ULTRASOUND IRRADIATION OF THE HYPOPHYSIS IN DISSEMINATED BREAST CANCER*

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INVESTIGATIONS concerning the interactions of ultrasonic energy* with tissue have led to the recognition of three general areas of clinical usefulness: diagnosis, diathermy, and modification of tissue structures.[6,9] The use of ultrasound to modify anterior pituitary glandular function for the palliation of advanced breast cancer rests within the last category.

Modification of tissue structure and/or function at internal body sites is accomplished by delivering focused high level precisely controlled ultrasound into the structures to be modified. Marked focal effects may be produced at a desired depth without damaging intervening tissue. This requires accurate control of dosage parameters and the sites of irradiation. The ultrasonic energy levels delivered to a tissue site within a few seconds are of a considerably higher order than those used in diagnosis and diathermy. For example, the levels currently employed to produce selective changes in the tissue components of the central nervous system lie between 100 and 2,000 watts/cm.^{2} and the durations of the exposure lie generally in the range from $\frac{1}{2}$ to 5 seconds.[5] The frequency of the ultrasound employed in the present human study was 980 kc./sec. In specifying the acoustic parameters of radiation, the acoustic particle velocity amplitude† is specified since it is the measured quantity rather than intensity. The amplitude was 350 cm./sec. and the duration of the exposure 2.5 seconds to 3.0 seconds at each site in the array. The interval between successive exposures was 2 minutes. The selective tissue action of interest here is produced by a nonthermal mechanism, with a positive temperature coefficient.

* Sound above 20 kc./sec. frequency.

† The particle velocity amplitude is the maximum value of the sinusoidally varying particle velocity of the medium.

PURPOSE

Effective palliation for disseminated mammary cancer is obtained through hormonal alterations by the use of exogenous drugs and ablative procedures of endocrine glands (adrenals, pituitary, and gonads). This study was designed to seek another potential method of hormonal palliation in advanced breast cancer; namely, using focused, high intensity ultrasound as the therapeutic tool.

In considering pituitary glandular destruction, the normal adult human hypophysis appears little changed by roentgen radiation in tissue doses up to 10,000 roentgens.[10] However, the implantation of ionizing energy sources within the pituitary and/or its fossa appears quite destructive.[12] Likewise, proton beams from an external source can destroy the gland[3,13] and surgical extirpation is effective.[16] With respect to surgical hypophysectomy, Van Buren and Bergenstal[17] have reported that a complete surgical hypophysectomy is not essential to induce regression in mammary cancer.

It was felt that a "partial" hypophysectomy might be readily accomplished with focused ultrasound and that it could be used repetitively upon a given patient, quickly and without discomfort. After a preliminary animal study,[11] 5 female pa-

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Supported in part by the American Cancer Society, Institutional Grant IN-10B, State University of Iowa, and the USPHS Clinical Research Center Program, College of Medicine, State University of Iowa.
Presented at the Forty-fourth Annual Meeting of the American Radium Society, New York City, April 2–4, 1962.

Am J Roentgenol Radium Ther Nucl Med
Jan;89(1):71-77
1963

tients with microscopically proved advanced breast cancer were selected for the investigation. The patients, families, and referring physicians were fully apprized of the procedural aspects and their willing concurrence and cooperation enlisted. The intent was to follow each patient in detail for the remainder of her life. A case report of each patient and more detailed procedural descriptions and assay were presented in a prior publication.[7]

TECHNIQUE OF IRRADIATION

Focused high intensity ultrasound has been used in the past decade in neurologic research on experimental animals at the Biophysical Research Laboratory of the University of Illinois, and, more recently, in a joint human research project by that laboratory and the Division of Neurosurgery at the State University of Iowa. In the human studies, the pathogenetic mechanisms underlying various disorders have been under scrutiny, *e.g.*, those germane to the tremor and rigidity of Parkinson's disease, the various involuntary movements of cerebral palsied patients, intractable pain, and the dysesthesias and dyskinesias which sometimes follow cerebral vascular accidents.[14] A single attempt at the destruction of an intracranial interpeduncular tumor has been made.

The pituitary gland irradiation was implemented in the advanced mammary cancer patients in a manner similar to the irradiation of brain structures. The technique is as follows: Because ultrasonic energy cannot penetrate the cranial bone without undue absorption, reflection and refraction, a lateral craniectomy is performed 2 to 3 weeks prior to irradiation. The scalp and muscles are repositioned by suture and the bone is saved for later replacement. The aperture in the calvarium is approximately 8×10 cm. and can accommodate the four converging beams from the four-beam focusing ultrasonic irradiator.

