Pituitary Irradiation with High-Energy Proton Beams
A Preliminary Report*

C. A. TOBIAS, J. H. LAWRENCE, J. L. BORN, R. K. McCOMBS, J. E. ROBERTS,
H. O. ANGER, B. V. A. LOW-BEER,† AND C. B. HUGGINS‡

(Donner Laboratory of Biophysics and Medical Physics, Donner Pavilion, and the Radiation Laboratory,
University of California, Berkeley, Calif.)

HYPOPHYSEAL PROTON IRRADIATION

An account is given below of the initial use of high-speed protons in human therapeutic investigations. The rationale for pituitary irradiation, the technic employed, and the initial physiological changes after proton irradiation of the pituitary gland are given in detail.

Roentgen irradiation of the human pituitary was performed by Gramegna in 1909 (49). Although experimental evidence suggests that overactive elements of the pituitary may be radiosensitive, statements in the literature seem to indicate that it is difficult, if not impossible, to influence the function of the normal pituitary by x-ray (27). Indeed, Crooke has stated that he has not observed histological changes in the human pituitary, even with fair amounts of irradiation (6). Because of the limitations imposed by the sensitivity of the skin and by the danger of injury to the brain, the doses of conventional roentgen irradiation have had to be small. Irradiation has been a frequently used therapeutic approach in pituitary tumors (37), Cushing’s syndrome (16, 39), and acromegaly (15, 39). Attempts have also been made to irradiate the pituitary in various other conditions—for example, hypertension (14) and exophthalmos (4, 7). Roentgen irradiation has also been attempted for cancer in the human being, particularly by Murphy and Schwippert for prostatic carcinoma (38) and by Kelly et al. for mammary carcinoma (17). However, in three patients with mammary carcinoma, even 10,000 r to the region of the hypophysis was not sufficient to cause notable depression in hormone production, histopathological damage, or remission of the disease (17). The technic of roentgen irradiation is still being extended and improved, as exemplified by the recent work of Santos (45).

The pioneer work of Lacassagne and his associates (23), the implantation of radioactive seeds into the pituitary, seemed to offer an alternative method for delivering large amounts of irradiation; indeed, radon seed implantation did affect the pituitary in acromegaly and Cushing’s syndrome (39). During the last few years Kisieliski and his associates have developed new methods for processing radioactive yttrium into seeds (21). This has led to the therapeutic clinical investigations of Kennedy et al., who implanted several yttrium seeds into the pituitary to give considerable doses of beta-particle irradiation in an attempt to stop hypophyseal function and to cause regression of carcinomas. This study is still in progress at the University of Chicago and at McGill University (19). Colloidal radioactive chromic phosphate was deposited in the human sella turcica by Rothenberg et al. (44). Forrest and Brown used pituitary radon implants (11).

Recent advances in surgical technics and postoperative management have made hypophysectomy feasible. Luft and Olivcrona in Sweden have...
reported hypophysectomy on some 37 cases of metastatic carcinoma of the breast (30, 31) and on some twenty cases of severe diabetes mellitus (32, 33). Kennedy and associates at the University of Minnesota have reported twelve cases of breast cancer (18). Currently, Pearson et al. (40) and others (1, 8, 12, 20, 22, 29, 41, 42, 47) are vigorously attacking the problems of hypophysectomy in cancer and other diseases. Hypophysectomy, even in the hands of an expert neurosurgeon, is not always achieved completely and is a difficult procedure.

The development of the cyclotron, betatron, linear accelerator, and other machines has made possible the production of beams of particles with possible applications in teletherapy (2, 35). The interesting nature and characteristics of high-energy protons and deuterons were pointed out by Robert Wilson in 1946 (53), and at that time careful consideration was given to their possible value in teletherapy. Up until that time, the only heavy nucleons that had been used in experimental cancer therapeutic investigations were neutrons (24-26, 48, 49). However, these particles did not prove superior to x-rays or gamma rays. As soon as the first high-energy synchrocyclotron was completed by E. O. Lawrence and his associates and the internal beam successfully deflected, animal studies were initiated by us (50) with a view to eventual application to cancer and have continued to the present time.

The demonstration that hypophysectomy might be of benefit in the palliative treatment of various diseases such as advanced breast cancer, fulminating juvenile diabetes with retinopathy, malignant exophthalmos, and malignant hypertension prompted the inquiry into the possible use of the proton beam to destroy or inhibit the function of the pituitary gland. The technic was perfected by extensive animal investigation, in which both 190 Mev deuterons and 340 Mev protons were employed, but only the 340 Mev proton beam was used in attempts to destroy the human pituitary, first in patients with advanced metastatic breast cancer.

