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RADIATION HYPOPHYSECTOMY WITH HIGH-ENERGY PROTON BEAMS

A Preliminary Report

Cornelius A. Tobias, J. E. Roberts, J. H. Lawrence,
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RADIATION HYPOPHYSECTOMY WITH HIGH-ENERGY PROTON BEAMS*

A Preliminary Report**

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INTRODUCTION

There is considerable evidence that the human pituitary gland is implicated in the pathogenesis of various serious diseases. In some of these conditions partial or complete removal of the gland may be of benefit. For the past several decades, attempts have been made by radiation and surgery to achieve complete hypophysectomy. It is only very recently that the surgical procedures have met with at least partial success.

Most of the difficulties in hypophysectomy are due to the central location of the hypophysis at the base of the skull, and to the sensitive structures of nerve, brain, and blood vessels that are surrounding and protecting it.

An account is given below of the initial use of accelerated high-speed protons in human therapeutic investigations: the rationale for proton hypophysectomy, the technique employed, and the initial physiological changes after proton hypophysectomy are given in detail.

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*With Appendix A, "Preparation of a Form-Fitting Plastic Mask for Radiation Therapy" by H. O. Anger and R. W. Pratt, and Appendix B, "Profile and Isodose Measurements of the 340-Mev Proton and 190-Mev Deuteron Beams by Photographic Densitometry" by G. P. Welch.

**The authors are indebted to Victor Burns, Graeme Welch, Mrs. Elizabeth Ward, R. W. Pratt, Jack Allen, and Ann Henderson for assistance at the cyclotron; to Shirley Belknap and Barbara Boysen for clinical tests; to Joseph Garcia, Charles Riggs, Julian Henry, and O. K. Anderson for preliminary studies of irradiation involving animals; to Philip Bean for engineering design work on the equipment; and to Aram Thomasian for his contribution on mathematical calculations. The authors are further indebted to the Donner Foundation for financial aid in the medical phases of this project. The physical aspects of these studies were supported by the Atomic Energy Commission.

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REVIEW OF THE AVAILABLE TECHNIQUES FOR HYPOPHYSECTOMY

A. Radiation

Irradiation of the human and animal pituitary by x-rays was reported as early as 1909.[1] It soon became clear that the hypophysis was fairly radioresistant.[2] Because of limitations imposed by sensitivity of the skin and danger of injury to the brain, the doses by conventional x-radiation had to be limited. Nevertheless, radiation has been a frequently used therapeutic approach in pituitary tumors,[3] Cushing's syndrome,[4,5] and acromegaly.[4,6] Attempts have also been made to irradiate the pituitary in various other conditions, for example hypertension[7] and malignant exophthalmos.[8,9] Pituitary radiation by x-rays has also been attempted in malignancy in the human, particularly for prostatic carcinoma[10] and mammary carcinoma.[11] The highest doses were probably delivered by Kelly et al.[11] However, in three mammary cancer patients even 15,000 r to the region of the hypophysis was not sufficient to cause noticeable depression in hormone production and histopathological damage, or remission of the disease. The technique of x-ray therapy is still being extended and improved, as exemplified by the recent work of Santos.[12]

Since the pioneer work of Lacassagne and his associates[13] the implantation of radioactive seeds seemed to offer a method of delivering large local doses to the pituitary; indeed radon implantation did affect the pituitary in acromegaly and Cushing's syndrome.[4] During the last few years, Kisielski and his associates[14] have developed new methods for processing radioactive yttrium into seeds; this led to the therapeutic clinical investigations of Kennedy et al.,[15] who implanted several yttrium seeds into the pituitary, and gave considerable doses of beta radiation in an attempt to stop hypophyseal function and to cause regressions in carcinomas. This study is still in progress at the University of Chicago and at McGill University.[16]

B. Surgery

Owing to great technical difficulties and associated severe trauma, it was only recently that complete surgical hypophysectomies were carried out with success, by Luft and Olivecrona in Sweden[17,18,19] and by Perrault and associates in France.[20] Luft and Olivecrona assembled 34 cases of metastatic carcinoma of the breast and 12 cases of diabetes mellitus for surgical hypophysectomy. A significant portion of the patients in whom hypophysectomy appeared complete showed objective remissions and subjective relief, which lasted for periods ranging to more than two years. Currently Ray, Pearson, and associates, and other groups, are vigorously attacking the problems of surgical hypophysectomy in cancer[21,22,23] and in diabetes mellitus.[24]

PROTON IRRADIATION TECHNIQUE

A. General Properties of Particles

High-energy protons, deuterons, and alpha particles have great advantages over other radiations in producing localized radiation damage in a deep region in tissue as suggested by Wilson.[25] The accelerated and properly focused particles propagate in a well-collimated and straight pencil of beam,

which may be directed to any portion of the body. As the particles penetrate, their scattering is so small (compared to electrons) that for practical purposes negligibly small amounts of radiation fall outside the main beam to irradiate neighboring tissue areas. Further, the approximately monoenergetic particles penetrate to a uniform and well-defined range, producing their maximum ionization just before they stop.

A suitable aperture, made of brass or other metal, is used to determine the shape of the radiation field, and the background ionization may be kept to less than 0.1% of the beam.

These properties were demonstrated in biological experiments by Tobias, Anger, and Lawrence.[26]

B. Biological Experimentation with 190-Mev Deuterons and 340-Mev Protons

Experience in the use of proton, deuteron, and alpha-particle beams was gained by investigating their biological effectiveness and mechanism of lethal action through localized irradiation of animal tissues.

The biological effectiveness of the high-energy portions of the deuteron and proton beam was found to be close to that of 200-kv x-rays. This could be predicted from physical data on the specific ionization and linear energy transfer of the particles. Experiments of this kind were done on mice,[26] yeast cells,[27] tradescantia microspores,[28] and fruit flies.[29]

The use of high-speed particles allows one to produce radiation-induced lesions in the animal body with microscopically sharp demarcation lines.[26] In small animals, cylindrical lesions of one mm diameter are easily produced. Since 1952, a sustained effort was made, in collaboration with the staff of the Institute of Experimental Biology, to study effects of the high-speed particles on the rat hypophysis.[30] Initial results were encouraging, and pituitary irradiation of young monkeys* and of normal mature dogs** and dogs with breast cancer** has also been undertaken, with technique similar to that for humans (described below).

When large single doses of more than 5000 rad*** deuterons or protons are given to the pituitary gland of animals the end result appears to be similar irrespective of the size of radiation dose: progressive atrophy of the entire gland results, accompanied by reduction in physiological function. The higher the dose, the sooner the physiological effects seem to manifest themselves. Single doses of the order of 30,000 rad are necessary to approximate the immediate effects of surgical hypophysectomy. To illustrate these statements, Fig. 1 shows the apparent onset in time of profound physiological changes resembling complete hypophysectomy. Data on rat, dog, and monkey follow reasonably well the same general relationship. Criteria for evaluation are chiefly rate of growth, thyroid function, and sizes of target organs.

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*In cooperation with Dr. Van Wagenen of Yale University.

**To be published.

***1 rad is equal to 100 ergs absorbed/g or 1.07 rep absorbed in tissue.

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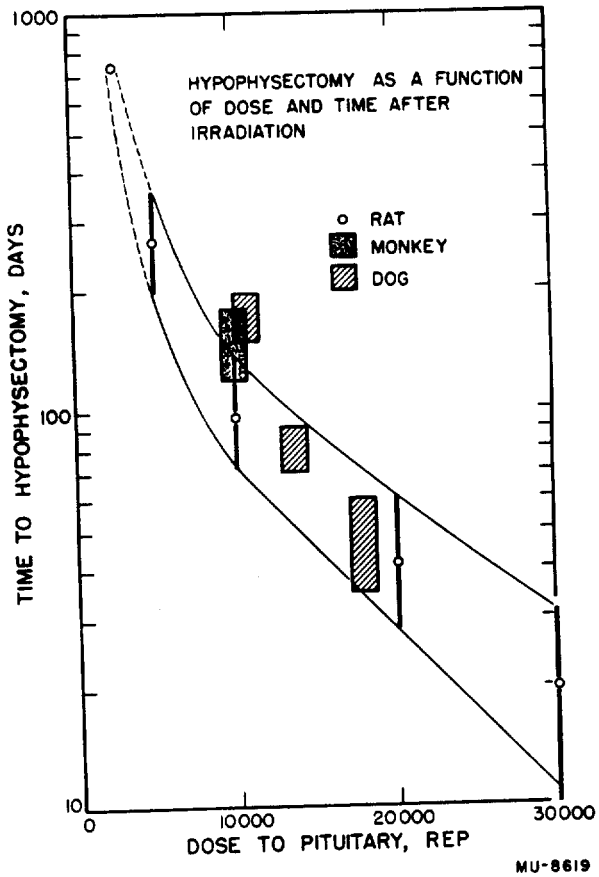

Fig. 1. The time of onset of marked changes due to radiation hypophysectomy is plotted against dose. Data for rats, dogs, and a few monkeys are included.

According to the above reasoning, when single doses are applied, hypophysectomy can be achieved with relatively moderate doses, although it may not be observed until a fairly long time after the initial radiation exposure. The delayed onset of the effects is a factor of great importance in deciding on the dose in humans.

The entire gland must be irradiated to achieve any lasting physiological changes in the target organs.

The effect of pituitary radiation on target organs does not progress simultaneously, but there is a definite pattern involved. In rats the first gland to show measurable functional changes is the thyroid. The I^{131} uptake may decrease within a few weeks after even a moderate dose. Effects on growth and adrenal function follow, while regression of the sex glands, regulated by the follicle-stimulating hormone (FSH), is usually chronologically last. The histopathology of the irradiated pituitary exhibits changes that indicate a pattern (in the rat), though differential effects are difficult to detect. The acidophiles seem to be first to regress, followed by basophils and, lastly, chromophobes.

Long-term studies with doses up to 10,000 rad given to the young Long-Evans rat indicate that onset and frequency of spontaneous tumors are reduced if the animals are irradiated in the first month of life. Life span of the animals that received large doses did not significantly differ from the life span of surgically hypophysectomized animals.

Nerve and brain tissue is more sensitive than pituitary tissue. Lethal effects from pituitary radiation, where the cause could be definitely ascertained, could be ascribed to nerve and brain lesions, particularly to necrosis and hemorrhage.

