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Human Pituitary Irradiation with Focused Ultrasound

An Initial Report on Effect in Advanced Breast Cancer

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The purpose of this presentation is to offer an initial report upon human anterior pituitary irradiation with focussed high-intensity ultrasound. Our efforts were prompted by the ever-recurring need for improved palliation in disseminated and advanced breast cancer, and our intent was to alter favorably the growth pattern of advancing mammary cancer through hormonal changes. The study included searches for objective changes in the neoplastic processes, scrutiny of certain physiological sequelae after such irradiation, and deliberations upon improvement in technique and methods. We believe this to be the first human study using this modality.

Primary surgical or radiological therapeutic measures in breast cancer meet failure with an appreciable predictable frequency.[1] The most effective palliation for disseminated cancer is obtained then through hormonal manipulation by the administration of exogenous drugs and/or ablative endocrine organ procedures. During the past decade the use of the latter has become more frequent. In techniques of destruction, the normal anterior pituitary gland appears to be little influenced by x-irradiation in tissue doses up to 10,000 r.[2] Implantation of ionizing radiation sources into the hypophysis was pioneered by Lacassagne[3] in 1934 as an alternate to external roentgen therapy, and, since then, ionizing energy sources of radiogold, yttrium, radon, and colloidal radioactive chromium phosphate have been implanted effectively in the pituitary and/or its fossa. Another alternate to external x-irradiation is the use of heavy-particle beams, such as the proton bean.[4] Luft and associates[5] have been prime motivators in establishing an acceptable surgical technique

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of extirpative hypophysectomy, so now, subsequently, much surgical experience has been collected on an essentially world-wide basis.

Hypophysectomy affects the hormonal activity of target organs. Other side-effects of less readily identifiable character may be possible. Especially pertinent to breast cancer is the withdrawal of the pituitary stimuli to the adrenals and ovaries. The effects of withdrawal can be brought about also by removal of these endocrine glands. Thus far at the State University of Iowa Hospitals, we have favored adrenalectomy with or without oophorectomy.[6]

Ideally, one might envision a method of hormonal environmental control whereby a predicted, repetitive alteration would be produced with repetitive remissions. As reported by Van Buren and Bergenstal,[7] complete surgical hypophysectomy is not essential for mammary cancer regression. Thus, a rationale of the use of focussed high-intensity ultrasound rests with the supposition that if a change in hormonal output can be produced by this technique resulting in neoplastic control, such hormonal alteration might be graded and easily repeated.

Focussed high-intensity ultrasound has been used for the past decade in fundamental neurological research upon experimental animals at the Biophysical Research Laboratory, University of Illinois.[8] For the past several years as a joint research project of the Biophysical Research Laboratory and the Department of Surgery (Neurosurgery), State University of Iowa, it has been used in human neurosurgery to study and treat the pathophysiological mechanisms underlying the hyperkinetic disorders and in certain intractable pains.[9] A further collaboration (with R.C.H. and J.T.B.) prompted the research efforts of this program.

Patients Chosen

Five female patients with advancing breast cancer were selected for ultrasonic irradiation of the hypophysis. These patients demonstrated a scattered age distribution from 46 to 64 years, and were beyond any expectation of cure. In each case, prior observations or information was available that in some measure permitted an evaluation of the biological propensities of the microscopically proved cancer. Four patients had both bony and soft tissue metastases, including, in one case, palpable liver metastases. One patient alone had had primary surgical therapy (a radical mastectomy), and her only demonstrable metastases were in bone.

In 3 instances, other anticancer regimens had been discontinued (one had no therapy) for at least 7 weeks prior to ultrasonic irradiation. In 2 instances, Patients 2 and 4, hormone therapy was continued to 19 and 17 days before ultrasonic irradiation.

At the outset, patients, families, and referring physicians were fully apprised of the procedural aspects of our endeavor and of the pros and cons germane to it. In each instance, concurrence and cooperation were willingly profferred. In the checking of therapeutic procedures, each patient served as her own control.

Clinical Résumé of Patients' Histories

PATIENT 1.—Aged 57 years, this woman had large, nodular liver metastases in addition to bone metastases, and had diabetes mellitus. She had been treated by oophorectomy and male and female hormones with subjective benefit from these therapies, although the diabetes mellitus was made more severe by the sex hormone therapy. She had had no anticancer therapy for 7 weeks prior to ultrasound. An array of 20 ultrasonic exposures was spaced in the hypophysis and she developed a right third cranial nerve palsy and then mild diabetes insipidus by the seventh postoperative day. The observation period was terminated after 5 months by death.

PATIENT 2.—Aged 64 years, this patient had arterial hypertension and exhibited a large firm breast with a huge cyst; she had pulmonary and osseous metastases. On a previous occasion x-ray therapy had cleared an ulcerated mass in the breast. The patient received 5 mg. of stilbestrol daily up to 19 days before ultrasound therapy. She was irradiated with 28 and 26 spaced ultrasonic exposures on each of 2 occasions, 8 months apart. After the first series, third and sixth cranial nerve palsies resulted and diabetes insipidus appeared on

the seventh day. This patient's breast mass softened and she became less hypertensive. Pulmonary and osseous metastases progressed slowly. The second irradiation sequence produced only a mild third nerve palsy. The observation period now exceeds 10 months.

PATIENT 3.—Patient 3, aged 49 years, had had a radical mastectomy 6 years before the ultrasound sequence. One year before, palliative therapy with ovarian x-irradiation was followed by a 5-month remission. No specific therapy was given for 6 months prior to delivery of 28 ultrasonic separated exposures to the pituitary area. Cranial nerve deficits did not appear; however, diabetes insipidus became evident on the third postradiative day. The patient showed no clinical improvement of her cancer, and, hence, a surgical hypophysectomy was carried out 3½ months later. Again, no clinical remission ensued. The period of observation after ultrasonic irradiation is 7 months, but the patient is essentially bedfast.