Precision focal irradiation is essential (Fig. 1). To secure site-specific localization, the patient's head is held immobile in a stereotaxic head holder. This is accomplished by the use of four stainless steel supporting rods which fit into superficial skull burr indentations made through short scalp incisions. The entire procedure may be performed during local or light general anesthesia and light sedation. The four-beam focusing transducer is supported and moved by an overhead calibrated carriage with a positioning accuracy of 0.1 mm. From calculations made using roentgenographic measurements, anatomically repetitive irradiation procedures can be accomplished. It is necessary also to employ a liquid transmitting medium (degassed saline) to conduct the acoustic energy from the irradiator to the skin.

The equipment described here is primarily intended for the modification and treatment of neurologic disorders, *i.e.*, for the irradiation of very small volumes of tissue. In the instance of the hypophyseal gland, 14 to 35 sites in the gland were successively exposed to the focused ultrasound as a three dimensional array to uniformly irradiate the glandular volume.

COMPLICATIONS OF ULTRASONIC IRRADIATION

Either as a consequence of direct or indirect irradiation of contiguous structures,

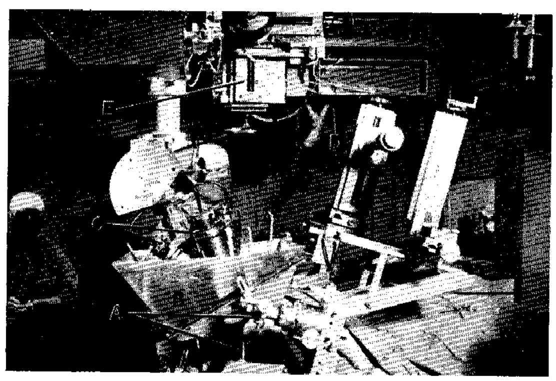

FIG. 1. The ultrasonic equipment is shown in the operating room. The patient's head is secured in the stereotaxic head holder (A). The transducers (C) are immersed in the degassed saline transmitting bath (B). The carriage control panel (D) and overhead positioning carriage are shown (E).

or of bone heating adjacent to the sella turcica, several complications resulted. These were regarded as sufficiently serious that we elected not to pursue the technique further until more suitable instrumentation is available. Each patient showed polyuria (anticipated) and, in 5 of the 6 irradiation sequences, recoverable palsies of the extra-ocular muscles (oculomotor and abducens nerves) ensued. Two patients developed severe visual changes: monocular blindness in one and a left homonymous hemianopsia in the other. One patient developed a right hemiplegia, probably in consequence of the ultrasound traversing recently traumatized tissue (degassing phenomenon). Another patient developed an upper extremity paresis due to a vascular accident, likely unrelated *per se* to the radiation.

OBSERVATIONS AND DISCUSSION

The earlier observations, including assay and procedural descriptions, have been reported. Longer term observations are now available, particularly upon 2 patients, one followed for 17 months to death with autopsy, and the other for 19 months to an approaching terminal state. This latter patient was 1 of 2 patients in whom a growth acceleration occurred after irradiation. These will be commented upon. In no instance was a favorable control of the cancer growth accomplished.

To sum up the *endocrine observations:* In each instance after irradiation an increased urinary excretion of 17-ketosteroids occurred. This lasted a median time of 2–4 days, after which normal values reappeared. In contrast, similar measurements in two sham-type operations (craniectomy and a uterine cervical dilatation and curettage) failed to produce this effect; however, the craniectomy was performed during deep anesthesia, and thus this procedure might not be strictly comparable to the others. To continue, transient depressed indices of thyroid function occurred after ultrasonic irradiation; the serum protein-bound iodine values and the thyroid radioiodine uptake determinations dropped sharply, then regained normal levels after a period of about 4 weeks. No patient developed myxedema from pituitary dysfunction. By contrast, after surgical hypophysectomy no such thyroid rebound or regain phenomena occurred. The gonadotrophin determinations showed no consistent pattern, but long-term observations demonstrated continued, although lowered, excretion levels. All patients developed diabetes insipidus at 3–7 days after the ultrasonic irradiation with a varying recovery rate toward normal after a few weeks. The fifth patient had more severe diabetes insipidus (7 liters daily of urine) and recovery was delayed for several months.

Periodic selected endocrine studies during 16 months and a complete autopsy examination were made upon a *twice* irradiated 64 year old patient. This patient continued to secrete gonadotrophins, modest declining amounts of 17-ketosteroids, and maintained an essentially normal thyroid status. Adenohypophyseal and neurohypophyseal function was evident to within 2 months of death. She died of the neoplasm after a terminal hospitalization in another city and we were permitted a complete postmortem examination.

The pituitary gland was found severely withered within the fossa (Fig. 2). However, on microscopic examination (Fig. 3), a small amount of viable anterior lobe pituitary tissue with patent vasculature was demonstrable. The neurohypophysis was similarly reduced in size. The adjacent bone was intact.