**Proton Irradiation Technic**

**General properties of heavy particle beams.**—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 (53). The particles, when focused, travel in a straight beam with little divergence and may be directed to any portion of the body. A suitable aperture, made of brass or other metal, is used to define the shape and size of the beam. As the particles penetrate tissue, their scattering is very small compared with electrons, and for practical purposes negligibly small amounts of radiation fall outside the main beam. The background ionization may be kept to less than 0.1 per cent of the beam.

Furthermore, heavy monoenergetic particles penetrate to a uniform and well defined range, producing their maximum ionization just before stopping. The 340-Mev protons used in the present study have ample range to traverse the entire human cranium. An autoradiograph of this beam is shown in Figure 1 as it crosses a 6-inch thick, solid piece of lucite. The straight path of travel and the relative lack of scatter can be seen. These properties were early demonstrated in biological and medical experiments by Tobias, Anger, and Lawrence (50).

**Biological experimentation.**—Experience in the use of proton, deuteron, and alpha particle beams was gained by investigating their biological effectiveness and their mechanism of lethal action through localized irradiation of animal tissues. The relative biological effectiveness per unit of ionization of the high-energy portions of the deuteron and proton beams 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 (50), yeast cells (55), and Tradescantia microspores (13).

The use of high-energy, heavy particles makes possible the production in the animal body of lesions with microscopically sharp demarcation lines (50). In small animals, cylindrical lesions 1 mm. in diameter are easily produced. Since 1952, a sustained effort has been made, in collaboration with the staff of the Institute of Experimental Biology of the University of California, to study effects of these high-speed particles on the rat hypophysis (51). Initial results were encouraging; and pituitary irradiation of young monkeys and of normal, mature dogs and dogs with mammary cancer has been undertaken, by a technic similar to that for human beings (described below).

When large, single doses of more than 5,000 rad of deuterons or protons are given to the pituitary glands of animals, progressive atrophy of the entire gland results, accompanied by reduction in physiological function. The end results appear within limits to be similar, regardless of the size

1 In cooperation with Dr. G. Van Wagenen, of Yale University.

2 To be published (in preparation).

3 1 rad = 100 ergs absorbed/gm, or 1.07 rep absorbed in tissue.
of the radiation dose. The higher the dose, the sooner the physiological effects become manifest. Single doses of the order of 30,000 rad are necessary to approximate the immediate effects of hypophysectomy. To illustrate, Chart 1 shows the apparent time of onset of physiological changes resembling complete hypophysectomy. Data on rats, dogs, and monkeys show the same general relationship. The chief criteria for evaluation of the extent of pituitary destruction are rate of growth, thyroid function, and sizes of target organs. The entire gland must be irradiated to achieve any lasting physiological changes in the target organs.

Thus, when single doses are applied, pituitary damage can be achieved with relatively moderate doses, although it may not be observed until fairly long after the radiation exposure. The delayed onset of the effects is a factor of great importance in deciding upon the amount of irradiation to be administered to human beings.

The effects of pituitary irradiation on target organs do 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 upon growth and adrenal function follow, while regression of the sex glands, regulated by the pituitary gonadotropins, is usually last. The histopathology of the irradiated pituitary exhibits changes that indicate a characteristic pattern (in the rat), although differential effects are difficult to evaluate quantitatively. The acidophiles seem to be the first to regress, followed by basophiles and then chromophobes.

Long-term studies with doses up to 10,000 rad given to young Long-Evans rats indicate that the frequency of spontaneous pituitary tumors is reduced and the time of onset is prolonged if the animals are irradiated in the 1st month of life. The life span of animals that received large doses did not differ significantly from the life span of hypophysectomized animals.

Nerve and brain tissue is more sensitive to radiation damage than pituitary tissue. Lethal effects from pituitary irradiation, when the cause could be definitely ascertained, could be ascribed to associated radiation-induced 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 lie very close to the pituitary in the dog. 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. There resulted a characteristic dose-time injury curve, which resembled the data obtained with the pituitary. The lower the dose, the longer the time required for the symptoms to appear and the less severe they usually were. Since the data on dogs are available for a period of only 30 months, additional information is needed, particularly for long postirradiation times. Chart 2 gives the data now available.