PATIENT 4.—Patient 4, 66 years old, visited her doctor with a breast tumor of 4 months' duration. The lesion was inoperable because of an inflammatory type of spread. After x-ray therapy, a control period of 6 months elapsed, following which she was given stilbestrol with a beneficial interval of 10 months. She was placed then upon 200 mg. of testosterone weekly. The last hormonal therapy was given 17 days prior to ultrasound irradiation, at which time 14 sites were irradiated. A homonymous hemianopsia was described by the patient, and further irradiation was withheld. Mild diabetes insipidus appeared on the fourth day. Surgical hypophysectomy was carried out 6 weeks after the ultrasonic procedure. During the period between ultrasonic irradiation and surgical hypophysectomy, the cancerous process advanced rapidly. At the time of preliminary craniectomy the patient developed a contralateral upper limb paresis due to a cerebrovascular accident at operation. The patient died 3 weeks after surgical hypophysectomy and 2 months after ultrasound.

PATIENT 5.—This patient, aged 46 years, had an enlarging mass in her breast for at least one pear. She had had no specific prior therapy. Thirty-five spaced ultrasound exposures were delivered to the hypophysis during halothane (Fluothane) anesthesia, after which time the patient developed a hemiparesis, paralysis of the third cranial nerve, and blindness in one eye. Diabetes insipidus appeared on the third postirradiation day. During the next 12 weeks of observation, the cancer advanced rapidly in an inflammatory manner and ulcerated. Adrenalectomy and oophorectomy were performed, and a striking visible remission in the neoplasm followed. The observation period following ultrasound is now 4 months.

Technique of Irradiation

The preparation of patients for ultrasonic irradiation of the hypophysis is similar to that employed for the irradiation of brain structures.[10] As a preliminary, lateral craniectomy is performed 2 or more weeks prior to irradiation. This is necessary because the focussed ultrasound cannot penetrate the skull without undue absorption, reflection, and refraction of the beam by bone. It is essential to remove a portion of the cranium of such size (approximately 8 x 10 cm.) that the cone of convergence of the focussed ultrasonic beam(s) can enter the brain without impinging upon the remaining calvarium. Upon removing a suitable portion of the skull, the scalp and muscle flaps are closed.

Precision irradiation of the hypophysis (or neural structures) requires (*a*) that the patient's skull be supported rigidly in a stereotaxic headholder and (*b*) that the focussing irradiator be precisely movable into position by a supporting system with calibrated scales reading directly in tenths of a millimeter. The head of the patient is secured in the stereotaxic headholder by 4 stainless steel supporting rods which pass through short incisions in the scalp and fit into superficial skull burr indentations. The tips of the supporting rods can be repositioned in space within 0.1-0.2 mm.; hence, the patient may later be subjected to anatomically accurate repetitive irradiation procedures. With the bone removed, repeated irradiation through the intact skin causes but minimal inconvenience to the patient. The bone is preserved, and, if desired at some later time, may be replaced to fill the defect in the vault.

The coordinates for placing the focus of the ultrasonic beam at an array of sites in the hypophysis are determined from measurements made on lateral, anteroposterior and approximately vertical roentgenograms. By this means, the configuration of the sella turcica is outlined. The corrected roentgenograms, upon interpretation, permit the focus of the ultrasonic beam with a geometric

accuracy of 0.2 to 0.4 mm. after passing the entire brain substance.

A transmitting liquid of physiological saline conducts the sound from the irradiator to the skin surface of the patient. This saline must be degassed in order to prevent the formation of gas bubbles ("cavitation") which would otherwise interfere with the passage of high intensity ultrasound. After the coupling pan is filled with degassed saline, the 4 ultrasonic transducers are submerged in the liquid within the pan and positioned with the focus upon the first site to be irradiated in the hypophysis. Since the focussing irradiator was primarily designed and intended for the modification and treatment of neurological disorders (in which many of the involved neural structures are of small volume, as compared to the hypophysis), it is necessary to place the focus successively in 30 to 40 sites in order to irradiate the glandular volume uniformly. The individual focussed sites in the array are spaced in the form of rectangular grid, with 2 mm. spacing between centers.

The ultrasonic frequency employed in this human study was approximately one megacycle per second. The acoustic particle velocity amplitude has been 350 cm. per second and the duration of the exposure between 2.5 and 3 seconds at each site in the array. In order to irradiate an entire pituitary gland, some 35 or more exposures would likely be required; the number of sites in the array would depend upon the tissue volume. An interval of 2 minutes (approximately) is permitted to elapse between successive exposures. The irradiation procedure can be regularly implemented with local anesthesia (only) at the cutaneous sites adjacent the headholding rods. With the patient awake, the sequential record is supplemented by the patient's verbal and other behavorial reports.

Laboratory Studies

Serial observations were made upon urinary 17-ketosteroids and upon serum protein-bound iodine and thyroid radioiodine uptake at 4 and 24 hours. The I^{131} uptake results were plotted for convenience as the mean of 4- and 24-hour values. Urinary collections were made daily, and the thyroid studies at 7-10 day intervals. The method of determination of the steroids follows:

Total 17-ketosteroids were removed from urine by acid hydrolysis and simultaneous extraction in toluene. The Zimmerman reaction with m-dinitrobenzene was used for quantitative estimation. The findings were expressed as milligrams per 24 hours and also as milligrams per gram of urine creatinine. The ratio tends to correct for inadvertent errors in urine collection.

The gonadotrophic hormones were absorbed on Kaolin by the method of Bradbury, Brown, and Brown.[11] They were assayed in the immature female rat; the ovarian weight increase was used as a quantitative estimation.

Other observations included, at irregular intervals, determinations of serum electrolytes and blood plasma proteins, serum cholesterol, serum alkaline phosphatase, fasting blood sugar, and glucose tolerance and liver function flocculation tests. The data derived from these studies revealed no consistent pattern or trends. The serum protein-bound iodine determinations were by the method of Barker.[12]

Simple water balance studies consisted of measured urinary output and specific gravity determinations by clinical urinometers. As a preliminary procedure, water was withheld in order to test the ability to concentrate urine. In the single instance of severe diabetes insipidus, the integrity of the neurohypophysis system was tested by the use of 2.5% saline infusion given intravenously at the rate of 0.25 ml. per kg. per minute for 45 minutes, in the presence of a water diuresis.