Lethal effects of this kind were usually preceded by damage to the third, fourth, and fifth cranial nerves, which in the dog lie very close to the pituitary. The lesions led to inability of the animals to move their eyelids, to permanently dilated pupils, and to loss of corneal sensitivity. A series of experiments was carried out to test the dose-time relationship in dog cranial nerve. A characteristic dose-time injury curve resulted, which resembled the data obtained with the pituitary. The lower the dose, the longer the time required for the symptoms to appear, and--in this case--they usually proved to be less severe in degree. Since the data on dogs are available only over a period of 16 months, additional information is needed, particularly for long postirradiation times. Figure 2 gives the data now available.

A temporary type of nerve damage was also observed in some of the animals; here the cranial nerves themselves had a low dose, but neighboring structures (pituitary and cavernous venous plexus) received heavy irradiation (in excess of 10,000 rad). The eye symptoms developed and increased in severity two to three weeks after irradiation, then partially or completely regressed six to eight weeks later. The symptoms were presumably due to pressure from edema of the nearby radiated structures.

When portions of the brain were given large doses along with the pituitary and cranial nerves (in dogs), in some cases coma and death followed the eye symptoms. At autopsy the heavily irradiated areas of the temporal lobes of the brain were found to be severely necrosed and liquified, with a

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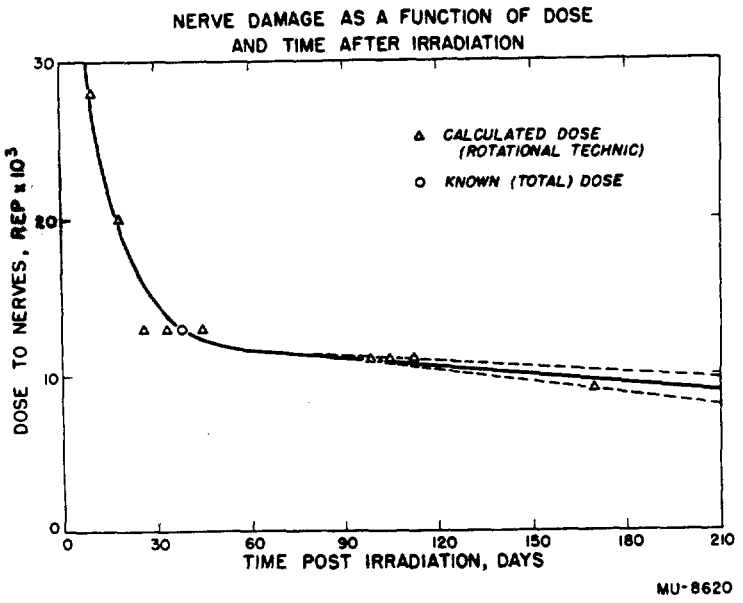

Fig. 2. The occurrence of cranial nerve damage in dogs as a function of time after various single doses of deuterons.

remarkably sharp demarcation line between necrosed portion and healthy, normal-appearing tissue. The size of the necrosed area at time of death was about the same in different dogs; a typical brain is shown in Fig. 3, from a beagle dog that received 40,000 rad and died in two weeks. Necrosis begins in the portion receiving the highest dose, and progresses to areas with lower doses. The immediate cause of death in some cases appeared to be hemorrhage, with accumulation of fluid in the brain and high intracranial pressure. The relatively meager data indicate that brain damage is a function not only of dose and time but also of the volume of tissue irradiated. It is difficult to compare the literature on radiation damage to the brain with the results reported here; most data in the literature involve doses to massive areas of irradiated brain tissue. Perhaps most pertinent are recent observations by Arnold et al.,[32] who observed delayed demyelinization and radionecrosis in dose ranges of 1500 to 5000 r of high-energy x-rays, and in addition acute inflammation, hemorrhages, edema, and necrosis in the range of 3000 to 14,000 r, with increasing severity at higher doses.

Further studies are being carried out on the relative effectiveness of fractionated and single doses on the central nervous system.

LOCALIZED HYPOTHALAMIC IRRADIATION

The technique described in this report has been employed over the past two years for irradiation of hypothalamic areas of rats. The main problem of interest is the mechanism of hypothalamic control of hypophyseal functions. Because of the low mortality and high aiming accuracy this technique appears to show promise as an investigational tool. The results of this work will be reported elsewhere in detail. Already proton or deuteron irradiation of hypothalamus has produced a range of effects in rats. Among these are retardation of growth, diabetes insipidus, glycosuria, hypothyroidism, and obesity.

DESCRIPTION OF IRRADIATION TECHNIQUE IN HUMAN PATIENTS

The radiosensitivity of the brain and skin is greater than that of the pituitary. For this reason the proton irradiation of the human pituitary was combined with the well-known rotational irradiation technique. The position of the proton beam was kept fixed in space and directed to cross the pituitary as well as the entire head with uniform ionization. During irradiation the head was rotated around its own pituitary body. The plane of rotation was chosen differently each day of the fractionated therapeutic irradiations. In this manner the cumulative dose to the pituitary gland was considerable, while surrounding blood vessels, cranial nerves, lobes of the brain, bone, and skin received progressively less irradiation in the order of enumeration.

A contemplated further improvement in technique would involve stopping the proton beam in the pituitary fossa by making use of the high dose peak of the Bragg ionization curve and thus eliminating irradiation of one hemisphere of the brain. As yet this modification has not been employed in our patients.

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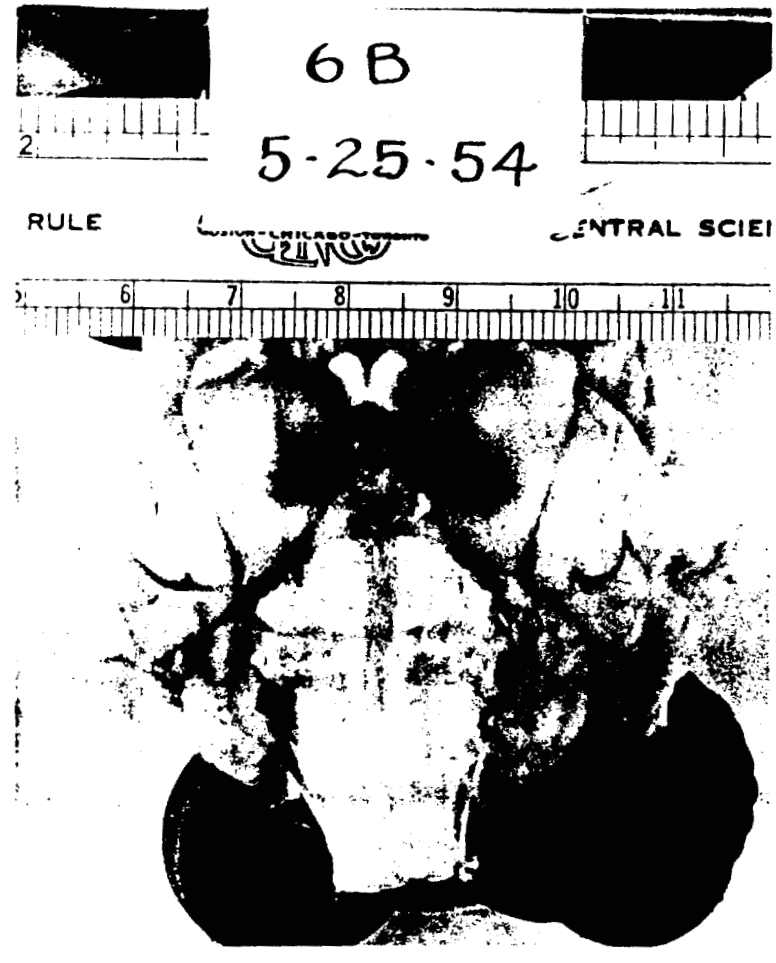

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Fig. 3. Photograph of the unstained brain of a fully grown male beagle dog after a single dose of 40,000 rad to the pituitary. Rotation of the head occurred in a single plane, so that the beam swept an arc of 90°. Dose at the necrotic areas (black) is estimated to be about 30,000 rad. The animal died of brain hemorrhage two weeks after irradiation.

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A. Treatment Room

With the generous help of the staff of the Berkeley 184-inch cyclotron* a new treatment room (shown in Fig. 4) was constructed for the human irradiation program. The collimated beam passes through two rooms suitable for irradiation: the one closer to the cyclotron is mainly for physics and chemistry use, while the farther room, carefully shielded to avoid stray radiation, is for medical use.

B Control of Proton Beam

The deflected beam passes along on an optical bench, and by means of electrical and mechanical techniques, it is brought to pass (within about 0 2 mm) along a line eight inches over the center of the optical bench and parallel to the tracks on the bench. The dose-monitoring ion chamber, main beam aperture, and focal spot of the diagnostic x-ray machine are all mounted so that the proton beam passes through their centers. The patient's head is held rigidly in an adjustable head rotator which is also mounted on the optical bench. Adjustment screws are provided to move the head holder in three directions X, Y, Z, with an index on each adjustment, so that on repeated treatments the index may be reset, and the head placed each time into a very closely correct position. This is checked by x-ray films before each treatment. Figure 5 gives the schematics of the alignment and Fig. 6 shows the actual treatment room.

The success of the multiple-plane rotational-irradiation technique depended on providing a firm mask to hold the patient's head during alignment and therapy on repeated occasions. Very satisfactory two-piece individual plastic masks have been developed for this purpose, utilizing fiberglass cloth and polyester resin. The mask is tightened on the head with thumbscrews, until it fits tightly enough so that the patient cannot move his head, (or sella turcica) more than about 0.5 mm in any direction. The masks are comfortable enough to wear for two hours at a time.

Figure 7a shows the sella turcica of one of the patients in alignment with the cross hairs, while Fig. 7b shows the autoradiograph of the shaped beam and its alignment with the sella. This latter picture was taken by first exposing the patient to the x-rays, then to a small dose of protons. One should bear in mind that the sella appears enlarged due to the finite distance of the focal spot of the x-ray machine, while the beam spot is actual size.

Figure 8 shows a typical vertical x-ray, taken along the Y axis. Here, the center of rotation in the sella was ascertained by obtaining symmetry, on both sides of the X cross hair, of the faint line representing the base of the sella and the walls of the sphenoid sinuses. The anterior clinoid processes and the ocular cavity are also checked for symmetry. On the vertical x-ray it was necessary to use a diagnostic x-ray machine with 0.3-mm focal spot to obtain the necessary resolution.