Microscopic studies of the tissues removed from 2 other patients by surgical hypophysectomy 6 and 14 weeks after ultrasonic irradiation showed modest central scarring and peripheral coagulation damage of the anterior glandular hypophysis. The coagulation damage was adjacent the bone. Both removed pituitary glands were judged grossly at surgery to be reduced to approximately 70–80 per cent of the estimated original size.

To summarize the *anticancer influences* after irradiation: No patient was benefited as a consequence of the ultrasonic irradiation other than in such a manner as would accompany increased care. This result does not militate against other efforts using this form of energy directly or indirectly in cancer diagnosis[15,18] and/or treatment.[1,2,4,8,19]

COMMENTS ON ACCELERATED CANCER GROWTH

In 2 patients, ages 66 and 46 years, there was acceleration of the neoplastic growth. In the older patient our postradiation observations were brief since she died 3 weeks after a conventional surgical hypophysectomy implemented as an urgent therapy 2 months after ultrasound irradiation. She presented with inflammatory breast carcinoma and during the preceding 2 years had had roentgen therapy, later oral stilbestrol, and then injected androgens. Preceding the ultrasound irradiation she had been on an inconstant regimen of 200 mg. of testosterone weekly. The last injection (100 mg.) had been given her 17 days before the ultrasound procedure during a period designated by us as a free therapeutic interval. Because of travel and other schedules we could not delay. The patient had a relatively small numerical array of 14 ultrasonic exposures which resulted in a relatively greater spacing between irradiation sites. She exhibited the described (but muted) pituitary target organ responses, including clinically mild diabetes insipidus. The cutaneous spread of the cancer began to accelerate rapidly and thus conventional surgical hypophysectomy was implemented to attain control. The gland was moderately scarred and reduced in size. This accelerated growth of cancer was judged significant, for by photographic documentation there had been no significant cutaneous changes in 8 months, but the withdrawal of exogenous testosterone only 17 days before the ultrasound therapy renders this interpretation somewhat ambiguous.

FIG. 2. This pituitary gland had been twice irradiated by 26 and 28 geometrically spaced exposures of ultrasound 8 months apart, the last 9 months prior to autopsy. The atrophied gland exhibited adenohypophyseal and neurohypophyseal function.

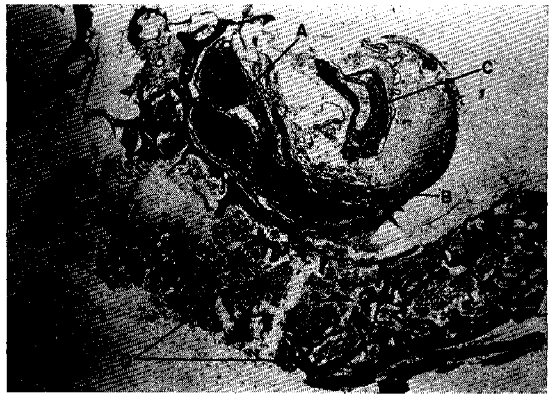

FIG. 3. The microscopic pattern of the hypophyseal gland in its fossa is seen; this is an anteroposterior section of the gland as seen in Figure 2. (A) Neurohypophysis; (B) adenohypophysis; (C) patent blood supply; and (D) essentially normal bone. Technical difficulty was experienced with the *in situ* fixation and hence the shredding artifacts of the bone.

The final patient in the series, 46 years of age, was in a premenopausal status; she was of an inattentive disposition, but it was reliably determined that she had had no prior therapy and had endured the tumor for at least a year, probably much longer. In addition to the breast replacement by cancer, she also had widespread osseous metastases. Fortunately, pre-operative photographs were made 3 weeks and

1 week before the irradiation and these helped confirm the history of a minimal but conspicuous recent change in the cancer growth pattern within the breast. Following irradiation delivered to 35 spaced sites within the pituitary gland, a rapid aggressive growth of the cancer appeared in the breast and thorax. In this instance, the further attempt at neoplastic control was through transabdominal surgical adrenalectomy and oophorectomy. By the seventeenth day following adreno-oophorectomy, cancer regression in the described soft tissues was striking. The breast became healed, soft and pliable as the regression continued. The sequence of events covering 16 months is shown in Figure 4, *A–H*. The osseous metastases proved more difficult to judge. The patient had suffered a hemiparesis as a radiation complication with subsequent disuse changes in the bone; moreover, as time passed, the bony response to cancer was of an osteoblastic type, quite difficult to assess. This patient is now approaching a terminal state because of renewed tumor growth, 16 months after removal of the ovaries and adrenals. Hormonal measurements following adreno-oophorectomy revealed, upon withdrawal of exogenous corticoid sources, sharply reduced urinary ketosteroid excretion levels (to less than 1 mg. per gm. of creatinine) and a functioning pituitary, as determined indirectly by the indices of normal thyroid function and directly by wavering excretion levels of gonadotrophins. The tumor growth responses after ultrasonic irradiation and later, after ablation of the ovaries and adrenals, were remarkably different.