Results

A. Clinical Observations upon the Cancer.—After the ultrasonic irradiation, no unequivocal favorable alterations in the growth patterns of the cancers occurred.

Patient 2, twice irradiated, improved clinically, and the breast cancer softened. In this one regard the issue of palliation is somewhat in doubt; however, this patient's parenchymatous pulmonary and osseous lesions continued to advance after the ultrasound.

In 2 instances, those of Patients 4 and 5, the clinical observations suggested that an acceleration of the cancer growth occurred. Each patient was subsequently subjected to a further surgical procedure, hypophysectomy in one instance and adrenalectomy with oophorectomy in the other. During the 3 weeks preceding the death of the hypophysectomized patient no clinical amelioration of the cancer was evident. In contrast, the cancer of the adreno-oophorectomized patient regressed markedly. This response to hormonal manipulation was striking by 3-4 weeks.

B. Hormonal Alterations.—1. Ketosteroids: In each instance, an increased excretion of urinary 17-ketosteroids followed ultrasonic irradiation (Fig. 2). This pattern could not be accounted for by the observed normal variations in the pattern of excretion. An associated transient fall in eosinophils in the peripheral blood was consistently observed.

2. Thyroid: A decrease in thyroid activity was regularly noted, and recovery was evident in all instances by about 3-5 weeks. In Patient 1 the thyroid tests were invalidated because she probably received inadvertently exogenous iodine during the control period. In contrast to the transient decrement of thyroid I^{131} uptake following ultrasonic irradiation, the radioactive iodine uptake remained depressed throughout the postoperative follow-up of the 2 patients subjected to surgical hypophysectomy.

C. Physiological Alterations.—Patient 5, 46 years old, had had irregular menses, with intervals up to 3 months, prior to ultrasonic irradiation. After ultrasound, no menstrual period ensued for 3 months, although the vaginal smear continued to show an estrogen effect. These data are nonconclusive. Patient 2, aged 63 years, exhibited vaginal bleeding 8 months after ultrasound. Clinical inquiries and microscopic examination of the endometrial tissues failed to reveal a cause.

After ultrasound, Patient 2 exhibited a lowering of blood pressure from mean levels of 210/110 to 150/190 mm. Hg. This might be imputed to the irradiation; however, a tentative alternate possibility is that the estrogen given orally up to 19 days prior to ultrasound therapy in doses of 5 mg. daily might have produced the arterial hypertension as a side-effect. A second downward fluctuation was noted also at the second sequence and in the absence of hormone.

Patient 1 had diabetes mellitus and was taking 35 units of insulin daily. The severity of the diabetes was ameliorated by withdrawal of exogenous male hormone 7 weeks prior to ultrasonic therapy. After ultrasonic irradiation, she required no exogenous insulin; however, the identification of cause-and-effect relationships here is somewhat equivocated by the fact that a trend toward dietary control was already noted after withdrawal of the exogenous hormone.

Fig. 1.—Schematic sketch of the irradiation technique. Omitted are the isotonic saline bath to transmit the sound from the focussing transducers to the skin and the stereotaxic head-holding equipment. In the insert, the close proximity of neural structures may be noted. *A*, neurohypophyseal tract; *B*, optic tract, and *C*, extraocular nerves (III, IV, and VI). Note also the bone defect created by prior lateral craniectomy.

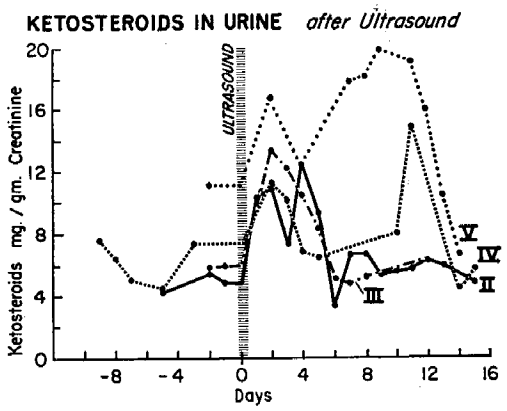

Fig. 2.—In every instance, a transient urinary ketosteroid excretory increase occurred after the ultrasound.

D. Water Balance.—All patients developed diabetes insipidus. The urinary outputs increased at 3-7 days after ultrasound, and were at modest levels of about 3,000 ml. daily. A discernible gradual trend toward recovery was evident.

Patient 5 had severe diabetes insipidus with a urinary excretion up to 7 liters daily. This condition responded well to vasopressin tannate (Pitressin Tannate in Oil). However, with overnight dehydration at the time of her adrenalectomy, the patient was able to concentrate to specific gravity levels of 1.016. Upon being tested for integrity of the neurohypophyseal system by the hypertonic saline test, she responded in a manner characteristic of the normal subject.

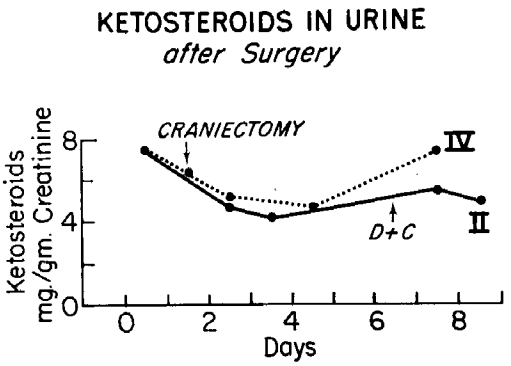

Fig. 3.—The urinary ketosteroid excretions are shown at the time of so-called sham operations, performed at the times indicated by the arrows.