Spatial alignment of both views of the sella was usually within ± 0.5 mm. Occasionally check x-rays were made with the patient forcibly trying to move his head out of alignment. These were always correct within 1 0 mm.

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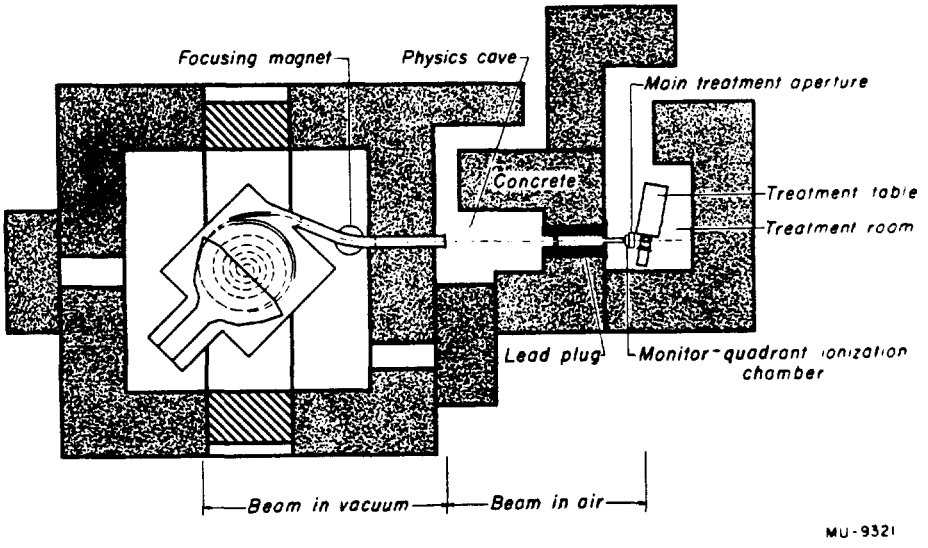

Fig. 4. General layout of the 184-inch cyclotron and treatment rooms (not to scale). The deflected beam passes through a room for physics experimentation and arrives at the treatment room beyond.

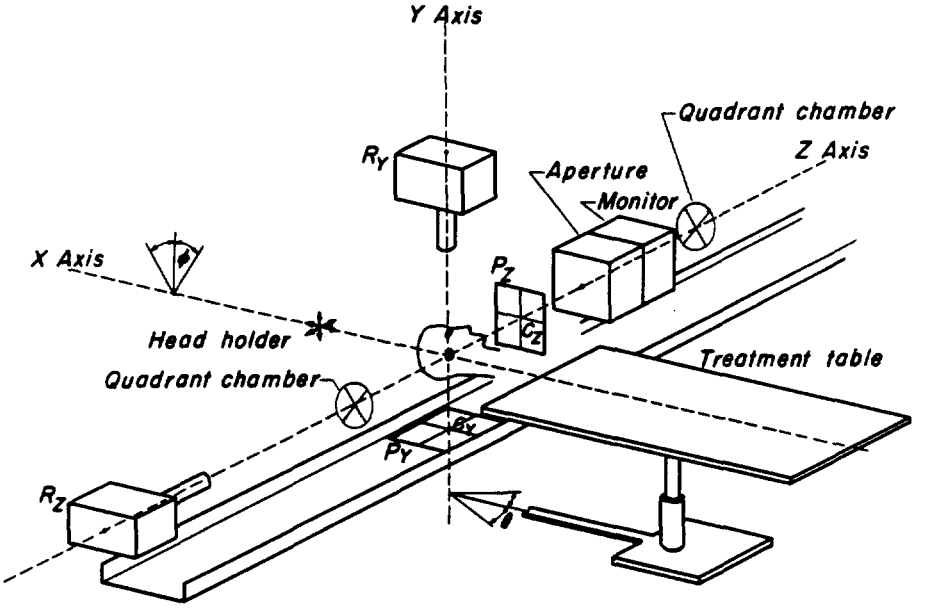

Fig. 5. Schematic of the positioning, alignment, and rotation of the human head. The optical treatment bench is aligned with the beam, while the patient lies on an adjustable table at some predetermined treatment angle. This angle is changed in 7.5° intervals on different treatment days. The head of the patient is held rigidly by a mask. Position of the head is checked by a lateral, horizontal diagnostic x-ray, taken by an x-ray machine rigidly mounted on the treatment bench. The sella turcica is aligned by moving set screws in the X (longitudinal) and Y (vertical) directions, until the center of the sella and the cross hairs marking the beam position are coincident.

With the vertical x-ray machine, mounted above the treatment plane, one obtains a frontal diagnostic picture. The patient's head is moved by set screws in the Z direction until the center of his sella coincides with the center of rotation of the head rotator, as marked by cross hairs.

Rotation of the head occurs around the longitudinal axis of the body (X); rotational limits of ± 30° or ± 35° are easily tolerated.

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Fig. 6. Photograph of the treatment room. The treatment bench occupies the upper part of the picture; the beam enters on the upper right side in a steel tube. The patient is lying in position ready for treatment, her head rigidly supported by a plastic mask. The plastic mask is fastened on the head positioner and rotator. Diagnostic x-ray machines used in the alignment are on the left side and at the top of the picture.

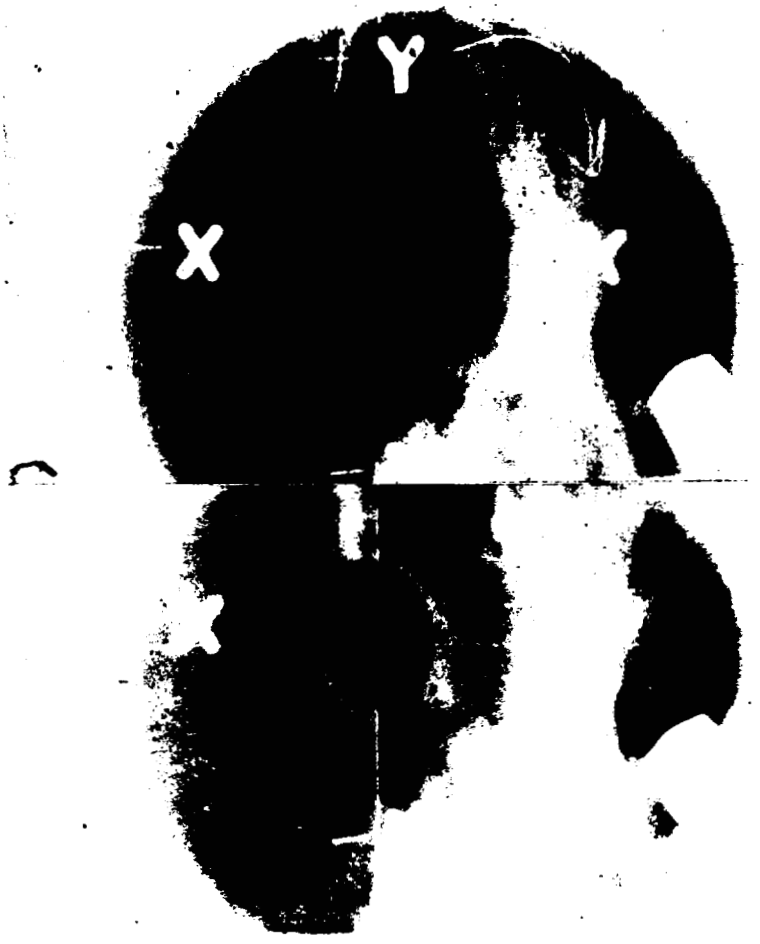

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Fig. 7. (a) Diagnostic x-ray of a patient's head in position for treatment. The cross hairs mark the center of the beam. The outlines of the sella turcica are clearly shown. The anterior clinoid processes nearly overlap.

(b) Autoradiograph of the beam may be obtained on any of the diagnostic x-ray film by briefly turning the proton beam on prior to developing the film. The black spot shows the shape of the beam, adjusted to fit each individual patient. The beam spot is actual size, while the x-ray picture of the sella is enlarged by 20% due to the finite focal distance of the x-ray machine.

Original has been enlarged 1.7 times.

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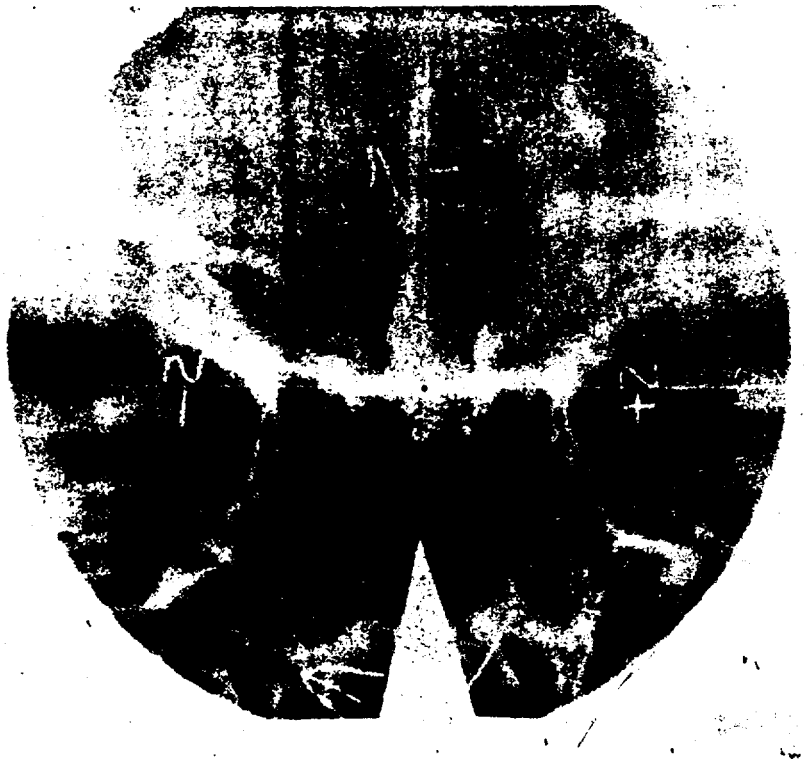

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Fig. 8. Vertical diagnostic x-ray of the skull (anterio-posterior projection). The symmetry of the sella turcica with respect to the cross hairs is checked chiefly from the location of the base of the sella (Grange's line). The anterior clinoid processes and positions of the ocular cavities and of the crystogale also are helpful. Original has been enlarged 1.6 times.