The available 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, since most
data in the literature involve irradiation to exten-
sive volumes of brain tissue, whereas in the pres-
cent work relatively small volumes receive large
quantities of irradiation (9, 34). Perhaps most
pertinent are the recent observations by Arnold et
al., who observed delayed demyelination and
radionecrosis in the dose ranges of 1,500–5,000 r
of high-energy x-rays and, in addition, acute in-
flammation, hemorrhage, edema, and necrosis in
the range of 3,000 to 14,000 r, with increasing
severity at higher doses (3).

We and our associates had occasion to use the
proton beam to irradiate the pituitary glands of
several dogs with spontaneous metastatic mam-
mary adenocarcinoma. In five of fifteen such ani-
mals, definite regression or arrest of growth of the
tumors was noted several weeks after irradiation.
The disease process has apparently been arrested
recently in one animal for over 30 months. Several
of the dogs irradiated without benefit had open,
infected, ulcerating tumors when placed under our
care and died soon thereafter.

**TREATMENT SCHEDULE, CONTROL OF PROTON
BEAM, AND DOSE DISTRIBUTION
IN HUMAN PATIENTS**

In the course of the present preliminary inves-
tigations the irradiation was given by a multiple-
plane, rotational technic to minimize the dose to
radiosensitive tissues within the cranium. The most
sensitive structures are directly above the pitui-
tary—particularly the optic tract and the hypo-
thalamus. These should be avoided by the radia-
tion as much as possible. Laterally, the carotid
artery and the cavernous venous plexus are located
near the hypophysis. These structures are known
to tolerate a higher dose than nerve tissue. Of the
cranial nerves, the third, fourth, fifth, and sixth
are closest. Beyond the cranial nerves extend the
temporal lobes of the brain, and close to the hy-
pophysis are the regions subserving the sense of
smell.

Proton irradiation of the human pituitary was
combined with the well known rotational irradia-
tion technic. The position of the proton beam was
kept fixed in space and directed to cross the pitui-
tary as well as the entire head with uniform ion-
ization. During irradiation the patient's head was
rotated to the right and left with the axis at the
center of the pituitary body. The axis of the rota-
tion was also varied over a wide range of angles,
as shown in Chart 3. In this manner, the cumula-
tive dose to the pituitary gland was considerable,
while surrounding blood vessels, cranial nerves,
lobes of the brain, bone, and skin received progres-
sively less irradiation in the order of enumeration.

The alignment of the beam and rotation of the
head were accomplished by the following technic:

The beam passed along an optical bench in a
line 8 inches above the center of, and parallel to,
the track of the bench. A dose-monitoring ioniza-
tion chamber, a beam-collimating aperture, and
the focal spot of a diagnostic x-ray machine were
all mounted on the track so that the proton beam
passed through their respective centers. The pa-
tient's head was held rigid in an adjustable head
rotator, which was also mounted on the optical
bench. Adjustment screws were provided to move
the head in three directions—X (along the axis of
the patient's body), Y (in the postero-anterior di-
rection), and Z (laterally)—with an index on each
adjustment so that on subsequent irradiation ses-
sions the patient's position could be reset. The
alignment of the patient's head was checked by
means of roentgenograms before each session, and
adjustments were made when necessary (see
Charts 3 and 4).

The success of the technic depended on provid-
ing a firm mask to hold the patient's head during
alignment and irradiation on repeated occasions.
Very satisfactory, two-piece individual plastic
masks were developed for this purpose, utilizing
fiber-glass cloth and polyester resin. The mask was
tightened on the head with thumbscrews until it
fitted tightly enough so that the patient could not
move her or his sella turcica more than about 0.5
mm. in any direction. The masks were comfortable
enough to wear up to 2 hours at a time.

Figure 2a shows a diagnostic roentgenogram of
the sella turcica of one of the patients in alignment
with the cross-hairs, while Figure 2b shows the
radiograph of the shaped beam and its alignment
with the sella. This latter view was taken by first
exposing the plate to the x-rays, then momentarily
turning on the proton beam. One should bear in
mind that on the original radiograph the sella ap-
peared enlarged because of divergence of the
x-rays from the focal spot of the x-ray machine,
while the beam spot was actual size.

A vertical diagnostic x-ray film was 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 repres-
senting the base of the sella and the walls of the
sphenoid sinuses. The anterior clinoid processes
and medial margins of the orbits were also checked
for symmetry (Fig. 3).