E. Microscopic Changes.—Patient 3 underwent surgical hypophysectomy 4 weeks after ultrasonic irradiation, Patient 4, 6 weeks after ultrasonic irradiation. The specimens removed in toto were fixed in Bouin's solution and stained with periodic acid-Schiff-hematoxylin-light green-orange G.

The most conspicuous histological change was a narrow, peripheral zone of stromal collapse with glandular destruction and replacement fibrosis. A few central areas of scarred fibrosis adjacent nodular glandular aggregates were present in the central portion of the gland (Figs. 6 and 7).

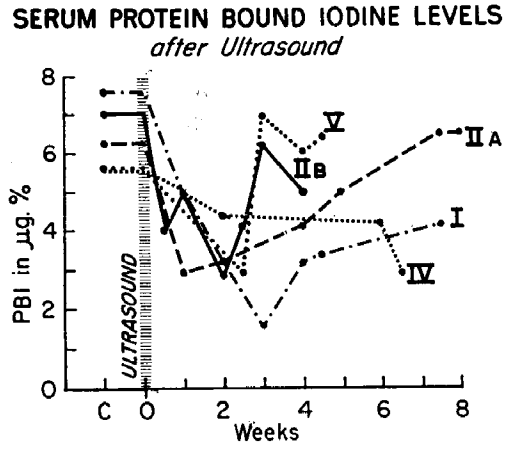

Fig. 4.—The serum protein-bound iodine values decreased after ultrasonic irradiation with recovery in about 3 to 5 weeks (except Case 4).

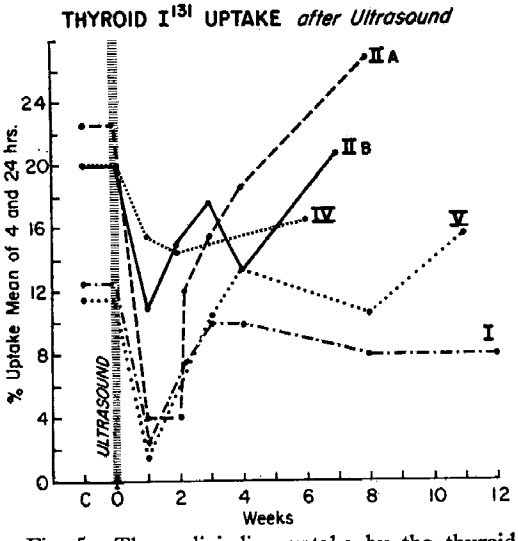

Fig. 5.—The radioiodine uptake by the thyroid (shown as the mean of 4- and 24-hour values) decreased after ultrasonic irradiation, with recovery by about 3 to 5 weeks.

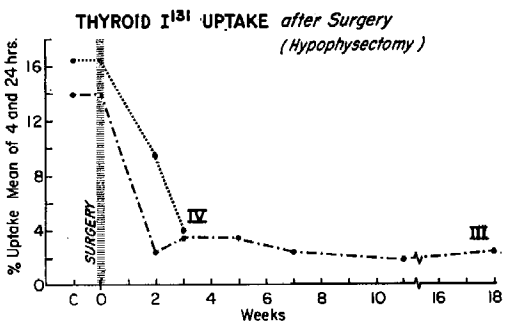

Fig. 6.—In contrast to Figure 6 (ultrasonic therapy), after surgical hypophysectomy no recovery of thyroid I^{131} uptake occurred.

The ovaries and adrenals from Patient 5, removed 12 weeks after ultrasonic irradiation, were examined by hematoxylin-eosin techniques and showed no discernible abnormality.

F. Gonadotrophins.—There was no consistent pattern of gonadotrophin excretion after ultrasound. Patient 2 excreted little or no gonadotrophin prior to or during the first month after the initial ultrasound. From the second through the eighth month she excreted moderately elevated amounts of gonadotrophin. During the first month after the second ultrasonic irradiation the excretion of gonadotrophin gradually declined until it was no longer detectable. Gonadotrophins disappeared from the urines of Patient 3 about one month after irradiation. Patient 1 continued to excrete reduced quantities of gonadotrophin as long as 4 months after irradiation. Patient 5 excreted gonadotrophin only during the first week after ultrasound and then again after adeno-oophorectomy. Whether this early excretory phase represents a stimulation of the pituitary or was just a lysis and release of cellular contents is a matter of conjecture.

G. Psychologic Status.—The abilities of patients to discriminate, generalize, abstract, recall, recognize, and exercise judgments comparable to those of which they were capable prior to operation were essentially unaltered in all instances, save that of the patient who developed hemiplegia. She exhibited a marked dysphasia from which an appreciable recovery was eventually realized.

During the ultrasonic exposure, the wakeful patients reported a moderate to severe transient retro-orbital pain, attended rarely by a subjective flash of light following some exposures.

H. Complications.—The complications were due to inadequate instrumentation (resulting in advertent bone heating) and those inaptitudes associated with a new experimental endeavor. (Direct irradiation could have damaged the neurohypophysis and optic pathways.) The complications imputable to bone heating may be synopsized as follows:

1. The least severe and not unexpected complication was a postirradiation polyuria. Each of 4 patients developed mild diabetes insipidus and the fifth developed severe diabetes insipidus necessitating exogenous therapy. No increase in the diabetes insipidus was noted following the second irradiation in Patient 2.

2. Recoverable palsies of the extraocular muscles innervated by the oculomotor and abducens nerves followed in 5 of the 6 sequences.

3. Patient 4 developed an enduring left hononymous hemianopsia and Patient 5 developed blindness in the right eye.

The complications imputable to surgical inexperience may be summarized as follows:

1. Patient 4 developed a paralysis of the right upper extremity incident to a vascular accident associated with removal of the lateral cranial plate.

2. Patient 5 developed a right hemiplegia, with subsequent partial recovery. This was ascribable to the ultrasound sequence traversing brain tissue recently traumatized incidental to craniectomy.