During the first treatment usually 6 to 8 sets of diagnostic x-rays were needed to bring the patient's head in alignment. On subsequent repeat treatments adjustment screws on the supporting head holder were preset to the positions that had previously given proper alignment, and usually one or two sets of diagnostic x-rays sufficed.

CONSIDERATIONS OF ANATOMY AND RADIOSENSITIVITY OF IMPORTANCE IN THE TREATMENT SCHEDULE

Relatively limited information is available concerning radiosensitivity of the brain and of the pituitary in the human. In addition to the animal data reported above, it is known that the brain is more sensitive to radiation than the pituitary and that 4800 roentgens of 50-kv x-rays given in a fractionated course over a large area may cause radionecrosis delayed by more than a year. (See, for example, References 31, 32, 33.)

In the course of the present preliminary investigations the therapy was given in such a way as to minimize the dose received by radiosensitive tissues in the head.

Figures 9a and 9b are scale drawings of sections through the sella turcica in the XZ and YZ planes. It is apparent that the most sensitive structures are right above the pituitary, particularly the optic nerve tract and the hypothalamus. These should be avoided by the radiation as much as possible Laterally, the carotid arteries and the cavernous venous plexus are closest to the hypophysis. These structures are known to tolerate a higher dose. Of the cranial nerves the third, fourth, fifth, and sixth are closest; beyond the cranial nerves extend the temporal lobes of the brain; close to the hypophysis are the regions serving the sense of smell.

The limits of rotation of the head were chosen $\pm 30^{\circ}$ or $\pm 35^{\circ}$ from the y axis. The limits of the angles were given by the requirement to completely avoid the eyes, so that cornea, retina, and lens are free from radiation. There are 11 planes of irradiation, each of which is about 7.5 degrees apart. The choice of the treatment planes is such that the brain stem and the pars optica, mamillary bodies, tuber cinereum, and infundibulum get negligible doses, since the beam does not cross these.

DOSE SCHEDULE

At present 800 to 1000 rad is given each of two to five treatment planes daily, three times a week, with the dose figure referred to the center of the pituitary. Owing to the rotation of the head, the daily dose at the cranial nerves is about 260 rad, and at the skin about 40 rad. The whole course of treatment takes 20 to 40 days, and total doses of 14,000, 16,000, 18,000, 20,000, 22,000, 26,000, and 30,000 rad were given to the center of the pituitary.

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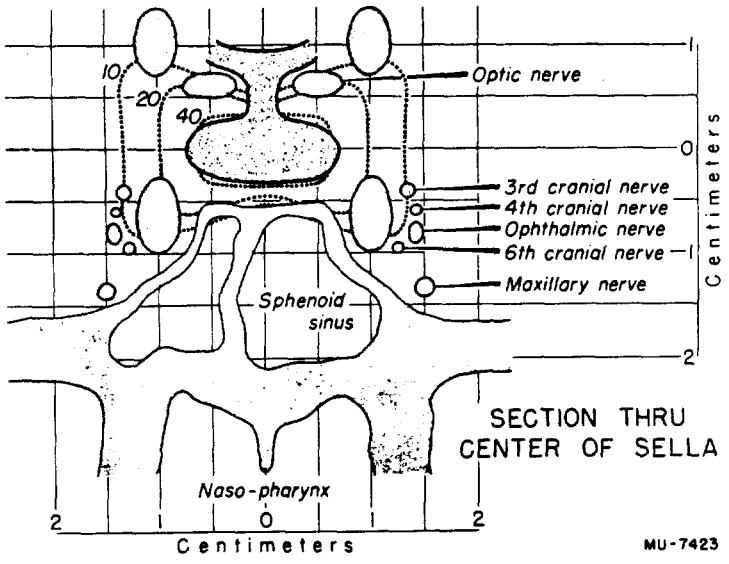

Fig. 9a. Schematic drawing of a section through the sella turcica in the XY treatment plane, with isodose curves superimposed over the anatomical structures. Locations of the optic nerves, cranial nerves, and blood vessels are shown.

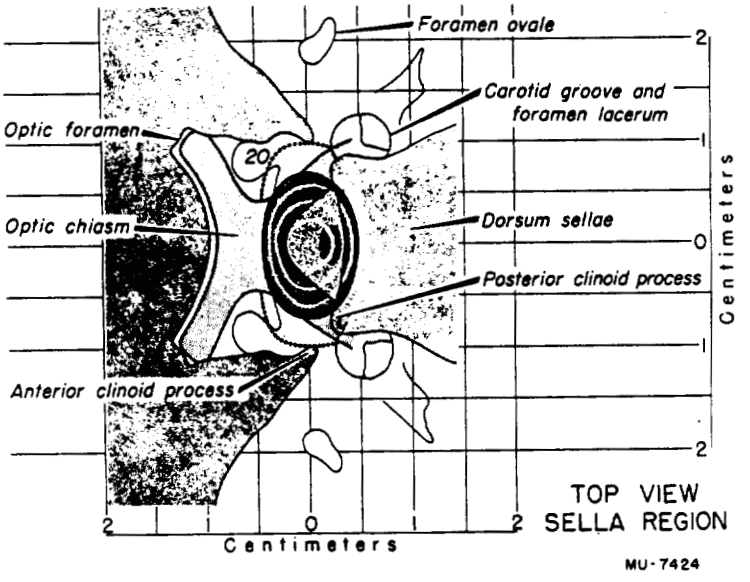

Fig. 9b. Schematic drawing of a section through the sella turcica in the YZ treatment plane indicating locations of the pituitary stalk and optic chiasm.

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ISODOSE CURVES

The elliptical beam apertures, multiple planes, and rotation make the evaulation of isodose curves a complex procedure. Two methods were utilized: measurement by photographic densitometry, and calculation from the known beam ionization profile. An autoradiograph of the proton beam as it crosses a solid piece of lucite is shown in Fig. 10.

A lucite phantom is used in place of the head and photographic film inside this phantom is exposed, using the same rotations as in patients. One complete set of rotations corresponding to the entire treatment schedule gave Fig. 11 (reproduced without retouching). The blackened area obviously corresponds to the size of the pituitary gland.

Calculated dose distributions are reproduced along the major axis XYZ in Fig. 12. The dose falls relatively slowly in the lateral Z direction where the hypophysis extends farther; towards the top of the head and to the front and back, the fall is very abrupt, insuring considerable degree of protection for the optic chiasm and hypothalamus. Figures 9a and 9b have a typical isodose chart superimposed over the anatomical detail of structure.

Since the pathways of irradiation center in the hypophysis, it is useful to evaluate the average hypophyseal dose by integrating over the isodose surfaces. The average dose in the patients treated so far was between 55% and 75% of the peak dose at the center of the gland. The size and shape of the sella turcica varies considerably among patients, and several different apertures and rotations were used. Isodose curves for each of these are being accumulated. See Appendix B for measurements of isodose surfaces.

DOSE RATE

Most patients received dose rates of 200 to 300 rad per minute; 800 rad is thus delivered in 4 to 2.7 minutes; in this length of time the head describes the 60-degree span of rotation 5.4 to 8 times. The beam is delivered in the form of microsecond pulses about 68 times per second; the instantaneous dose rate therefore is high.

BACKGROUND CONSIDERATIONS

Detailed measurements were carried out on the background dose distribution around the proton beam near the body of the patient and in the treatment room. The entire treatment room was shielded in such a manner that beyond a radius of 1.5 inches from the beam the whole body of the patient receives everywhere less than 0.1% of the peak dose. In a full course of therapy, the patient receives less than 20 rad total-body dose, most of which is radiation near minimum ionization. There is also a thermal neutron flux* of 4000 neutrons/cm^2 sec. Outside the shielded area, personnel delivering the dose and

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*The authors are indebted to Dr. Burton J. Moyer and Boyd Thompson for these data.

ZN-1347

Fig. 10. Autoradiograph of the 340-Mev proton beam as it crosses a 6-inch-wide piece of solid lucite. The beam enters from the left. Part of the loss of definition on the right comes from the slightly divergent nature of the beam and part of it from multiple elastic scattering. Original has been enlarged 1.5 times.

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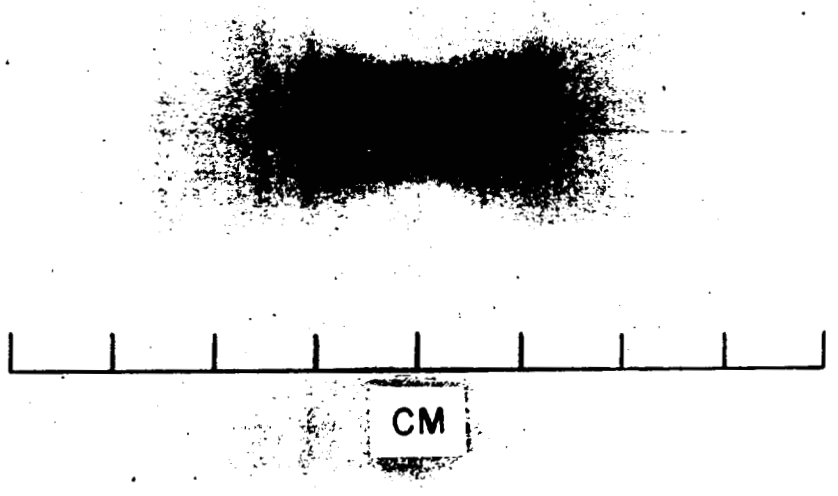

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Fig. 11. Autoradiograph of the proton beam on film placed in the lucite head phantom, exposed to a full set of rotations and position angles corresponding to the entire treatment schedule in human. The blackened area is the region of high dose. Note that the shape and size of this area closely correspond to the shape and size of the human hypophysis. (Rotation limits ± 30°, treatment plane orientation angles ± 30°, ± 22.5°, ± 15°, ± 7.5°, 0°. Beam aperture an ellipse with 8.5 mm major axis and 5.5 mm minor axis.)

