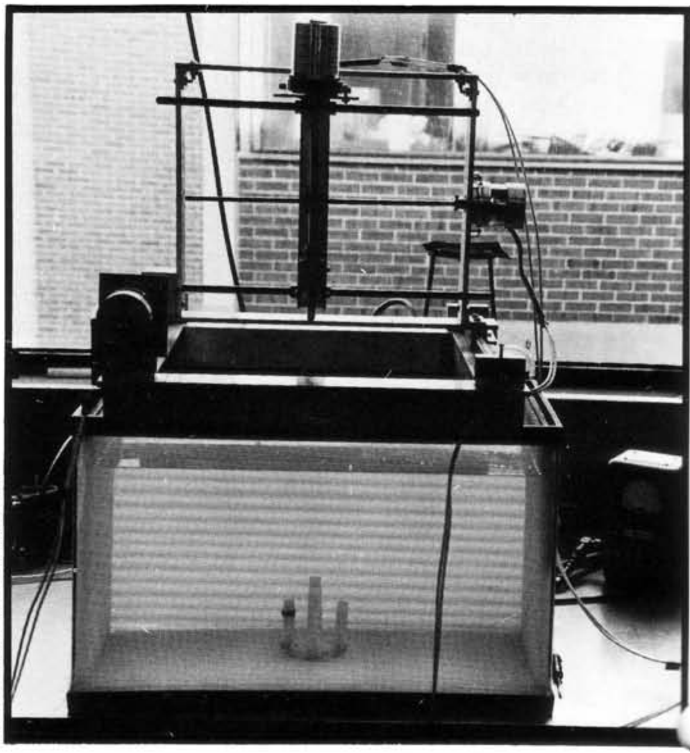


photo courtesy of Dr. Ketterer

Prototype of focused beam scanning ultrasound hyperthermia system.

methods were combined, the response rate of tumor regression jumped to an almost incredible 80 percent!

There are a number of ways of delivering this heat to cancerous tumors in the human body. These range from the crude methods of the past century where patients were exposed to virulent streptococci to induce the desired high temperatures, to the three-dimensional, scanning, focused beams of ultrasound currently under investigation by Dr. Fred Ketterer of the Moore School.

The limitations in hyperthermia's usefulness appear to result directly from the systems used to create this artificial heating of tumors. Some researchers are heating the patients' entire body in order to reach the tumors. They wrap the patients in hot water bottle type plastic sheets to raise the total body temperature. In this way, they are certain to affect all the cancer in the body, not only the major tumors. Naturally, however, the entire human body cannot be held at a temperature high enough to damage tumors (43=C, or about 110=F) for any length of time without sustaining severe damage itself.

Because heating the whole body is painful and impractical, and heating only the tumor is difficult to do precisely, other scientists are experimenting with "regional hyperthermia." In this process, a region of the body is heated, leaving the rest of the body relatively free from intrusion. Two researchers at St. Joseph's Hospital in Houston, John Stehlin and Beppino Giovanella, have devised a method that looks promising. An artery in an arm or leg is spliced and injected with blood which has already been heated to the desired temperature. This method affords a bit more latitude in determining temperatures than does the method of heating the whole body.

More common techniques in use throughout the country involve various types of electromagnetic radiation. At radio frequencies (those frequencies between approximately 500kHz and 30MHz) there are two possible approaches: capacitive and inductive. In the capacitive method, two conducting plates are placed around the tissue containing the tumor. Electrical engineering students will immediately recognize that this forms a capacitor, with the tissue between these plates acting as a dielectric. Depending on their dielectric constant (the "permittivity") some tissues will be heated more and others less intensively at a given frequency. Tissue with a lower dielectric constant will be heated more efficiently than tissue with a higher constant. This is unfortunate, for it has been determined that, compared with other tissue, fatty tissues have a relatively low dielectric constant. Since all subjects have a layer of adipose tissue beneath the skin, this layer absorbs most of the heat, diverting it from the desired areas and producing undesirable results. Noted researcher Neymann in 1939, "The subcutaneous adipose tissue is liquefied...this melted fat later forms hard indurated tumors which in time may become infected."

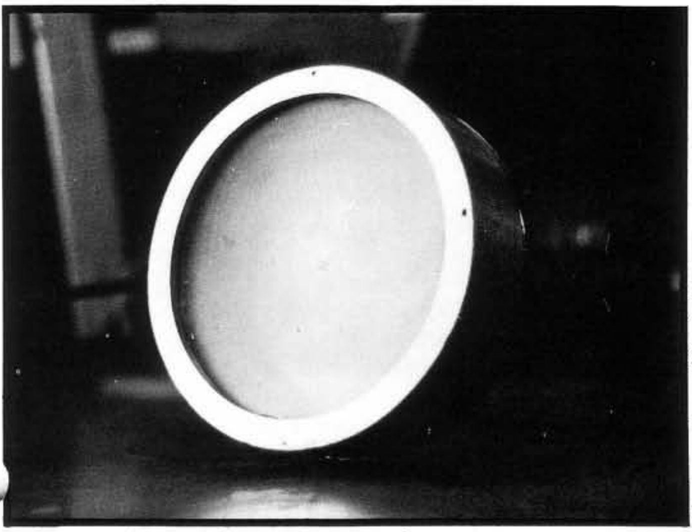
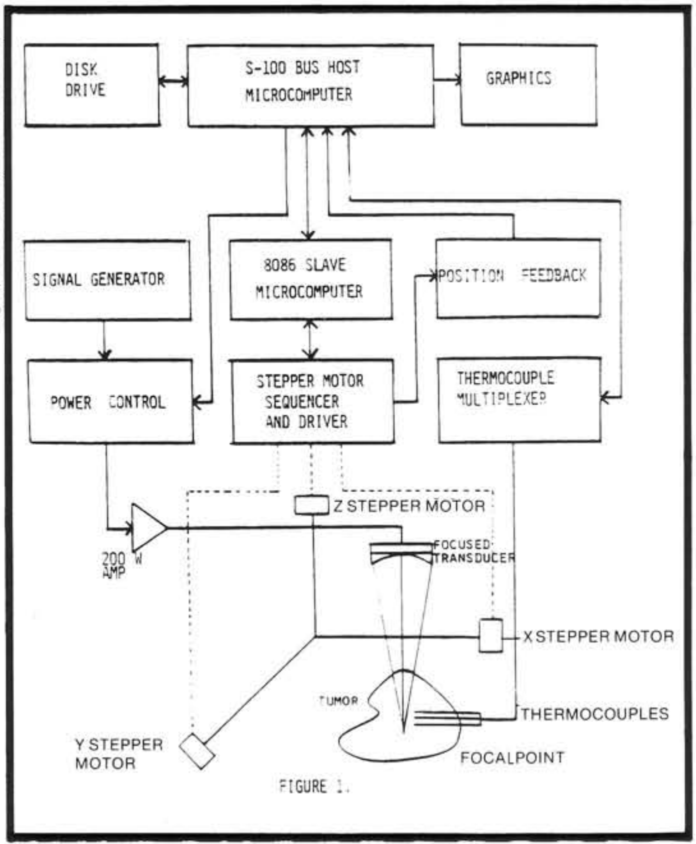