3. One patient suffered a minor wound infection.

Comment

The data suggest that high-frequency focused ultrasonic irradiation to the anterior pituitary gland may alter hormonal

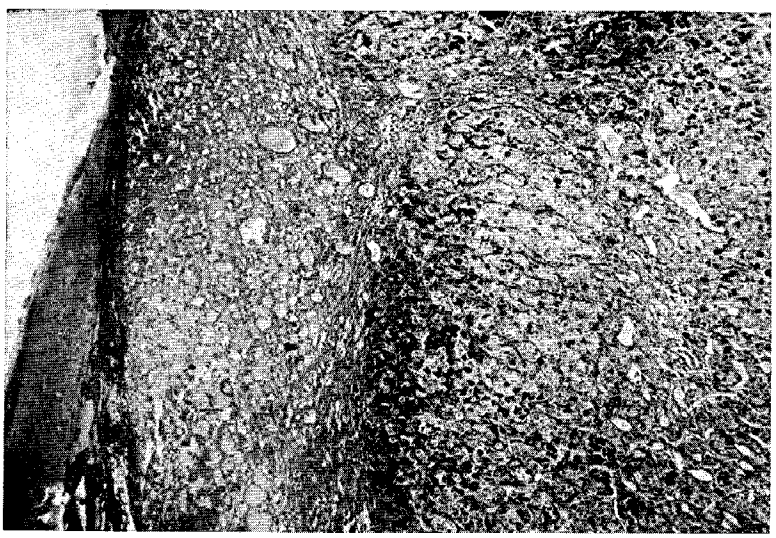

Fig. 7.—On the left is postsurgical fibrin collection, then a narrow zone of glandular destruction, and toward the right, essentially normal pituitary cellular structures. Likely, thermal energy accounted for the zone of glandular destruction depicted.

conditions, but our hopes for evidences of neoplastic control are not at hand. In all of our 5 patients, a transient interference in the thyroid hormonal mechanisms and a transient increase excretion of urinary ketosteroids regularly followed ultrasonic irradiation. Sham operations (without ultrasound) failed to effect a comparable ketosteroid stimulation in Patient 4, who underwent craniectomy and developed severe complications, and in Patient 2, who underwent a uterine diagnostic dilatation and curettage. The intravenous drip administration of adrenocorticotrophic hormone to Patient 2 reproduced an increased excretion of ketosteroids. Data presented by Moore [13] indicate that ordinary surgical trauma per se does not markedly elevate 17-ketosteroid excretion, although the 17-hydroxycorticoids are increased. In one patient tested, the urinary hydroxycorticoids became elevated also, following the ketosteroid excretory pattern.

One thesis of the 17-ketosteroid change might assume that the effect was related directly to the ultrasonic irradiation of the anterior pituitary gland; another, that this was a stress phenomenon associated with a

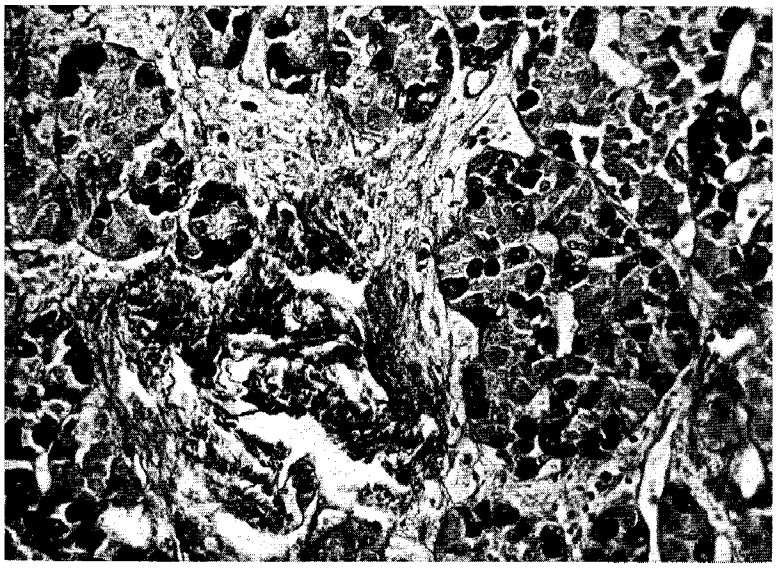

Fig. 8.—This microscopic section of essentially normal pituitary gland shows some central scarring judged to be an aftermath of the effects induced by the ultrasonic irradiation.

surgical situation. The latter seemed relatively untenable, since craniectomy and a uterine dilatation and curettage in Patients 5 and 2 as sham procedures did not induce reproducible similar steroid changes. Whether the ultrasound in penetrating the brain tissues produces a unique mode of stimulation has not been explored adequately.

As a possible further index of hormonal alteration, consequent upon ultrasound, the clinical observation is presented that Patient 5 had an accelerated cancer growth, interpreted as a valid observation; this cancer regressed strikingly after adrenalectomy and oophorectomy, indicating a hormonal sensitivity to cancer growth. Patient 4 had a suggestive accelerated inflammatory neoplastic growth, but this observation was difficult to document. The patient had responded subjectively seemingly to prior exogenous hormonal manipulation and the hormone was withdrawn only 17 days before irradiation with ultrasound. The matter of acceleration here must remain conjectural; the patient died too soon after surgical hypophysectomy to justify a firm opinion regarding the effect of the latter procedure. Of interest, neither patient lactated after ultrasound.

Patient 5 suffered a paresis believed due to the beam passing through tissues disturbed recently by surgery. In such tissues, "cavitation" may occur, and at such sites an untoward heating effect is possible with focal damage. To avoid such, irradiation should be deferred for at least 2 weeks after the tissues have been disturbed by surgery.

The optic pathways and extraocular nerve damage appeared to arise wholly or in part from the technical fault of local heating adjacent the hypophyseal target by beam side lobes. The absorption coefficient of the bony sella turcica is such as to convert incident sound energy in considerable part to heat. With the present instrument (designed for quite another use in neurosurgery), the "side lobes" of the sound beams thus heat bone interface adjacent the sella turcica. The diabetes insipidus was not unexpected; it possibly resulted from damage of direct focal irradiation, and the optic pathway damages might have resulted from direct irradiation also.