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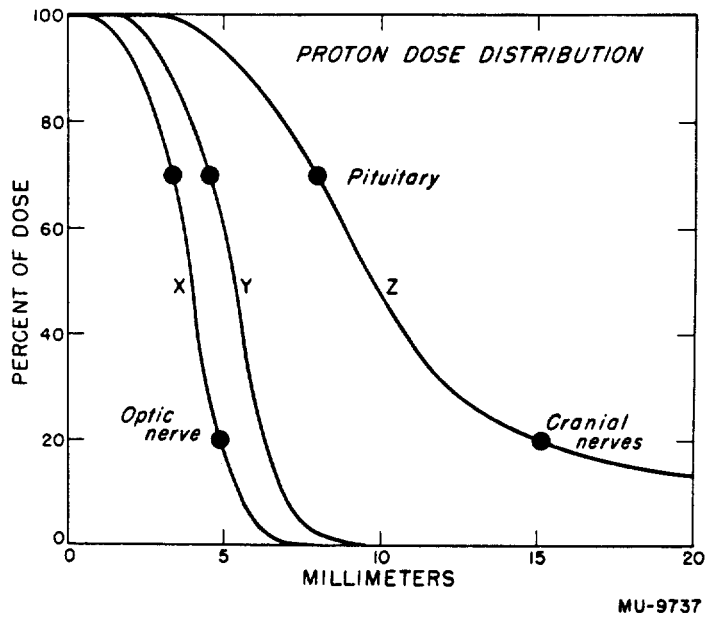

Fig. 12. Dose distribution along the three major axes of the head, X (longitudinal), Y (A-P), and Z (lateral). Note that the dose level is 10% to 20% of the peak dose at the cranial nerves and temporal brain lobes. Parts of the optic nerves receive 20% to 30% of peak dose, while most of the optic chiasm and hypothalamus are essentially free from dose.

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taking care of the patient receive a fast neutron dose of 420 Mev/cm^2 sec near the treatment room door and 50 Mev/cm^2 sec elsewhere while the beam is on, high-energy gamma rays of less than 1 mr/hour, and about 100 slow neutrons/cm^2 sec.

CRITERIA FOR SELECTING PATIENTS FOR PITUITARY PROTON-BEAM IRRADIATION

It was felt that for the present time only patients with cancer who have had all other available therapy should be exposed to protons. In addition, an attempt is being made to select patients who have a realistic chance of deriving benefit from pituitary ablation. Thus the criteria for acceptance at present are as follows:

a. The patient should have mammary carcinoma. She should have had conventional surgical and radiological treatment.

b. The patient should have received a trial of hormone therapy, or surgical or radiation oophorectomy and adrenalectomy.

c. There must be objective evidence showing the presence of progressing metastatic lesions for which none of the above-mentioned procedures holds out further hope.

d. The patient should be younger than 60 years of age and--apart from the carcinomatous process--in fair physical condition. Initially, desperate cases were selected who did not satisfy these criteria and were near terminal.

On the basis of experience with adrenalectomy by Huggins et al. it is felt that nondifferentiated carcinomas of the breast are controlled by the pituitary-adrenal-ovarian system to a lesser degree than the well-differentiated type

CLINICAL STUDIES

Clinical studies and observations are being carried out in three separate fields in order to obtain as complete information as possible: (a) endocrinological tests, (b) neurological examinations, and (c) effect on tumor growth. Endocrinological tests include many phases:

Thyroid function tests are made by means of I^{131} uptake, protein-bound iodine determinations, and basal metabolism measurements.

Pituitary gonadotrophin activity is followed by urinary follicle-stimulating hormone determinations (FSH) and, where possible, urinary estrogen excretion studies.

Adrenal function tests are of no use since the patients thus far studied have been previously adrenalectomised and are receiving supporting steroids. Urinary ketosteroids are assayed, however, in most cases.

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In view of the possible presence of a pituitary hemopoietic factor, blood-volume measurements and iron-turnover measurements are carried out as needed.

Water balance is studied by urine output and specific gravity measurements, as well as water-loading tests, and by studies with tritiated water.

Sugar tolerance and blood sugar determinations are carried out routinely.

Neurological examination includes tests for cranial nerve damage, visual-field studies, and tests for acuity of the sense of smell and touch.

Unfortunately, there are no conclusive tests available for obtaining information about the state of proliferation of tumor cells. The Huggins serum coagulation test is being done periodically. In addition diagnostic x-ray examinations give information about bone and lung metastases; skin metastases are observed directly; biopsies are obtained if advisable. Serum alkaline and acid phosphatase levels and calcium excretion have been measured routinely. These may give evidence of healing or progression of bone metastases. In addition all conventional clinical laboratory observations are made.

TREATMENT SCHEDULE

Early treatment schedules followed the present clinical radiotherapeutic practice of dose fractionation by administration of several repeat irradiations. Three doses were given weekly, (Monday, Wednesday, Friday). This limitation was necessitated by the availability of the cyclotron. The dose at the center of the pituitary was 800 rad in a plane. Two or more planes were frequently used on a given day. The dose schedule was conservative and probably inadequate in the earlier cases. With accumulated experience and in the absence of contraindications, the daily dose was raised to higher values, until at present as much as 5000 rad may be given in a single day, in five different plane orientations of the body with respect to the proton beam, and ± 35° rotation of the head in each orientation. The dose at the center of the pituitary gland at the end of the treatment (usually 20 to 40 days) was from 14,000 rad to 30,000 rad.

CLINICAL OBSERVATIONS IN THE COURSE OF THERAPY

None of the patients treated so far has shown objective or subjective clinical signs of immediate physiological effects from the radiation. In the course of 200 individual exposures, severe headache was reported in two instances during the day following exposure; however this could not be definitely associated with the treatments. Radiation invoked no sensation; blood pressure and temperature remained normal.

No obvious evidence was found for secretion or dumping of hormones from the pituitary in the first 24 hours after exposure to protons. This effect was observed in rats by Mateyko and Edelman.[33]

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Undesirable skin effects, which may include erythema, epilation, and ulceration, were all completely absent during the first 5 to 9 months following exposure, no doubt because of the low doses delivered to the skin.

Neurological observations indicate likewise a complete absence of undesirable side effects on the cranial nerves, temporal lobes, or optic chiasm up to the date of preparation of this report. However, it will be necessary to continue these observations for a considerably longer time.

PHYSIOLOGICAL OBSERVATIONS IN THE POSTTREATMENT PERIOD

Significant depression of pituitary functions was observed in all patients during the postirradiation period.

A. Thyroid Function

Over a period of five months there is a decline of thyroid function, as evidenced by the 24-hour uptake of radioactive I^{131} administered orally. Two sets of data for individual patients are shown in Figs. 13 and 14. At the end of six months, iodine uptakes that had been in the normal and high range became as low as 3% and 5% respectively, in the same range (2% to 8%) as one obtains with surgically hypophysectomized patients. Values for protein-bound iodine, (shown also in Figs. 13, 14) decline, but in some patients show a curious and at present unexplained rise. Basal metabolic rates decrease, but less significantly. However, clinically, myxedema so far was absent or only mild.

There was indication that the iodine uptake decreased during the treatment period, increased again in the month following proton exposures, then slowly and progressively decreased again.

B. Urinary FSH

The initial FSH values were almost uniformly high, in the range of postmenopausal women. In each instance where measurement was possible, a decrease occurred; but great fluctuations are found in the FSH titer. After five months of posttreatment period, the FSH is too small to be measured, and (as far as our observations allow us to determine) stays at zero level. (See Figs. 13, 14.)

C. Urinary Estrogen

Only in one patient was measurable urinary estrogen level observed This patient had incomplete adrenalectomy previously. In one month after completion of pituitary radiation the urinary estrogen fell to zero.

In order to obtain a general view of the endocrinological findings in the first 10 patients irradiated, Table I lists pre- and posttreatment iodine uptake and urinary FSH values. At 30,000 rad, the induced function changes begin to occur within the first 30 days and present a definite pattern. This is illustrated in patient M. S., Table II.

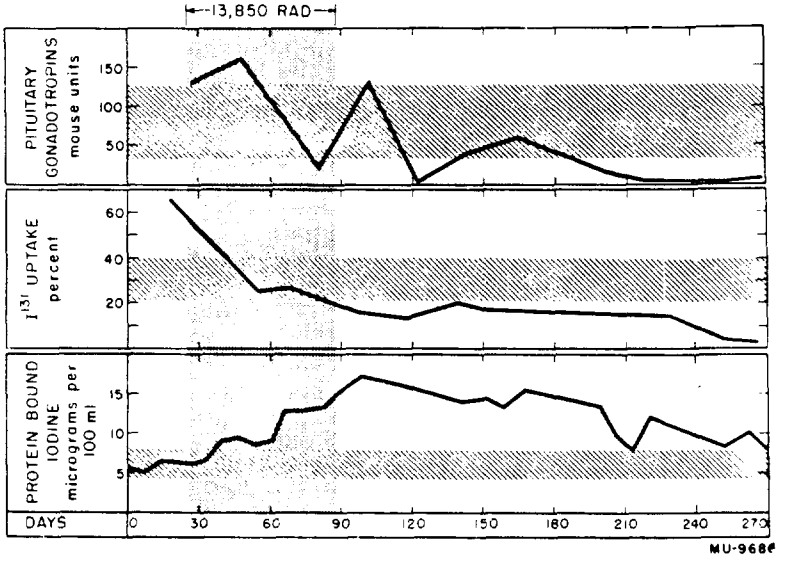

Fig. 13. I^{131} uptake, protein-bound iodine (PBI), and urinary FSH values in patient Mrs. M. W. (multiple skeletal and liver metastases), who received 13,850 rad in 63 days. Note the gradual decrease of I^{131} uptake and FSH until in about 6 months they are in the hypophysectomy range. The PBI values somewhat unaccountably increased for a considerable period of time.