Alignment of both views of the sella with the
cross-hair was usually within ± 0.5 mm. Occasion-
ally check x-rays were made, with the patient

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*To be reported in detail (in preparation).
forcibly trying to move the head out of alignment. These were always correct to within 1.0 mm.

The limits of rotation of the head about the body axis (X) were chosen as ±30° or ±35° from the vertical line of symmetry (Y). These values were selected because of the need for avoiding the eyes completely, so that the cornea, retina, and lens would not be irradiated. There were eleven planes of irradiation, which were about 7.5° apart. The choice of the treatment planes was such that the brain stem and the pars optica, mammillary bodies, tuber cinereum, and infundibulum received negligible radiation, since the beam did not cross these at any time.

The elliptical beam apertures, multiple planes, and rotation make the determination of isodose curves a complex procedure. Two methods were utilized: measurement by photographic densitometry and calculation from the known beam ionization profile.

In the first procedure a lucite phantom was used in place of the head, and photographic film inside this phantom was exposed to the beam, using the same rotations as for patients. One set of exposures with rotation corresponding to an entire irradiation schedule is given in Figure 4 (reproduced without retouching). The blackened area corresponds to the size of the pituitary gland.

Dose distributions along the major axes X, Y, and Z, obtained by film dosimetry, are given in Chart 4. The dose falls relatively slowly in the lateral, or Z, direction, where the hypophysis ex-

**CHART 3.**—A schematic drawing of the apparatus for proton irradiation of the human hypophysis

**CHART 4.**—Proton dose distribution along the three axes of the cranium, in terms of the peak dose at the center of the hypophysis.
tends farther. Toward the top of the head (X axis) and to the front and back (Y axis), the fall is very abrupt, insuring a considerable degree of protection for the optic chiasm and hypothalamus.

It is useful to evaluate the average hypophysial dose by integrating over the isodose surfaces. The average dose in the pituitary of the patients irradiated thus far has been between 55 per cent and 75 per cent of the peak dose at the center of the gland. The size and shape of the sella turcica vary considerably among patients, and several different apertures and rotations have been used.

TABLE 1

PREVIOUS MEDICAL AND SURGICAL TREATMENT OF PATIENTS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Oophorectomy</td>
<td>19</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>16</td>
</tr>
<tr>
<td>Estrogen, androgen</td>
<td>13</td>
</tr>
<tr>
<td>Roentgen therapy</td>
<td>22</td>
</tr>
</tbody>
</table>

CHART 5.—Metastatic involvement at the time of entry

To minimize permanent damage to capillaries and blood vessels in human beings, the well known radiological procedure of delivering fractionated doses was followed. Partial justification for this procedure was obtained by comparing dogs receiving single doses with dogs given fractionated exposures. In the latter group hemorrhage occurred, but only at much higher doses.

Most patients received average dose rates of 200–300 rad/min. The beam was delivered in the form of microsecond pulses about 68 times/second. The instantaneous rate therefore was very high.

In a full course of irradiation the patient received less than 20 rad total-body dose, most of which was radiation near minimum specific ionization. Beyond a radius of 1.5 inches from the beam, the whole body of the patient received everywhere less than 0.1 per cent of the peak dose.

SELECTION OF PATIENTS

Twenty-six patients with metastatic breast carcinoma received pituitary proton irradiation. These patients were carefully selected according to the following criteria: (a) The generally accepted forms of surgical and radiological treatment had to have been tried or determined to be of no benefit to the patient. (b) There had to be objective evidence for the presence of progressive metastatic lesions. (c) The response of the patient to palliative procedures such as oophorectomy, adrenalectomy, or endocrine therapy had to have been evaluated and, when deemed of more immediate benefit in extending the life or comfort of the patient, accomplished prior to acceptance of the patient for pituitary irradiation.

The patients ranged in age from 27 to 70 years, the average age being 46.6 years. The duration of their illness from the time of histological diagnosis to pituitary irradiation varied between the extremes of 0.1 year and 15.5 years, with an average of 4.7 years.

A summary of the medical and surgical treatment undergone by the 26 patients in this series prior to receiving pituitary irradiation is represented in Table 1. Thirteen of the earlier patients irradiated had previously had bilateral adrenalectomy and oophorectomy, many with remissions lasting from several months to several years. Two-thirds of all the patients were rapidly failing at the onset of pituitary irradiation and could be classed as terminal.

All the patients had metastatic lesions at the time of entry, as shown in Chart 5. Nineteen patients had metastases to bone, and at least twelve of these had additional metastases to other organs. The seven patients without osseus metastases had metastatic involvement of the lung, liver, skin, other breast, or viscera.