Of the various complications, the optic pathway damages were enduring. The extraocular nerves recovered, essentially completely, by 4 or 5 months. Partial recovery was evident in all cases by the seventh to 10th week. The intensity of the diabetes insipidus lessened, although pretreatment levels of urinary volume were exceeded by about a liter. In the single patient exhibiting severe diabetes insipidus (5,000 to 7,000 ml. daily), the response to stress imposed by the hypertonic saline test was similar to that of a normal subject. This suggests that the physiological damage imposed upon the neurohypophysis is nonpermanent and that still further improvement may be anticipated.

Microscopic observation of tissue removed by subsequent surgical hypophysectomy shows that major pituitary glandular damage was peripheral—i.e., adjacent to the bone where thermal energy would be expended. Central scarred areas were noted also; the extent of cellular repopulation is unknown.

To look to the future and improved techniques—the irradiation equipment in this sequence of therapeutic endeavors produced, as stated, a beam which had relatively high acoustic level "side lobes" which induced heat production at bony interfaces neighboring the sella turcica, hence causing adjacent thermal damage. This heating effect can be circumvented by employing a transducer of a different design, as shown experimentally in the cat,[14] e.g., a transducer equipped with a wide-angle or wide-aperture lens for focusing the beam. Such equipment, although now in the process of development, has not been used on human subjects.

These observations upon the use of ultrasound are presented reservedly. This is a new concept in cancer palliation. The guiding landmarks were those arrived at through a moderately extensive experience

at the State University of Iowa in the investigation and modification of the hyperkinetic and hypertonic disorders by ultrasonic neurosurgical methods. The choice of values of the ultrasonic dosage parameters were extrapolations of these studies, and other extensive experimental experiences in the irradiation of gray and white matter of the central nervous system of animals, as well as the pituitary glands of cats,[14] at the biophysics laboratory of the University of Illinois.

No patient was critically harmed in consequence of the ultrasonic irradiation, although in several instances regrettable nerve damages occurred. Any benefits received by the patients were indirect, i.e., those of increased clinical care. We conclude that damage to the pituitary gland can be brought about by this method, and with more adequate instrumentation, the physiology and pathophysiology of the organ may be explored further and the findings possibly exploited for therapeutic purposes.

Conclusions

Five patients with disseminated incurable breast cancer underwent craniectomy and ultrasonic irradiation of the pituitary gland.

Our initial objective, that of controlling the growth of advanced mammary cancer, was not attained. However, collateral observations revealed that ultrasonic irradiation of the hypophysis results in (*a*) histological structural changes in the gland and (*b*) certain consistent transient alterations of hormonal (thyroid and steroid) activities known to be influenced by the pituitary gland.

Potentially, ultrasonic irradiation constitutes a new tool for studying basic scientific and clinical phenomena relative to the hypophysis.

The complications that arise in the present series appear in the main to be ascribable to inadequacies of the ultrasonic instrument employed. Owing to the "side lobes" of the ultrasonic beams directed at the target organ, the instrument used in this investigation proved incapable of surmounting the difficulties posed by bony structures encasing the hypophysis. The possibility of revising the instrument and thus amending this deficit has been discussed.

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DISCUSSION

OF PAPERS BY HALEY ET AL., HURLEY ET AL., AND HICKEY ET AL.

DR. EDWARD F. SCANLON, Evanston, Ill.: The tumor-host relationship in tumors has been receiving an increasing amount of attention in recent months and, like so many papers in this field, Dr. Haley's paper raises almost as many questions as it answers.

It is well known by recent evidence that those tissues which show injury are probably more susceptible to tumor implantation via metastasis. For instance, those patients with a migrating type of polyphlebitis with untreated cancer have a poorer prognosis and a greater incidence of widespread dissemination of their cancer than other patients.

So, it raises the question here from Dr. Haley's work as to whether this effect on his implantation of tumor is due to local trauma, or whether it is due to some actual mechanism taking place between the tumor that is injected and the local bed site. There are many radiotherapists who will tell you that the tumor bed is more important than the tumor itself in its response to irradiation. Could it be that this bed in which he implants his tumor is the important thing, rather than some reaction between the host and the tumor bed?

I would like to ask Dr. Haley if he has injected this tumor away from the site of injury in animals that have been injured, and what has been the response and the effect of the relationship here in such cases.

His group and other groups, too, have shown that cystine given parenterally will have a very marked effect on wound healing even in the absence of tumor, and I wonder what effect this has on the tumor itself if the tumor is injected away from the wound site and cystine is given and cystine is not given. Has he given any radioactive cystine to see if this is taken up by the tumor itself, or is this effect mitigated totally through the tumor bed?

The final point I want to raise is on the fixed tissue response to tumor transplantation. It would be very interesting if he had done the autogenous tumor, because this is an unusual response and is not the usual histological appearance of reaction against autologous tissue. I wonder if he plans that work.

DR. RUDOLF J. NOER, Louisville: At the risk of some repetition, I think it might be in order to say a bit more about the national adjuvant chemotherapy program to which I referred a few minutes ago. This has particular bearing on the very interesting results reported in the paper by Dr. Hurley.

About 3½ years ago a number of institutions, many of which are represented in this room, began a cooperative study of chemotherapy given at the time of operation and immediately succeeding operation—curative operation—for carcinoma of the lung, stomach, colon, breast, and, more recently, ovary. All followed a uniform protocol. The patients were carefully studied preoperatively. Everyone agreed to carry out the same operative procedures and the same type of follow-ups. Nitrogen mustard was used for the lung, thio-tepa for the stomach, colon, and breast. Chlorambucil was used for the ovary.

I speak to you not as a representative nor spokesman for these groups, but merely as a participant, though I suppose I could be called a spokesman for the breast group. The early toxicity in the nitrogen mustard administration in the lung was referred to earlier this morning. That is the statement that I contradicted a bit. The first 6 months of the study did produce a significantly higher early mortality in both groups, but particularly in the Veterans Administration group. There was not a great difference in the university hospital groups.

