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BIOLOGICAL STUDIES OF RADIATION EFFECTS

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RADIATION THERAPY AND RADIATION BIOLOGY

CLINICAL AND METABOLIC STUDIES IN PATIENTS AFTER ALPHA-PARTICLE IRRADIATION TO THE PITUITARY

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Pituitary irradiation of patients with advanced metastatic mammary carcinoma, pituitary tumors, and endocrine-controlled diseases has continued. By April 1959 105 patients have received pituitary irradiation, and 27 of these have been irradiated during the past six months The principal modifications that have been made in irradiation techniques during the past six months are: (a) the size of the aperture shaping the beam has been increased in size so that a larger volume of irradiation is delivered to the pituitary gland; (b) pituitary irradiation has been done on all twelve planes at each of the six irradiation sessions in an effort to distribute the irradiation equally in time and space to all planes treated and (c) the time interval over which the irradiation dosage is fractionated has been shortened to 11 days

In view of the changes made it is desirable to review the results of the clinical and metabolic studies of all patients so as to evaluate the effectiveness of pituitary irradiation at the higher dose levels

The largest group of patients irradiated were those with mammary carcinoma All of these had progressive metastatic disease and in most instances were in an advanced stage, previously having been subjected to all conventional forms of therapy and in some instances, bilateral adrenalectomies Of the total number of patients receiving pituitary irradiation with high-energy particles from the 184-inch cyclotron at the Lawrence Radiation Laboratory of the University of California, the type and distribution of cases is listed below.

	Patients Irradiated
Cancer of the breast	82
Acromegaly	7
Diabetes mellitus	8
Chronic lymphatic leukemia	1
Acute leukemia	1
Malignant exophthalmus	2
Dysgerminoma	1
Cancer of the adrenals	1

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Selection of patients for irradiation was done after careful clinical and laboratory investigation. All patients were in a progressive state of disease and were no longer considered responsive to the usual conventional forms of treatment. The patients with diabetes mellitus had progressive retinopathy and in some instances nephropathy. They were typical long-term diabetics difficult to control. The acromegalics were all symptomatic and two of them had diabetes associated with their acromegaly. The majority of these had received one or more courses of conventional 200-kv x-ray therapy.

The early schedule of irradition was based on prior experience gained from animal studies. Since the effect of high-energy particles in suppressing the function of the human pituitary gland was not known, it was necessary to investigate its effects by starting conservatively with low dosages. These were gradually increased towards an optimal level as histological studies, patient response, and sequelae indicated. On the present schedule the patients receive pituitary irradiation on three times weekly for 2 weeks. The highest total amount given has been 30,000 rad for the patients with advanced metastatic mammary carcinoma. At a dose range of 26,000 to 30,000 rad it is believed that complete radiation hypophysectomy can be obtained. The patients with diabetes mellitus received up to 24,000 rad and those with acromegaly up to 7,200. These doses were calculated to the center of the pituitary, the average hypophyseal dose integrated over the isodose surfaces being between 55% and 75% of the peak dose at the center of the gland.

Changes in pituitary function were measured before and after irradiation by determination of the urinary excretion of pituitary gonadotropins and by effects on the target end organs, namely the thyroid, adrenals, and ovaries. The iodine uptake of the thyroid gland, the protein-bound iodine, the 24-hour urinary steroid excretion, and the 24-hour urinary estrogen excretion were considered as important indicia of the effects of pituitary irradiation on the target end organs.

Laboratory and clinical evidence of decreased pituitary and target-end-organ function followed a dose-time relationship. The onset of a decline in the hormone excretion of the above endocrine organs occurred sooner with the higher amounts of irradiation. In addition, when the total amount of irradiation was fractionated over a shorter time the biological effectiveness was further enhanced, as evidenced by a still earlier decline. The degree of histological destruction on necropsy examination also showed that both the total amount of irradiation and the period over which it was given were essential in determining the biological effectiveness of the dose given.

The endocrine assessments done on these patients after high doses of irradiation indicate a pronounced decrease in pituitary and end-organ function. They are of further interest in determining the time of onset of this decrease following irradiation and the order in which definitive falls in the various measurements were noted.

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The earliest changes observed were the decrease of the pituitary gonadotropins excreted in the urine This change occurred in all patients who received the higher dosages of alpha-particle irradiation except those whose initial gonadotropin excretion was in the extremely low range. This decrease was evident in the majority of patients as early as the first week following the completion of irradiation, and seemed to be the most sensitive of all indications, as it occurred even in those patients receiving low doses of irradiation

In determining adrenocortical function, measurements of the 17-ketosteroids and--more recently--of the 20,21-ketols have been of value. The 17-ketosteroids in more than half the high-dose group have shown a marked drop by the end of the first month By the end of the second month 80% of this patient group have shown an average decrease of 40% in the urinary excretion of 17-ketosteroids.

There was no definitive fall of the iodine ^{131} uptake of the thyroid gland at the end of the first week in the same high-dose group receiving irradiation with alpha particles, but by the end of 2 months two-thirds showed an average fall of 40%. This showed a close correspondence to results obtained in the same dose range with proton particles. The protein-bound iodine showed a concomitant decrease.

Total estrogens and the estrone, estradiol, and estriol fractions were determined on all patients by the revised method of Brown (Edinborough) Serial determinations, however, are available on only a relatively small number of the patients receiving high dosages of alpha particles On all eight of these patients the total estrogens averaged a 60% fall from pre-irradiation levels within the first 3 to 4 months. An equivalent fall was found in estrone, estradiol, and estriol levels

Clinical Management

Since there was no morbidity as a result of pituitary irradiation, those patients who were ambulatory could be treated on an outpatient basis and did not require hospitalization Follow-up studies were done on all patients at intervals of 4 to 6 weeks in order to evaluate response to irradiation as manifested by a decrease in pituitary function, and to follow the clinical course of their disease.