During irradiation the patients were hospitalized in the Donner Pavilion. They returned at intervals of from 3 to 4 months for follow-up studies whenever possible. The patients came from all parts of the United States; and this created definite problems in obtaining follow-up studies, particularly since it was desired that all follow-up laboratory and other studies be done at Donner Laboratory to insure uniformity and continuity.

6 Pituitary proton irradiation was also administered to four patients with the following diseases: (a) acute lymphatic leukemia, (b) embryonal dysgerminoma of the testis, (c) chronic lymphatic leukemia and diabetes mellitus, and (d) malignant exophthalmos. Data from these patients are not included in the present report. In the patient with malignant exophthalmos the loss of sight was so imminent that surgical removal of the upper orbit was necessary shortly after proton irradiation, and the effect of proton irradiation could not be observed.
SCHEDULE OF PITUITARY IRRADIATION

Proton irradiation to the pituitary was given in fractionated doses 3 times a week. The earlier patients in the series were started on small doses of irradiation, and the course of irradiation covered a protracted period. The total amount of irradiation given was also small compared with that received by the later cases. As this study proceeded and the effects were observed, the amount of irradiation administered to the hypophysis at a single time and the cumulative total were increased, while the time required for the entire course of irradiation was shortened. This is shown in Chart 6. Thus, the first patient received 14,000 rad over a 63-day interval, while some of the later patients received as much as 30,000 rad in six sessions within a 2-week period.

Several patients complained of immediate post-irradiation head pain. This could be ascribed to manipulation of the neck during rotation or to pressure from the head mask. Neither during nor after irradiation did patients experience auditory or visual auras. One patient has recently developed syncopy preceded by an olfactory aura. No indications of increased intracranial pressure, as manifested by papilledema, hyperthermia, vomiting, or vasomotor changes, were noted. No electrolyte disturbances were detected following irradiation sessions.

A few weeks following completion of irradiation, five patients, those receiving the heaviest levels of irradiation, developed severe head pains lasting for a few days. The pains were usually said to be throbbing, sharp, deep within the skull, and relieved by aspirin. In all cases they soon disappeared completely. There was a striking resemblance to the headaches described in acromegaly and other pituitary disorders.

CHANGES IN PITUITARY FUNCTION

The most valuable criteria for assessing the changes in pituitary function following pituitary irradiation have been uptake of radio-iodine by the thyroid gland and 24-hour urinary pituitary gonadotropin excretion.

Radio-iodine uptake.—Chart 7 shows the changes in radio-iodine uptake following pituitary irradiation. Of eighteen patients for whom sufficient data are available there was marked depression of iodine uptake in eleven, in some instances reaching values as low as 5 per cent, which is in the range observed following hypophysectomy (28).

In six patients there was no significant change, although in four of these six it was initially low. In one patient there was a slight rise.

Gonadotropin excretion.—Chart 8 shows the changes in 24-hour urinary gonadotropin excretion following pituitary irradiation with reference to dose and time. In eight of sixteen patients for
whom complete data are available, there was a marked drop in gonadotropin excretion. This was usually apparent by the time the course of irradiation was completed, falling to zero or near zero in from 8 to 12 weeks following irradiation. In six patients there was no change in gonadotropin excretion, but in these the excretion was initially at the lowest concentration detectable (5 mouse units). Only one patient showed a rise in excretion.

Biochemical Changes after Irradiation

Protein-bound iodine.—The protein-bound iodine showed no consistent change following irradiation. In a few instances it rose to very high values, despite a drop in the $^{131}$I uptake. This unusual finding is under study.

Serum alkaline-acid phosphatases.—In the absence of osseous metastases and primary liver disease the elevation of serum alkaline phosphatase strongly suggests metastatic liver involvement (36). Conversely, in the absence of primary liver disease and metastatic liver involvement, elevation of serum alkaline phosphatase suggests an increase in regenerative activity in the bones at the sites of metastatic deposits (34).

Chart 9 shows the changes in serum alkaline phosphatase in patients with osseous metastases

![Chart 9](chart9.png)

Chart 9.—Changes in serum alkaline phosphatase following pituitary irradiation.

In three patients gonadotropin excretion rose during the course of irradiation, later dropping to a level below normal. The elevation was not greater than could be accounted for by the inexactness of the bioassay.