photo courtesy of Dr. Ketterer

Closeup of curved ceramic transducer.

graphic courtesy of Dave Cooper



The hyperthermia delivery system shown in functional block form.

This problem is solved by using inductive rather than capacitive heating. With the inductive method, it is the "permeability," not the permittivity, that is important. Since the permeability of all tissues is very nearly identical, the fatty layers are not preferentially heated. The catch is that although these permeabilities are similar, they are also low. This result means that low efficiencies are inevitable: huge power inputs are required to obtain desirable temperatures.

Another common technique for inducing hyperthermia is the use of focused microwaves. With microwaves, however, it is difficult to reach deep tumors. For efficient heating, a very high frequency must be used, but for deep penetration, a much lower frequency is needed.

One of the more promising methods being investigated at Penn involves sound waves at frequencies far outside the range of human hearing: ultrasound.

Normally thought of as a purely diagnostic tool used as an alternative to X rays, ultrasound can also be used to effectively heat tumors. Researchers first used ultrasound as a method for heating tumors early in the 1930's, with the same problems as many other techniques, such as excessive skin heating and preferential heating. Unfortunately, at any given frequency, bone and skin have the highest attenuation coefficients, and these tissues will be heated preferentially. While this may not be quite as damaging as liquefying the fat layers, these phenomena present special problems.

This skin heating for example, poses a dilemma. To keep the skin temperature within comfortable limits, it is essential that it be cooled. But if the skin is cooled, the resulting vasoconstriction may raise the temperatures beneath the skin to hazardous levels.

Reflections are one special problem introduced by ultrasound. Since the attenuation constant of bone is much greater than that of the surrounding tissue (mostly muscle), an impedance mismatch results. Impedance mismatches of any kind always cause reflections, and ultrasound is no exception. The wave incident on the bone will be reflected back into the muscle tissue, potentially causing dangerous "hot spots." To eliminate these dangerous problems, Padmakar Lele of MIT recently began using focused beams of ultrasound rather than the simple unfocused beams that had been used previously. Quartz transducers which are applied with high voltages at the desired frequency convert this electrical energy into an ultrasonic beam which is focused by a polyethylene lens. The result is a conical shaped region of acoustic energy which can generate a small spot of high temperature deep inside the body, at the focal point of the lens. The size and temperature of this spot are determined by the size of the lens used and the wavelength of the beam. Usually, a very small focal region is desired, and this is scanned through the entire tumor to obtain a uniform temperature distribution.

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In the not too distant future, artificial hyperthermia will be a major consideration in the treatment of cancer. But currently, it is far from being a routine procedure, as questions must still be answered concerning the long term side effects of the treatment. Of more pressing concern is the technology used to deliver the heat and to monitor the temperatures. It is not an easy task (see box), but the solution is actively being investigated at Penn's School of Engineering and Applied Science. ▲

Delivering Heat to the Tumors

The hyperthermia delivery system currently under development at Penn is shown below in functional block form. Its purpose is to generate a predetermined temperature distribution in tumors of any shape and size and at any depth within the body. This is accomplished by rapidly scanning the focal point of the focused beam through an arbitrarily shaped tumor in a predetermined pattern, while sampling the tumor temperature using thermocouple probes, and modulating the power output at each scan position.

Since all this takes place in real time, two microcomputers in parallel are used to provide the necessary speed. The host computer monitors the tumor temperature by means of thermocouples inserted into the tumor, and monitors the position of the focal point of the ultrasound beam. The temperature samples obtained are plugged into a mathematical model of the tumor in order to estimate the temperature distribution. This calculated temperature is compared with the desired temperature, and an error signal is generated if there is a difference. The intensity of the ultrasound beam is proportional to the magnitude of this error signal.

Before treatment begins, the dimensions of the tumor are input to the host computer, where they are incorporated into a set of parametric equations describing the scanning path to be followed. This program is compiled and downloaded to a high speed SDK-86 board, which contains a fast 16 bit Intel 8086 microprocessor. This processor can solve the parametric path equations fast enough to run the stepper motors in real time. Usually, a helical path is followed through the tumor. A number of different layers are scanned in this manner, heating the entire tumor, uniformly, in all three dimensions.

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