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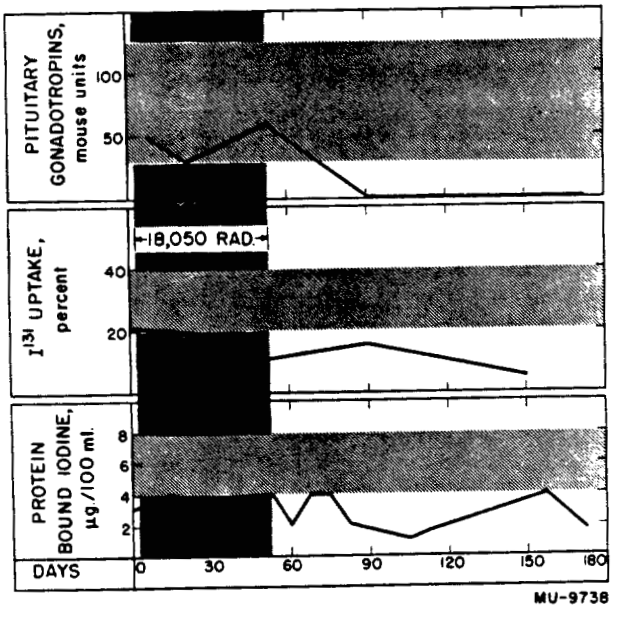

Fig. 14. I^{131} uptake, PBI, and FSH values in patient Mrs. A. S. (extensive carcinoma metastases in cuirass and pulmonary metastases).

Patient	Peak dose radiation	Days	I^{131} Uptake		PBI		FSH	
M.W.	13,800	245	66	2.5	5.4	8.0	>130	<5
A.R.	12,880	122	23	16.5	6.0	9.1	>80	>100
E.P.	13,200	28	30	16	4.3	4.1	>160	<80
C.D.	16,280	105	30.5	17	8.9	7.3	>160	>120
K.C.	16,400	141	30	16.5	7.3	2.3	>140	10
A.S.	18,050	165	21	6.4	3.0	3.2	>50	<5
C.H.	17,940	81	27	16	4.2	3.9	—	—
A.T.	19,900	44	35	24	5.7	4.3	>200	<80
B.G.	18,400	34	33	35	30	22.5	>80	<5
E.H.	22,000	98	19	2.2	16.5	13.3	>80	>15
R.H.	26,000	42	15	19.5	5.1	3.8	<5	<5
M.S.	30,000	68	10	3.7	4.7	4.1	>250	5

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Table I

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PITUITARY PROTON IRRADIATION - TYPICAL LABORATORY DATA
PATIENT M. S., MULTIPLE BONE METASTASES

Time	Dose RAD	Blood Proteins Total g.%	Albumin g.%	Globulin g.%	Phosphatase Acid G.U.	Alkaline G.U.
1 day	0	5.8	3.9	1.8	6	15.6
30 days	30,000	6.9	4.2	2.7	5.8	16.4
90 days	30,000	7.2	4.9	2.3	5.3	19.7
Normal range		6-8	4.5-5.5	1.5-3.0	.5-4	5-13

Urine Calcium mg./24 hrs.	Thyroid Uptake %/24 hrs.	PBI µg./100 ml.	Urine Gonadotropins Mouse units	Blood RBC million	Hemoglobin %	grams
1107	10	4.5	>160	2.4	53	7.7
689	6	1.2	<80 >10	3.2	57	8.3
1410	3.7	4.1	5	2.9	64	9.3
50-300	20-40	4-8	32-128	4-5	76-108	11-15

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Table II

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WATER TURNOVER

Because of the great fluctuation of water intake and urine output, cumulative curves were plotted, in which the total water turnover was graphically shown. In this fashion, one finds that water turnover of all patients is generally high. It is questionable whether a mild diabetes insipidus exists in the postirradiation period. Blood volume and serum protein, serum cholesterol, sugar tolerance, and water-loading tests have so far not significantly aided in evaluating pituitary effects; these fluctuated in the normal range, except where the values were off normal because of complications already present owing to the disease process.

ALKALINE AND ACID PHOSPHATASE

In the presence of bone metastases alkaline phosphatase and acid phosphatase measurements are of some value; in some as yet not precisely determined way these depend on pituitary function. While tumor growth is actively infiltrating the skeleton the alkaline phosphatase is frequently low, and the acid phosphatase high. While deposition of new bone occurs the alkaline phosphatase is usually high. Thus high alkaline phosphatase is indicative of bone recovery, unless complicating factors are present. In several patients the pattern of alkaline and acid phosphatase has changed after radiation (see, e.g., Figs. 15a and 15b). Complete evaluation of the significance of these findings will have to wait, however, until more data have been accumulated.

CALCIUM EXCRETION

Bone deposition sometimes depresses calcium excretion in the urine and Figs. 15a and 15b show typical data obtained. This measurement is complicated by the fact that pituitary ablation and prolonged bed rest both cause decalcification of bone.

DISCUSSION OF THE PHYSIOLOGICAL CHANGES

One observes a definite depression of the physiological function of the pituitary gland in a period of six months, in the absence of undesirable side effects. While this result is encouraging and has perhaps not been attained previously by irradiation, the authors feel it desirable to try to accelerate atrophy of the pituitary gland further by the application of higher doses and by further improved technique in order to obtain more profound effects in a shorter time.

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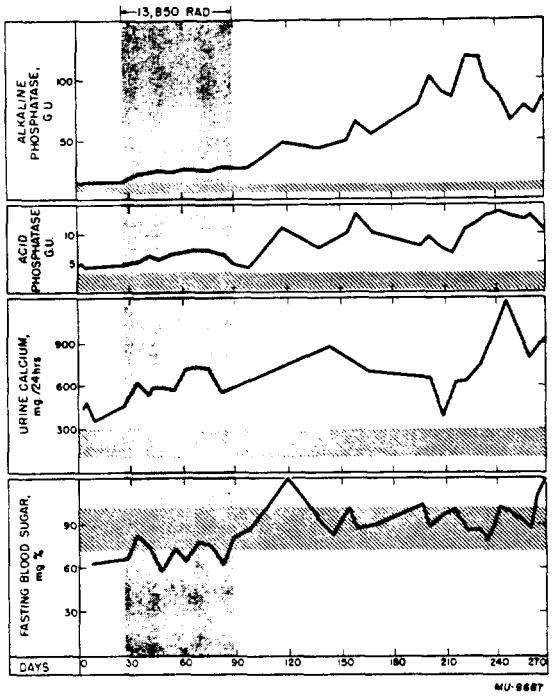

Fig. 15a. Alkaline and acid phosphatase, fasting blood sugar, and urinary calcium secretion for patient Mrs. M. W.

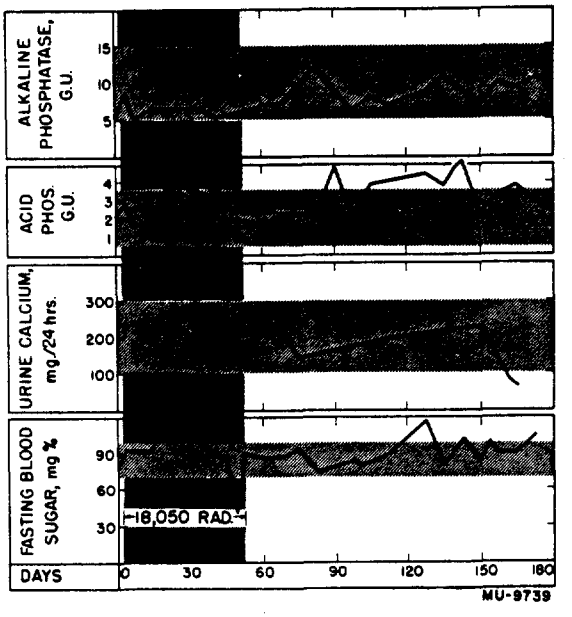

Fig. 15b. Alkaline and acid phosphatase, fasting blood sugar, and urinary calcium secretion for patient Mrs. A. S.

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CLINICAL MANAGEMENT OF PATIENTS FOLLOWING PITUITARY IRRADIATION

All the patients receiving pituitary irradiation have previously had bilateral adrenalectomies and oophorectomies and were on maintainance doses of cortisone ranging from 37.5 to 75 mg daily with NaCl supplement and DOCA where postural hypotension existed. Following pituitary irradiation no additional substitution therapy, including pituitary extracts, has been necessary although in several cases the dosage of cortisone has been increased with subjective improvement to the patient. It was believed desirable to place several of the patients on 2 grains of thyroid extract daily. This, however, was on an empirical basis.

THERAPEUTIC EFFECTIVENESS OF PITUITARY IRRADIATION PROCEDURE IN CANCER

At the time of this writing it is too early to give an objective evaluation of the therapeutical usefulness of this new method. Some evidence is already being obtained, however, that tumor proliferation and hormonal balance are intimately related. In order to obtain a reliable estimation of the value of this therapy much more time and experience will have to be accumulated to determine optimum dosage and timing. Report on this phase of the investigation is being deferred to a later date.

SUMMARY

1. Initial use of high-energy 340-Mev protons in a human therapeutic investigation is reported.

2. Localized irradiation of the human pituitary gland was achieved by a combination of multiple-port and rotational application of the high-energy particles. This procedure allows accurate delivery of high doses to the pituitary gland, with much lower doses to surrounding bone, brain, nerves, and skin.

3. The patients were advanced cases of metastatic carcinoma of the breast, who had previous mastectomy, x-ray therapy, hormone administration, oophorectomy, and adrenalectomy.

4. Definite evidence of depression in pituitary hormone output and control of target organs was achieved with peak doses of 14,000 to 30,000 rad at the center of the pituitary. The effects were delayed and gradual in their onset. Undesirable side effects were absent.

5. So far only 9 months' experience on 12 patients is available. Full evaluation of the pituitary-ablation and cancer-therapeutic effectiveness will have to be made at a later time.

APPENDIX

A. Preparation of a Form-Fitting Plastic Mask for Radiation Therapy

Hal O Anger and Richard W. Pratt

The form-fitting mask that holds the patient's head in a fixed position during alignment and bombardment is made in the following way.

The patient's head is first covered with a close-fitting seamless rubber cap made by cutting the stem off a rubber balloon of suitable size. Then a dividing strip of aluminum foil is taped to the cap as shown in Fig. 16. The foil is notched at frequent intervals to allow it to conform to the shape of the head and at the same time stand perpendicular to the cap. The notches are covered with tape to form an uninterrupted dividing strip. Then the back half of the patient's head is covered first with plaster of Paris and then with plaster bandage.