Comparison of Charts 7 and 8 shows that the fall in gonadotropin excretion occurs somewhat sooner than the fall in $^{131}$I uptake. This is, of course, not surprising, since a decrease in gonadotropin production is a direct effect of pituitary damage, whereas depression of $^{131}$I uptake is a secondary effect.

![Chart 10](chart10.png)

Chart 10.—Changes in serum acid phosphatase following pituitary irradiation.

Urinary calcium excretion.—On unregulated diets there was a significant decrease in urinary calcium excretion in two patients out of twenty. Both had osseous metastases. Those who did not have metastases to bone had normal levels of urinary calcium excretion both before and after irradiation. Values for urinary calcium excretion are summarized in Chart 11.
Serum calcium.—The serum calcium was elevated in only three patients, all of whom sustained pathological fractures; and here simultaneous hypercalcuria was observed.

Urinary corticosteroid excretion.—Charts 12 and 13 show the changes in 24-hour urinary 17-hydroxy- and 17-ketosteroid excretion. Sixteen patients in these groups were without adrenals and required replacement therapy, generally constant in amount. As noted below, all the other patients were given adrenal corticoid replacement therapy as needed following irradiation. In the patients with intact adrenals (some with intact ovaries) the fraction of total-body weight contributed by water. Chart 14 shows the changes.

Hematological changes.—Nine months after irradiation two patients without demonstrable osseous metastases or occult blood loss showed moderately diminished red-cell counts, hemoglobins, and total red-cell volumes, but normal plasma volumes. Whether this is related to a pituitary erythropoietic factor deficit is now under investigation (52). Studies on the rate of red-cell production and duration of red-cell life were carried out on several patients with the use of Fe59 and glycine-C14, but the findings seem to be related to the presence of neoplasm and not to pituitary irradiation (5, 10).

Roentgenological Changes

Serial skeletal and chest surveys have been made regularly in all patients. In five, three of whom were adrenalectomized and oophorecto-
mized, and one oophorectomized only, there was unmistakable evidence that some of the osseous metastases were calcifying; and in two others the osseous metastases remained stationary for several months. In one patient, with intact ovaries and adrenals, recurrent pleural effusion, with demonstrable tumor cells, resolved after irradiation and has not recurred at this writing (19 months after proton irradiation). In three others, pulmonary metastases remained stationary for as long as 1 year after irradiation; one of these had intact ovaries and adrenals.

CLINICAL CHANGES

Three patients developed diabetes insipidus, which was managed satisfactorily by vasopressin tannate in oil, then by posterior pituitary principle nasal insufflation. With respect to the criteria for panhypopituitarism, as laid down by Sheehan and Summers (46), our patients have not shown complete loss of pubic or axillary hair, absence of normal skin pigmentation, thinning of the eyebrows, absence of sweating, or loss of normal oiliness of the axillae. Several patients became lethargic and weak, despite what was considered to be adequate replacement therapy; and it was not known whether this was ascribable to the progression of their disease or to pituitary suppression. The initial breast lesion in one patient over a period of several months changed markedly in consistency and size so as to be no longer palpable. The affected portion of the breast became freely movable from the underlying tissue. Biopsy, however, still disclosed the presence of tumor cells.

One patient with abdominal carcinomatosis had required, prior to irradiation, frequent paracenteses; during a surgical attempt at adrenalectomy and oophorectomy, the intra-abdominal metastases were found to be so extensive as to preclude this procedure, and she was therefore selected as a candidate for pituitary irradiation. At the time of beginning pituitary irradiation paracentesis of 3,500 cc. of fluid was done, and 7 mc. of colloidal chromic radiophosphate was instilled into the peritoneal cavity. The patient did not require paracentesis in the year which elapsed after irradiation until her death. Until the final 2 months of her life her general physical improvement was marked, with weight increase and disappearance of nausea, vomiting, and anorexia. There was no apparent progression of her disease before these last 2 months.

With radiation levels of 26,000 rad and higher, third, fourth, and sixth cranial nerve palsies have been observed. These have remained stationary or improved and have not been a serious problem to the patients. One patient receiving 30,000 rad has developed uncinate fits, which have been controlled satisfactorily by anticonvulsant therapy. Patients who received 22,000 rad or more developed linear epilated areas over both temporal regions, usually within a month after exposure. The hair regrew in the ensuing months; and no erythema, ulceration, or bronzing of the skin has been noted.