Mammary Carcinoma

Replacement therapy did not constitute a problem with this group of patients It was commenced when the measurement of urinary steroids and iodine uptake declined to low levels. On hypophysectomizing doses of irradiation, early signs of adrenocortical insufficiency were observed as manifested by anorexia, fatigability, nausea, vomiting, and in some cases by fall in blood pressure and by low-grade fever These signs of adrenocortical insufficiency were well correlated with a fall in the levels of the 17-ketosteroids and the 20, 21-ketols At high dose levels the signs of

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adrenocortical insufficiency were almost predictable in their onset at the end of 3 to 4 weeks following irradiation. The patients in this category responded immediately to corticoid replacement therapy with disappearance of their signs of adrenocortical insufficiency. Diminished thyroid function was reflected in decreased I^{131} uptake, with a somewhat less marked fall in the level of the protein-bound iodine. The only complications following irradiation were encountered in those receiving the higher doses of irradiation. Most of these developed a mild transitory diabetes insipidus several weeks after irradiation. In those few cases with daily urine volumes in excess of 5 liters, satisfactory control was achieved with the use of pitressin tannate in oil. Many in this group also developed a transitory diplopia, and in two instances ptosis of one eyelid. These eye signs gradually disappeared over a period of several months.

Decrease in pituitary and target-end-organ function could not always be correlated with improvement in those patients with advanced metastatic mammary carcinoma. Some showed arrest or remissions, while in others the metastatic disease continued to progress despite similar evidence of depression of pituitary activity. Objective evidence of arrest or remissions was obtained in both osseous and soft-tissue metastases except in those with marked liver or brain invasion. Twenty-nine patients of the group of 82 with metastatic carcinoma irradiatied with high-energy particles are now living. Ten of these are living for more than 1 year following irradiation, the longest now being 4 years postirradiation. Eight of these are in an excellent state of remission. The largest and most beneficial response was obtained in the group of patients receiving the highest amounts of irradiation, which ranged from 26,000 to 30,000 rad.

Acromegaly

Seven patients with acromegaly received irradiation to the pituitary with alpha particles in dosages ranging from 4,000 to 7,200 rad. Those receiving the lower amounts of irradiation were those who had previously received one or more courses of conventional 200-kv x-ray. Two of the group who had, associated with their disease, a diabetes necessitating management with insulin no longer required insulin following irradiation. In all these patients subjective symptioms of headache, loss of potency, and ease of fatgability were present and were difficult to evalutate. All but one patient claimed marked relief following irradiation. There was a fall in serum phosphorus in all patients receiving 7,200 rad.

Diabetes Mellitus

Eight patients with diabetes mellitus received alpha-particle irradiation in the dose range 18,000 to 24,000 rad. These patients had marked diabetic retinopathy and in some instances nephropathy. While downward adjustments in insulin dosage were necessitated in some patients following alpha-particle irradiation in the 18—22,000-rad dose range, no definite pattern of decreased insulin requirements could be ascertained. Marked change, however, occurred in those patients receiving the higher dosages. One patient who received the higher dose of 24,000 rad over an 18-day period, became hypersensitative to insulin and by the end of the fifth week postirradiati no longer required any insulin. Two patients who received the same high dose over a shorter period of time had a rapid onset of adrenocortical

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insufficiency, which complicated the clinical management of their diabetes. With the institution of replacement therapy their diabetes was brought under control with less insulin. Since these latter patients were irradiated within the past few months it is still too early to determine whether their retinopathy and nephropathy will show beneficial responses.

Post-mortem examination have been made of 53 of the 60 deceased patients. Varying degrees of destruction of the pituitary gland were seen, depending on the dose of irradiation, the time over which it was given, and the length of survival. On dosages of more than 20,000 rad cellular necrosis was seen. With still higher doses damage to the pituitary without evidence of injury to the surrounding structures and cranial nerves became more marked, and necrosis of approximately 90% of the cellular elements of the pituitary was seen as early as the fifth day following the completion of irradiation. On all patients, even those receiving lesser amounts of irradiation, the degree of destruction was progressive with the length of survival so that on some of those surviving for many months necrosis of 95 to 98% of the entire gland was observed. In no case was there histological evidence of pituitary regeneration.

Direct injury to the cells of the pituitary as well as vascular damage within the gland was observed. No detectable injury, either grossly or histologically, was found in the brain or surrounding cranial nerve.

SUMMARY

High-energy protons and alpha particles from the 184-inch cyclotron at the Lawrence Radiation Laboratory of the University of California have been used for pituitary irradiation. One hundred and three patients have been irradiated. Most of these patients had metastatic mammary carcinoma, and promising effects have been shown on patients with this and various pituitary and hormonally dependent diseases. Peak doses of 14,000 to 30,000 rad have been delivered to the center of the pituitary. At the higher hypophysectomizing dose level, decreased pituitary function and marked gross and microscopic damage to the pituitary have been demonstrated. Decrease in pituitary function and the consequent effects on the target end organs were manifested in depression of the thyroid iodine ^{131} uptake and decrease in 24-hour pituitary gonadotropins, urinary steroids, and estrogen excretion. These correlated well with clinical evidence of hypopituitarism.

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