The last 2 patients merit additional comment. Very likely they possessed neoplasms exquisitely sensitive to hormonal manipulation. One of them had had 10 months of benefit while on oral stilbestrol; however, because the injected androgen caused fluid retention, it was not administered regularly and was regarded as of little benefit.

The second patient of the two cited exhibited obvious acceleration of the cancer growth following irradiation. After removal of the adrenals and the ovaries such growth was favorably retarded. In relationship to these phenomena, such release from regulatory forces prompts interesting specula-

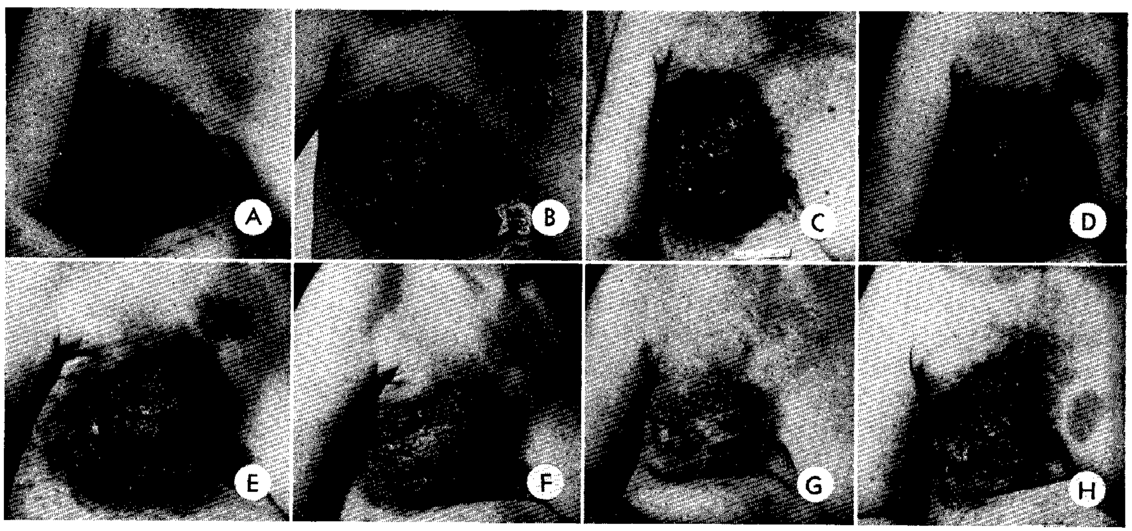

Fig. 4. This pictorial sequence portrays the increased mammary cancer growth after ultrasonic irradiation of the pituitary gland in Patient 5. The continuum shows also the striking response to adrenal and ovarian ablation. (*A*) Three weeks and (*B*) 1 week pre-ultrasonic irradiation of pituitary, (*C*) $4\frac{1}{2}$ weeks post irradiation, (*D*) 12 weeks post irradiation and 2 days pre-adreno-oophorectomy, (*E*), (*F*), (*G*) and (*H*) $2\frac{1}{2}$ weeks, 5 weeks, 8 months, and 12 months post-adreno-oophorectomy.

tion as to the interplay of quantitative and qualitative hormonal factors and their potential for augmenting, deterring, or otherwise modifying on-going cancer processes. The observations attest again to the lack of autonomy in breast neoplastic growth.

SUMMARY

The purpose of this study was the initial exploration of a possible new method for controlling disseminated mammary cancer. Focused ultrasonic irradiation was employed to produce pituitary tissue alterations and, thus, regulatory control of cancer growth by endogenous hormonal changes. Using a technique previously developed for modifying brain structures by precisely controlled ultrasonic energy, 5 patients were irradiated in 6 sequences.

Following irradiation, transient measurable alterations in the hormonal output of certain pituitary target organs as well as diabetes insipidus occurred. No control of the mammary cancer was seen; hence, the primary objective was not attained. Since stimulation of the cancer followed irradiation in 2 patients, it appeared that a loss of a regulatory mechanism took place. The hastened cancer growth was controlled by ablative adrenal and ovarian surgical removal in one patient; the other failed to withstand surgical hypophysectomy and, thereby, was insufficiently observed. No suggestions regarding basic mechanisms to explain the observed changes have been forthcoming.

The exploitation of ultrasonic radiation in the study of the human hypophysis is limited at this time by the lack of instrumentation specifically designed to irradiate the hypophysis without inducing neurologic complications. Such instruments can, we are confident, be designed.

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Reprinted from
The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine
Vol. LXXXIX, No. 1, January, 1963

PRINTED IN U.S.A.