After the plaster had hardened, the patient reclines face up and the eyes are covered with cone-shaped pieces of celluloid cut to fit the contour around the eyes (Fig. 17). The upper part of the face is covered with a skin cream and then with plaster of Paris and plaster bandage, taking particular care to get the plaster under the brow ridges so the completed mask will fit closely there (Fig. 18). After the plaster has hardened, the front half of the plaster mask is pulled off, and then the back half is easily slipped off.

The irregularities in the parting foil make it possible to join the two halves of the plaster mask exactly as they were on the patient's head. The two halves are taped together, thus forming a mold, and the inside is covered with a greaseless hand cream. Then dental stone is poured into the mold to form a positive replica of the head. After it has hardened, the two halves of the mold are removed and the flash marks and any small holes in the positive replica are smoothed out.

Mold-release compound made for use with plastics is then applied to the replica. The plastic that is used to make the final mask is a polyester resin* which, when hardener is added, hardens at room temperature in a few hours. The resin, with hardener added is painted onto the replica and strips of Fiberglas or other cloth are applied at the same time. Since x-ray radiographs must be taken through the mask, cotton or nylon cloth is used in place of the Fiberglas cloth where the x-ray beam passes, since the Fiberglas cloth shows on the radiograph.

By this method, a shell of cloth-reinforced plastic is built up until a thickness of about 1/8 inch is reached. This is shown in Fig. 19.

At this point a lucite flange, machined to fit the contour of the mask at a plane a little below the midline, is attached to the back half of the mask with Fiberglas cloth and more of the plastic. Then the bottom edge is trimmed and the mask is cut in two along a plane transverse to the median plane. Eye holes are cut to allow the patient to see. Four small slotted metal flanges are

*Apcolite Boat "A" Resin. Taylor and Art Inc., Oakland 6, California.

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Fig. 16. Preparation of the plaster-of-Paris mask. Note the rubber cap and dividing aluminum foil.

Fig. 17. Protection of the patient's eyes with celluloid cups.

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Fig. 18. The complete plaster-of-Paris mask.

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Fig. 19. Cloth-reinforced plastic mask in preparation.

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attached to the front half and matching jointed screws are attached to the lucite flange. The jointed screws are used with wing nuts to fasten the two halves of the mask together when it is fitted onto the patient. They allow rapid release of the patient if necessary. The completed mask is shown in Fig. 20.

B. Profile and Isodose Measurements of the 340-Mev Proton and 190-Mev Deuteron Beams by Photographic Densitometry

Graeme P. Welch

Introduction

Dose-distribution measurements of particle beams from the Berkeley cyclotrons as used for biological work have been made by Tobias et al.[26] using an extrapolation chamber, by Sayeg[35] and Birge and Sayeg* scanning with a small aperture between beam and ion chamber, by Sayeg* activating a mosaic of polyethylene squares and subsequently counting annihilation gamma rays from carbon-11, and by Welch* scanning a small CdS crystal photoconductor through the beam and measuring the change in conductivity.

The problem of hypophysectomy requires, in addition to a concentration of radiation within the pituitary, a minimum of irradiation to surrounding tissues. This is accomplished by using a two-axis rotation technique, which in effect spreads the radiation everywhere within a conical volume as a function of the distance from the apex. As an illustration refer to Figs. 10 and 11 in the body of the report. Figure 10 is a picture of the beam progressing from left to right and shows qualitatively how little lateral scatter there is and how pencil-like the whole beam is. Figure 11 was taken at the same position as Fig. 10, but now the phantom containing the film was rotated as was done for a complete treatment of a patient. Rotation was continuous ± 30 degrees about a horizontal axis perpendicular to the film during each of nine exposures covering ± 30 degrees, at 7-1/2 degree intervals, about a vertical axis lying in the plane of the film. Note here that everywhere within the ± 30 degrees except near the rotation axis the intensity is much reduced and qualitatively is in proportion to the distance from the axis.

Dose measurements on a system employing this technique would be quite laborious by any of the methods previously used, since a time-integrated picture of the irradiation is needed. This suggested that a photographic method should be tried.

The property of a photographic emulsion that makes it suitable for quantitative radiation measurements is the dependence of blackening on exposure; more specifically, over quite a wide range the density is proportional to the log exposure.[36] Thus a film exposed to the beam gives a picture with gradations of blackening depending on the number of striking particles per unit area. Densities within very small areas are readily measured with a standard spectrographic microdensitometer and the data thus obtained are reduced by modifications of methods described by Harrison.[37]

*To be published.

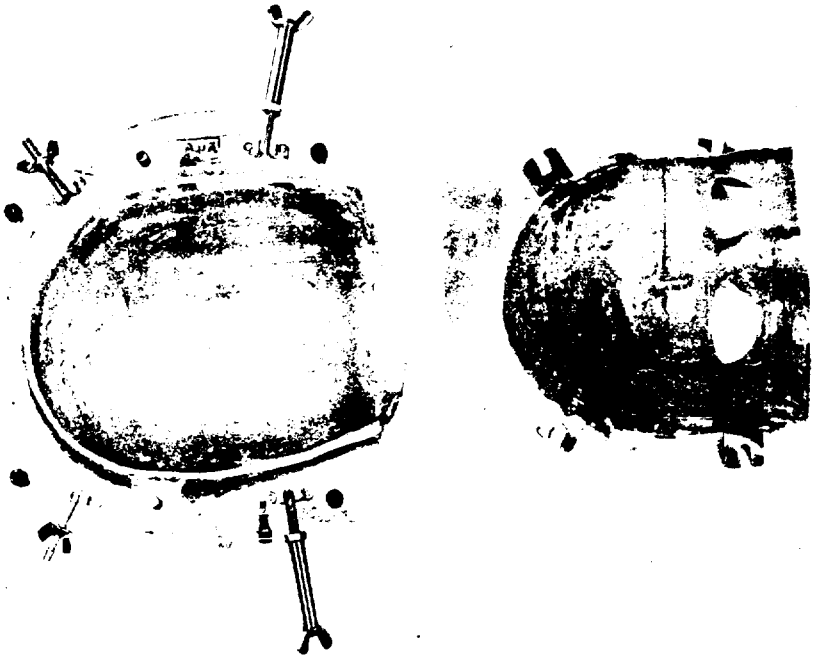

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Fig. 20. The completed mask with flange and quick-release fastening attachments.

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Equipment and Procedure

A schematic diagram of the equipment arrangement is shown in Fig. 21. All components indicated there except the phantom are the same as used for the therapy and are discussed in the main report. The phantom, containing the photographic films, is constructed of 6-by-7-inch pairs of sheets of 1/32-inch black bakelite alternating with lucite of various thicknesses from 1/8 to one inch. Six inches is its total thickness. The external lucite surface that faces the beam is spherical, with a diameter of six inches, so that the amount of absorber through which the beam passes is constant with rotation, analogous to the human pituitary irradiation conditions. Four-by-five-inch sheets of photographic film (EK Super pancro-press) are held in a light-tight pocket between each pair of the black bakelite sheets, one of which has a depression, of the film's dimensions, milled in it. The six-inch-thick stack made of these parts contained usually between ten and twenty films and was aligned in the head-holding rotating mechanism, with the central film containing the two axes of rotation. Nine exposures corresponding to a complete treatment schedule were made, one in each plane at 7.5-degree intervals about the vertical axis, and each with rotation ± 30 degrees about the horizontal axis.

The film's sensitivity is such that ten rad of 340-Mev protons gives a density slightly greater than 1 and, although this is outside the linear region, the curvature at this density is not so rapid as to make accurate calibration difficult.

For calibration a film in a black bakelite pocket with three inches of lucite on each side was given a series of seven exposures from 12 to 0.2 rad. Each dose was 1/2 the previous one, an arrangement that gives good distribution of data for plotting an approximately logarithmic function such as a film response.

The standard of reference for these measurements was the ion chamber used by Tobias et al.[26] It has a sensitive volume 0.5 inch in diameter by 0.5 inch long, was used with a collecting potential of 4000 volts, and was connected to a UCRL electrometer.

All films pertaining to one experiment were developed simultaneously in fine-grain developer (EK Microdol). Temperatures of all three solutions (developer, wash, hypo) were equalized in order to minimize grain size.

Densitometric measurements were made with an Applied Research Laboratories spectrographic densitometer with 0.02-by-0.7-mm slit. This was in turn connected to a Leeds and Northrup Speedomax recorder which, as the film passed beneath the densitometer slit, continuously recorded densities (in terms of percent light transmission) on a moving chart.

Data Reduction

A calibration curve was constructed for each set of data by plotting the percent transmissions at the centers of the calibration exposures vs their corresponding radiation doses. Figure 22 is typical

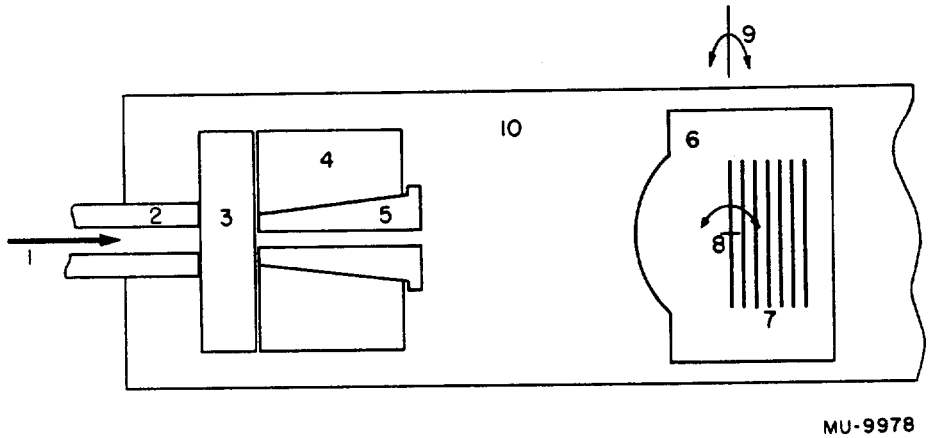

Fig. 21. Schematic arrangement of equipment for photographing proton beam, top view, approximately 1/4 scale.