SUBJECTIVE CHANGES

Fourteen of the nineteen patients with osseous metastases had skeletal pain. Following pituitary irradiation, seven of these patients had some diminution of their pain as indicated by increased mobility and decrease or discontinuance of narcotics. One patient was for a time able to walk without a cane. Another, who had been bedridden for some 6 months, was able for a time to move about in a walker. Five patients showed no response. The alleviation of pain from bony metastases could not be correlated with objective evidence of improvement.

REPLACEMENT THERAPY

An uninterrupted maintenance schedule of deoxycorticosterone acetate and cortisone was continued, of course, for adrenalectomized patients, although a few were changed from cortisone to prednisone after the introduction of the latter. Upon the clinical appearance of the need for adrenal replacement among the patients with intact adrenals prednisone, or, later, prednisolone, 10 mg. daily, was started, with satisfactory response. Four patients appeared to be mildly myxedematous, and they, together with several others, were given thyroid extract, 1–2 grains daily. Several patients who, prior to pituitary irradiation, had been started on testosterone by their physicians, continued receiving it. In these patients testosterone had been unsuccessful in preventing the progression of metastases, and it was continued only for its possible benefit in promoting protein anabolism. Pitressin was given to three patients as previously mentioned.

SURVIVING PATIENTS

There are two patients surviving from the series of 26 at the time of writing. Both are 20 months postirradiation, and one is still in an excellent state of remission.

Survival statistics on all patients in the series are shown in Table 2. The table also indicates the arrests and remissions obtained following pituitary irradiation and their duration. In assessing the results of pituitary irradiation we have used the assumption of Woodard et al. that cancer of the
<table>
<thead>
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<th>Age of patient</th>
<th>Metastases</th>
<th>Status at entry</th>
<th>Previous therapy*</th>
<th>Total dose (rads)</th>
<th>Irradiation time interval (days)</th>
<th>Post-irradiation survival (months)</th>
<th>Estimated duration of arrest or remission (months)</th>
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<td>8</td>
<td>3</td>
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<tr>
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<td>Nearly terminal</td>
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<td>0</td>
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<td>X,H,A,O</td>
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<td>21</td>
<td>8</td>
<td>6</td>
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<tr>
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<td>30,000</td>
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<td>5</td>
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Note: This patient also had a uterine carcinoma

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<th>Age of patient</th>
<th>Metastases</th>
<th>Status at entry</th>
<th>Previous therapy*</th>
<th>Total dose (rads)</th>
<th>Irradiation time interval (days)</th>
<th>Post-irradiation survival (months)</th>
<th>Estimated duration of arrest or remission (months)</th>
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<td>12</td>
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</tbody>
</table>

* M = mastectomy; A = adrenalectomy; O = oophorectomy; X = x-ray therapy; H = estrogen and/or testosterone.
† (L) = Living.
necropsy findings of the effects of pituitary irrad-
come to necropsy. General autopsy findings will
breast, if untreated, will show measurable progres-
sion in 4–5 months (54). Subjective improvement
is not considered sufficient as a criterion of benefit.
Twenty-two of the 24 deceased patients have
come to necropsy. General autopsy findings will
not be discussed here. Of primary interest are the
necropsy findings of the effects of pituitary irradi-
ation upon the pituitary gland and the target
organs.

There was a marked difference in the pituitaries
of those patients who received low, medium, and
high levels of irradiation. Low levels of irradiation
were considered as ranging from 13,000 through
19,000 rad; medium, from 20,000 through 26,000
rad; and high, above 26,000 rad. Pituitary damage
resulting from proton irradiation was discernible on
cut section in those patients receiving the medium
and high levels of irradiation who survived for suf-
cient time for necrosis to be grossly apparent.
Generally, this time was approximately 5 months.
Microscopic evidence of histological damage was
apparent in all patients who received over 20,000
rad, regardless of the time interval between irradi-
ation and death. Among those receiving less than
20,000 rad, necrosis in the histological sections was
encountered infrequently; and the moderate de-
gree of fibrosis, shrinkage of cells from the base-
ment membrane, and increased vascularity were
not considered confirmatory of irradiation dam-
age. Figures 5 and 6 are photomicrographs of his-
tological sections of pituitaries from patients re-
ceiving higher levels of pituitary irradiation.