As a result of this early toxicity the dosage was reduced by 25% in all of the studies, both nitrogen mustard and thio-tepa. Since the dosage has been reduced, there has been no increased mortality attributable to the chemotherapeutic agents given in conjunction with the operative therapy.

The most striking results have been obtained in breast carcinoma, as I said earlier. These results are being reported before the American Surgical Association in March. They show, in the early follow-up period, a significant decrease in recurrence rate in the patients who received thio-tepa, in contrast to those who by a double-blind technique received only a placebo in connection with their operation.

The study is about complete and the breast group is about to start another study with a much larger number of institutions cooperating, which will

evaluate another chemotherapeutic agent, namely, 5-fluorouracil, which, as you heard this morning, is more toxic, and also the effect of postoperative irradiation in patients with positive nodes, and the possible effect of castration in the premenopausal woman.

I believe this is the first truly randomized study of these things which has been undertaken, and I think the study over the next 5 years should produce some very interesting and significant results. The problem, of course, is to find a chemotherapeutic agent which is effective and which can still be tolerated by the patient. There are many agents which would be effective were they not so toxic.

I am impelled to tell you of one of the most interesting slides I have ever seen. At the meetings held occasionally at the Cancer Chemotherapy National Service Center in Washington, Dr. Jones, an internist, commonly reports for the New Agents Committee, which is making a very thorough study of new drugs as they appear. On this particular day he had spent about 45 minutes telling us about 15 new agents which did all sorts of things to patients, but did not do much to their cancers.

He finished up by throwing on the screen a lantern slide which showed a Hollywood-style laboratory bench stretched across the room, with retorts and stills and things of that sort. Standing in front of it was a little man facing a bearded gentleman, the little man saying, "Professor Ehrlich, we have already tried 605 of these and none of them is worth a damn, and I say the hell with it!"

The implication, of course, is appropriate. It may be that a good therapeutic agent will appear on the scene some of these days, a consummation devoutly to be wished for. It is terribly important that these studies go on. There is probably not one of these agents, it has been said, that does not have one or two almost miraculous authenticated cures to its credit. Someday someone may come up with the answer to a proper chemotherapeutic agent.

In closing, I would like to compliment Dr. Hickey on a most interesting presentation. I know absolutely nothing about ultrasound, but I think it is heartening to see someone trying to do something to alleviate the suffering of the patients with extensive recurrent or late carcinoma of the breast. They are truly miserable, and if any agent can be found that will give them relief, the time spent in finding it will have been well spent.

DR. CLAUDE R. HITCHCOCK, Minneapolis: Good taste indicates that I should not rise again this morning, but I do want to make one or two comments.

First, I think these 3 papers have been very interesting and very nicely presented.

In answer to Dr. Noer's comments, in making my remarks, I did not have in mind the study in pulmonary cancer in the adjuvant group; rather, I had in mind the gastric lesion study in which, in certain veterans' hospitals (where I have the data at hand), the results were quite serious.

I have been impressed in the last year with how many practicing surgeons in our community are beginning to toy with cancer chemotherapeutic agents. I am completely committed to the use of these materials in study programs in many centers in the country; but with a fairly extensive clinical experience with many of these agents, I feel that the time is not ripe for doctors generally to be using them on patients in the community at large.

I don't know how others feel about it, but I have had deaths in my own hospital from these drugs. They have been reported to you this morning, and there are more reports in the literature. It is on that basis that I cautioned against using some of these drugs, particularly for perfusion work.

In regard to the paper by Dr. Hurley, I really appreciated seeing his results. I must admit they are in excess of my own figures as far as assessed improvements are concerned.

I would like to ask him to expand on how he assesses the improvement in the patient, for it has been my experience that when I go to the difficulty (both from the standpoint of the patient and of myself) of reoperating upon patients with abdominal carcinoma, and exploring them every 5 or 6 months during the course of chemotherapy, my own clinical impression is quite different from what I find as I am in the abdomen palpating the liver and the sites of tumors that I knew were present.

In other words, in some instances I can say that when I looked again into the abdomen, the tumors were gone. In other instances, I may think they are gone, but unfortunately they are there, growing only too vigorously.

I think this is another aspect of the problem of chemotherapy that we must take seriously into consideration, namely, how we assess these patients in terms of their response so that we have the best kind of objective evidence that they have improved.

Concerning Dr. Hickey's paper, I was, to say the least, fascinated. During the past 10 or 12 years, many in this room have been aware that considerable interest in ultrasonics has been manifested in several places in our country. In Denver, Dr. Douglas Howrey has done a great deal of work with ultrasound. In Minneapolis, Dr. John Wild has done a great deal of work with it. And it is my understanding, after talking with both of these gentlemen, that they feel this modality has a significant place in medicine for the future in terms of doing tomography of the body (cutting across with transverse sections, and so on, and getting beautiful pictorial representations of organs

and their relationships). I have been assured by both of these men that this is a totally harmless method.

I would be amazed if we could apply ultrasound to the body for any significant period of time and not have some specific tissue damage result. So, I would like to ask Dr. Hickey if he will dilate very briefly on what were the length of times of exposure and what were the frequencies and wave lengths.

DR. E. THURSTON THIEME, Ann Arbor, Mich.: With my very meager experience I hesitate somewhat to comment, but the assay of palliation is very difficult, as Dr. Hitchcock pointed out. We have had a few brief experiences and some tragedy with them which I thought I would tell you about.

One was a 42-year-old woman operated on for carcinoma of the junction of the esophagus and stomach. At operation it was felt this could not be resected because of local extension and widespread lymph-node involvement. A biopsy was taken. After this she had 5-fluorouracil and was reoperated on. At that time it was felt the lesion was highly resectable, and it was resected without difficulty.