1. proton beam
2. steel pipe, 1 inch i.d., 1-inch wall
3. monitor ion chamber
4. brass aperture block 5 inches thick
5. interchangeable brass aperture
6. phantom of lucite and black bakelite
7. photographic films
8. vertical axis, rotation ± 30° in 9 steps at 7.5° intervals
9. horizontal axis, rotation continuous ± 30°
10. equipment bench, machined from 8-inch steel channel

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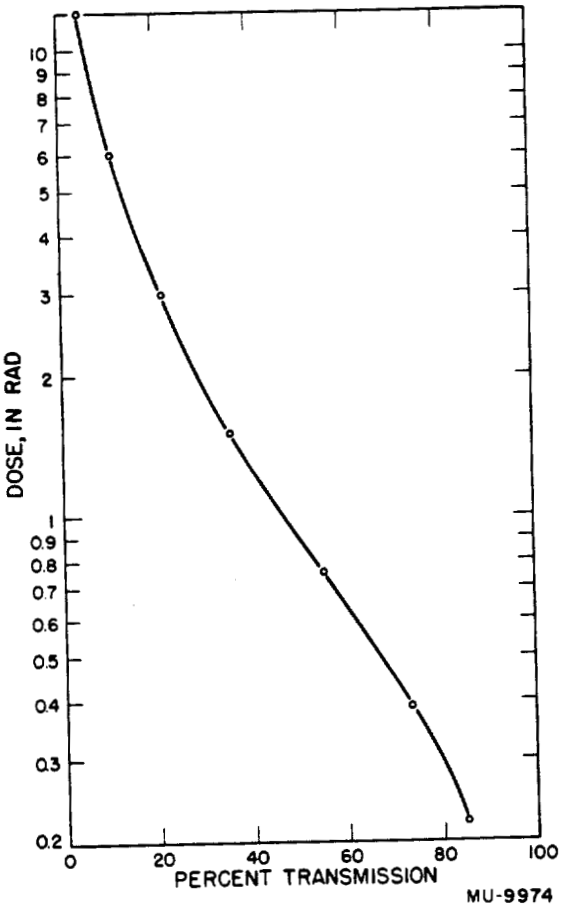

Fig. 22. Film calibration curve September 17, 1954.

The densitometer is designed so that the background may be set at 100 percent transmission, thus eliminating a background correction from the subsequent calculations. An unexposed film developed with the experimental films showed no detectable difference in background. The total dose given the calibration film was 24 rad and, since the calibration only extends down to 0.2 rad, the best one can say from this and the comparison with the unexposed film is that the background due to radiation is much less than 1/120 of the radiation dose. Comparative measurements were made of normal emulsion background and 0.75 rad dose exposure (which was the smallest actually used) with a small area from which the emulsion was removed. The calibration-point density was 1.7 times the emulsion density so that the measurements were never limited by background. (See also Background Considerations, pg. 19.)

Two types of dose information were desired, (a) the intensity profiles along the three axes--vertical, horizontal, and beam--which meet at the center of the pituitary and (b) isodose curves in the vertical and horizontal planes which contain the beam axis. Data for (a) come from scans along vertical and horizontal axes of the central film and from measurements at the center of each of the other films. Vertical and horizontal scans on all films are required to supply data for (b).

In either case densities measured on scanning the films from the rotated phantom were converted to irradiation intensities by means of the calibration curve and then to percentages of maximum intensity. These were then plotted vs distance from the rotation center (i.e., distance from intersection of the three axes).

Discussion of data

Intensity profiles for the 5.5-by-8.5-mm elliptical aperture are shown in Fig. 23. From the longitudinal profile it may be seen that the dose falls approximately as the inverse square of distance beyond 9 mm. Hence for the human setup, by extrapolation, the dose at the skin falls to about three percent of the pituitary dose. The horizontal and vertical profile curves fall much more rapidly at the edge of the field (about 30 percent/mm), thus giving assurance that proximal sensitive nerve structures will receive negligible doses.

Isodose curves in the first quadrant of the horizontal plane are shown in Fig. 24 for the 5.5-by-8.5-mm elliptical aperture. These curves extend into the second quadrant as mirror images, owing to symmetry. As is shown in Fig. 10 in the body of the report, the beam is quite well collimated, so one may expect the curves in the remaining two quadrants to be similar to those of the first two. Figure 25 shows a similar set of curves for the vertical plane.

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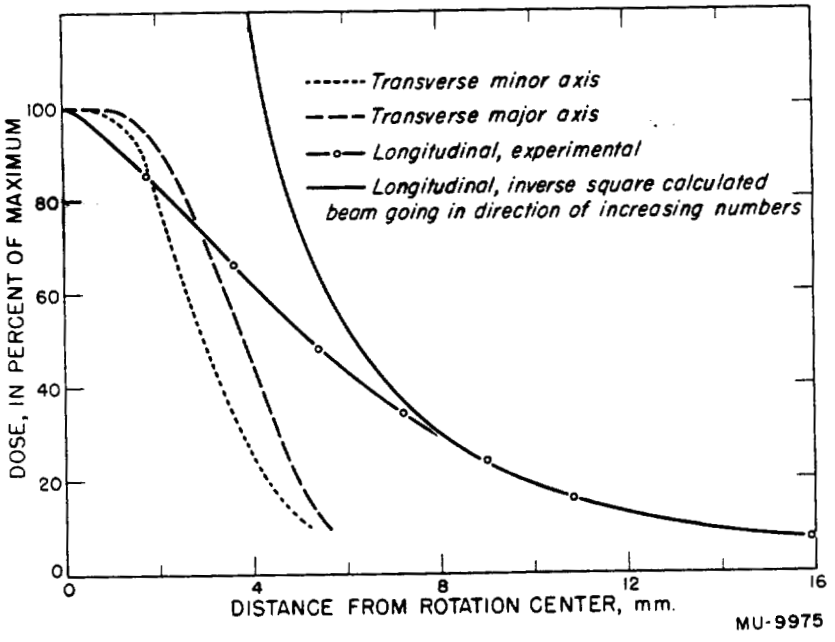

Fig. 23. Intensity profiles. 340-Mev protons September 17, 1954. Elliptical aperture, 5.5 by 8.5 mm, major axis vertical; horizontal rotation ± 30°, continuous; vertical rotation ± 30°, 9 positions at 7.5° intervals. ----- transverse minor axis, — — transverse major axis, —·—· longitudinal, experimental, ——— longitudinal, inverse square, calculated. Beam going in direction of increasing numbers.

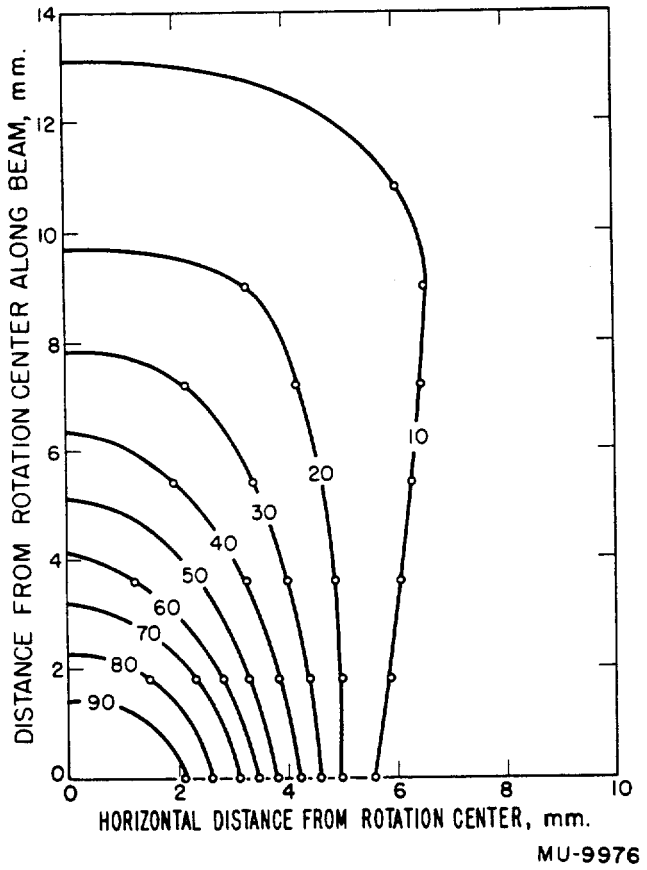

Fig. 24. Isodose curves September 17, 1954. Horizontal plane. Elliptical aperture, 5.5 by 8.5 mm, major axis vertical. Horizontal rotation ± 30°, continuous; vertical rotation ± 30°, 9 positions at 7.5° intervals.

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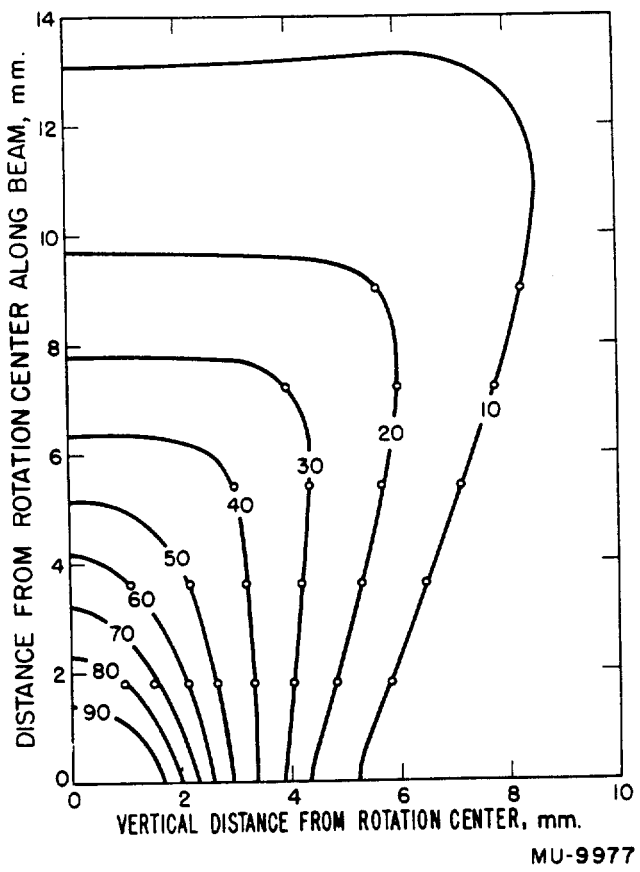

Fig. 25. Isodose curves September 17, 1954. Vertical plane. Elliptical aperture, 5.5 by 8.5 mm, major axis vertical. Horizontal rotation ± 30°, continuous; vertical rotation ± 30°, 9 positions at 7.5° intervals.

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