An example of the destructive effect of proton
irradiation upon the pituitary gland is shown in
Figure 7, which illustrates the sella turcica and
pituitary of a patient who received 30,000 rad in
a period of 14 days and survived 14 months.6
There appeared to be nothing whatever in the
sella. Dissection produced only a lining 1-ml. thick
in the sella. This pituitary remnant, together with
its investing membranes, is shown in Figure 8.6
The microscopic section is shown in Figure 9. Fig-
ure 10 shows the brain, shiny and glistening, dem-
strating no evidence of the terrific bombard-
ment which destroyed the pituitary.6

Thyroid.—Histologically, the thyroid glands in
all patients showed involution at all levels of ir-
radiation irrespective of the interval between ir-
radiation and death, with the exception of two
cases, one in which the patient died before irradia-
tion could be completed and the other in which the
patient survived only 12 days. Microscopic exami-
nation of the thyroid further showed that the
acini were distended with old colloid material and
that the epithelium was low-cuboidal in type.

Photomicrographs of thyroid sections from the
patients whose pituitaries appear in Figures 5 and
6 are shown in Figures 11 and 12. Neither of these
patients received thyroid extract.

Adrenals.—Microscopic examination of the
adrenal glands could lead to no definite conclu-
sions, because supportive steroid therapy was
given. Evidence of adrenal atrophy in four of the
seven patients coming to necropsy with intact
adrenals could be ascribed to large doses of corti-
sone given in the terminal stages. Three of the seven
showed tumor infiltration.

Ovaries.—Only five of the cases coming to
autopsy had intact ovaries. The atrophy noted in
four of these could not be considered as exclusiv-
ely of pituitary origin, since one of the patients had
had x-ray castration and three had had testoster-
one terminally. The ovaries of the fourth and
fifth patients were heavily invaded with tumor.

Brain and cranial nerves.—No gross evidence of
injury has been detected in the brain or cranial
nerves. Preparation of these specimens is kindly
being done by Dr. Nathan Malamud.7 The re-

SUMMARY

There has been described a multiple-plane, ro-
tational technic for irradiation of the human pitui-

ary gland with the 340-Mev proton beam from
the 184-inch synchrocyclotron. Peak doses of
14,000–30,000 rad at the center of the pituitary
have been administered to 26 patients with meta-
static breast cancer, and decreased pituitary func-
tion and gross and microscopic damage of the
pituitary gland have been demonstrated. The most
common laboratory findings were depression of
I131 uptake by the thyroid and decrease of 24-hour
urinary gonadotropins. There was clinical evidence
of improvement in a few of the patients treated.
Four patients with acute lymphatic leukemia, em-

bryonal dysgerminoma of the testis, chronic
lymphatic leukemia and diabetes mellitus, and
malignant exophthalmos have also been irradiated,
but they are not reported in detail at this time.

ACKNOWLEDGMENTS

The authors are indebted to Victor Burns, Graeme Welch,
Betty Ward, R. W. Pratt, Jack Allen, and Ann Henderson for
assistance at the cyclotron; to Shirley Belknap and Barbara
Boysen for laboratory assistance; to Joseph Garcia, Charles
Riggs, Julian Henry, and O. K. Anderson for preliminary

7 Associate Clinical Professor of Neuropathology, Depart-
ment of Pathology, University of California School of Medi-
cine, San Francisco.

Photomicrographs of thyroid sections from the
patients whose pituitaries appear in Figures 5 and
6 are shown in Figures 11 and 12. Neither of these
patients received thyroid extract.
studies of irradiation involving animals; to Philip Bean for engineering design work on the equipment; and to Aram Thomas for his contribution to the mathematical calculations. The use of the cyclotron was made possible by the kind cooperation of Professors Robert Thornton, Marvin Martin, Elmer Kelly, James Vale, the cyclotron crew, the accelerator technicians, and the electronics group. Finally, the study would have been impossible without the tireless efforts of the physicians who referred patients for irradiation and gave splendid cooperation following the patients and securing pathological examinations.

REFERENCES


FIG. 7.—A photograph of the sella turcica from a patient who received 30,000 rad and survived 14 months.

FIG. 8.—A photograph of the pituitary remnant dissected from the sella turcica shown in Figure 7.
Fig. 9.—A photomicrograph of a section of the pituitary shown in Figs. 7 and 8 (X84).

Fig. 10.—A photograph of the brain from the case in Figures 7-9.

Fig. 11.—A photomicrograph of the thyroid from the patient whose pituitary is shown in Figure 5 (X400).

Fig. 12.—A photomicrograph of the thyroid from the patient whose pituitary is shown in Figure 6 (X400).
Pituitary Irradiation with High-Energy Proton Beams A Preliminary Report


Cancer Res 1958;18:121-134.

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