She appeared to be having a normal postoperative course, when on the 10th postoperative day she collapsed; her thoracotomy wound opened and she eventually died. At autopsy there was no evidence of neoplasm of the stomach left within the abdomen that could be found. She did have a small hypernephroma of the kidney that we did not know about.

A second patient had carcinoma of the sigmoid colon resected with recurrence one year later. She was reoperated on, and it was felt doubtful that this could be removed with a combined abdominoperineal resection. She received 5-fluorouracil and was reoperated on 6 weeks later. There was no evidence that we could see that the lesion had been changed. However, a combined abdominoperineal resection was done. The neoplasm was left behind.

On the ninth postoperative day she had a sharp rise in temperature, became extremely toxic, was put on a hypothermic blanket, and survived. She is still alive 8 months later, with palliation.

A third patient had a carcinoma of the ovary, and 4 years later returned with signs of intestinal obstruction. She was operated on. The pelvis seemed to be a mass of neoplasm. The left lobe of the liver was replaced with neoplasm. A short-circuiting operation was done for relief of the obstruction. She was then given 5-fluorouracil and 15 months later returned, having been treated on an outpatient basis, because of vaginal discharge.

She asked for laparotomy, which was done. There were 2 or 3 nodules of neoplasm in the pelvis. The small intestine was entirely free of any gross neoplasm that we could see. Nine months later she is still on an outpatient basis. The left lobe of the liver appeared unchanged.

I rather hesitate to mention a fourth patient who had resection of the colon considered palliative. He returned 9 months later with a large mass in the lower quadrant. He was given 5-fluorouracil without biopsy to prove that the mass was neoplastic. After discharge he returned 3 days later and promptly died. At autopsy no evidence of neoplasm of the colon was found, and his death was attributed to complete desquamation of his large bowel mucosa.

So, these are some evidences of palliation as seen at second operation. I wish Dr. Hitchcock had time to dilate on this further, because he intimated that he has done this frequently, and I would like to know whether he has also had these tragedies postoperatively.

DR. HALEY: Dr. Scanlon asked a number of questions. One was the question of cystine utilization by the tumor, and whether we have given radioactive cystine. We have attempted this, but for technical reasons in our laboratory have not been able to define it. We have attempted to use sulfur 35-labeled cystine and determine its location in the tumor by radioautography. We have had technical problems with the radioautography, so I don't have an answer to this question.

Secondly, Dr. Scanlon asked about using isologous tumors and isologous strains of animals on this fixed-tissue reaction on which we showed the fibroblastic reaction to tumors in the wounds. This, of course, is a very critical study that must be done. Currently we are doing it in hamsters, using a spontaneous transplantable hamster tumor that we received from Dr. Fortner. We are also working with a transplantable rat tumor, the Guerin tumor, and are getting ready to do it with the Walker tumor. However, this is possibly what we will tell you about next year if it still looks like it is worth talking about.

Third, Dr. Scanlon asked what happens if tumor is injected away from the wound in a wounded animal. Other investigators have shown that the effect of wounding, presumably the release of hydrocortisone and similar compounds by the adrenal, will stimulate tumor growth in this situation. Since the submission of this abstract we have done some related studies that throw a little light on this question.

We have done one experiment with 200 gm. rats, all of which received tumor, all of which received rather large doses of testosterone, a total of 8 mg. of testosterone propionate. Half of the animals were wounded and half not wounded, and tumor was injected into the same site in both groups.

This is a fascinating study to us at the moment, since the wound tumors in this group come out to be only about one-third the size of those in the nonwounded animals; that is, the tumors averaged over 1.5 gm. in the unwounded animals and about 500 mg. or 0.5 gm. in the wounded animals.

There were 2 exceptions. There were 2 wounded animals with very large tumors, around 1.5 gm. On checking back our protocols, in the description of these 2 large tumors as taken out at the time of killing of the animals, they were found to be 1 in. away from the actual incision. In other words, the cells that had been injected had migrated away, and when they got away from the immediate site of the incision very large tumors showing no inhibition developed, whereas the other tumors that were just in the wound did show inhibition. I think this suggests that there are both local factors and systemic factors involved.

Concerning Dr. Scanlon's fourth question—the effect we showed, purely the effect of local trauma or an interaction between the tumor and a specific site or bed, I think both factors are involved here, and our problem now is to try to define the importance of each.

DR. HURLEY: Dr. Hitchcock, our criteria for response were fairly similar to those used by Dr. Gurreri at the University of Wisconsin. The objective criteria related to measurable or radiographically visible tumors, and we expected at least a one-quarter reduction in the size of the tumor mass. As the paper points out, these were actively growing and symptomatic tumors, and we saw increase in size of the tumor before therapy so that we could not anticipate much more than one-quarter reduction in size. Occasionally we saw 50% or 75% reduction in the tumor size. Subjective parameters were relief of pain and improvement in performance status, and so on.

With very rare exceptions we did not reexplore these patients. We have never reexplored a patient who had no tumor in whom we found tumor prior to therapy. The others reexplored had about the same volume of tumor present as at the first exploration when recurrence was documented.

DR. HICKEY: In presenting this material in 10 minutes, I omitted the mathematics and physics involved. I might comment that our co-workers were sophisticated physicists.

In answer to Dr. Hitchcock's questions, the ultrasonic frequency was 1 megacycle per second. The acoustic particle velocity was 350 cm. per second, and the duration of each exposure in the array was 2.5 to 3 seconds, with a 2-minute interval between each exposure in this geographical grid that we outlined to irradiate the pituitary gland.

Through the mathematics involved it is possible to focus with accuracy after it has passed through the brain within 0.2 mm. This equipment we have been using has a high acoustic level side lobe, and this high side lobe produces the complication of heating, thus the side-effects and the palsies we encountered.

No patient was improved unequivocally by the irradiation, but in the total picture this is false, obviously, because it is the responsibility of any clinical investigator to care for his patients. These patients received a great deal of improved clinical care, and thus benefited indirectly.

One final thought: if any of you are thinking of purchasing such a piece of apparatus, I would suggest that it is moderately expensive.