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BIOLOGICAL AND MEDICAL STUDIES WITH HIGH ENERGY PARTICLE ACCELERATORS

by

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In contrast with the widespread use of x-rays, gamma rays and electrons, accelerated positive ions have been applied to biological studies in relatively few laboratories. Working at the Radiation Laboratory of the University of California[5], the authors found several areas of radiobiological interest relating to heavy ions, some of which are described below.

Protons, deuterons and alpha particles of some hundred million volts of energy have been used for producing highly localized radio lesions in accurately predetermined positions in the body. Because of the reduced scattering and deep penetration of these particles, they can be made to travel in narrow, almost parallel bundles or even brought to focus.

The linear energy transfer of accelerated heavy ions increases as they slow down in matter, until the ionization comes to a broad maximum at the "Bragg ionization peak" just before the end of the range of the particles. This phenomenon may be used to deliver high doses at almost any desired predetermined depth in tissue, with intervening and deeper layers of tissue hardly affected at all.

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The linear energy transfer of heavy ions increases as the square of their charge, so that it is now possible to investigate the quality and quantity of radiation effects in domains of ionization which previously were not easily accessible to the experimental approach. Since primary cosmic radiation in interplanetary space has many highly ionizing primaries, and since nuclear transmutations produced in the living body also produce heavy recoils, there is potential practical interest in this field as well.

Finally, there are several machines in existence now which produce brief pulses of unusually intense heavy ions, followed by radiationless intervals. These machines may in the future give opportunity for studies of radiation-produced intermediates in the millisecond, and perhaps later microsecond, intervals and for explorations of dose rate effects leading to better understanding of the kinetics involved.

Below is a brief description of some selected areas of current interest.

STUDIES WITH VERY HEAVILY IONIZING PARTICLES

Fluke, Brustad, Birge and Tobias have for the past few years been engaged in studying small biological systems and macromolecules with the beams of heavy ions from the 60-inch cyclotron and the Berkeley Heavy Ion Linear Accelerator (1). The available radiations include protons, deuterons, alpha particles, and carbon, nitrogen, oxygen, and neon ions, all with energies corresponding to ten million electron volts per nucleon. Heavy ions of this energy pass through material as nuclei stripped of electrons. As a consequence of the high nuclear charge, these particles are characterized by very high values of linear energy transfer (LET), up to 10^{10} ev g^{-1} cm^2 or five times the highest ionization of alpha particles. Their range in biological material, however, is only a few hundred microns.

Intense monoenergetic beams of these particles permit studies which bear on the consequences of fission fragments and other recoil nuclei produced within an organism, and on the hazards of heavy primary cosmic-ray particles which will be encountered in space travel. The radiations are also of theoretical interest in testing the validity of various theories of the biological action of ionizing radiation. The target theory of Dessauer (2), Lea (3) and Pollard (4) emphasizes the direct action of individual ions or ion clusters. The intermediate action theory of Zirkle and Tobias (5) considers the migration of exitation energy and the formation of chemical intermediates. The role of multiple ion pairs placed close together in tracks may be clarified by the work with heavy ions. The results of heavy ion irradiation indicate the importance of delta rays and offer hope of further elucidation of mechanisms of delta ray effect.

A schematic diagram of the apparatus used for the heavy ion irradiations is shown in Figure 1. Here the material is irradiated in the dry state in vacuum, and the dose is measured by means of a Faraday chamber. For irradiations in air the beam is allowed to pass through the thin end window, and the dose is measured by means of an ionization chamber.

The materials studied thus far include vegetative yeast cells of Saccharomyces cerevisiae by Birge and Sayeg (6) (7), dry spores of B. subtilis, dry T-1 bacteriophage, and the enzymes lysozyme trypsin and desoxyribonuclease by Fluke and Brustad (8) (9). All these materials show an exponential dose-effect relationship. Consequently it is possible to express the results of irradiation as cross section values, or the apparent area that the various molecules or organisms present to the bombarding particles. This description is convenient for heavy ions, where the exposure is often measured as the density of bombarding particles over an area rather than as the energy absorbed per unit mass. In this representation a constant relative biological effectiveness (RBE) corresponds to a cross section that is proportional to linear energy transfer (LET). On the other hand, a cross section that approaches a constant value for increasing LET corresponds to a rapidly falling RBE.

The data are summarized in Figure 2, where the measured inactivation cross section is plotted as a function of LET for several different systems. In earlier work the haploid (5) yeast cells and B. subtilis spores (10) had both shown an increasing RBE at the highest LET values attainable with alpha particles. Both these materials are now shown to have a decreasing RBE at still higher LET. Dry T-1 bacteriophage shows a relatively flat RBE for radiations of intermediate LET, and a decreasing RBE at very high LET. Preliminary calculations of the effect of delta rays indicate that for high LET the corrected cross section is not larger than the virus particle silhouette and may be smaller.

While the heavy particle experiments on phage T-1 and bacterial spores give cross sections in fairly good agreement with the models previously obtained for the mechanism of inactivation, the lysozyme cross sections with oxygen nuclei are considerably (about 10 times) higher than one would expect from simple hit theory on the basis of the known molecular weight. It is well known that when the measured cross sections are corrected for delta rays the inactivation cross sections will be reduced. If a large part of the effect on lysozyme is due to delta rays, experiments of this type might give us more definite knowledge about the delta ray energy distribution than we have now. The possibility remains that further refinements beyond accounting for delta rays will have to be made in the theory of action of radiations before the cross section data of Figure 2 can be fully explained.

The techniques also make it possible to irradiate the surface of animal tissues and to irradiate thin layers of wet biochemical systems.

BIOLOGICAL STUDIES WITH 340 MEV PROTONS, 190 MEV DEUTERONS AND ~~300~~ 380 MEV ALPHA PARTICLES

Since our report on the initial development of techniques for biological uses of high energy deuterons (11), we have carried out a number of studies. Most of these take advantage of the fact that the proton, deuteron or helium particles may be collimated to form a small penetrating pencil of rays which may be used to produce localized radiation damage in various deep-lying body structures.

Interest in these investigations centers about the physiological processes which are partially or fully controlled by activity of the pituitary gland and by hypothalamic control centers. For many years physiological investigations tended to show that homeostasis, the balance and control of the level of a great many physiological processes, lies in the hypothalamus, but it has not been fully resolved whether or not each homeostatic variable, e.g., temperature, water turnover, etc., is controlled independently, and the extent to which the various centers are involved in the so-called "stress reaction". The advantages of ion beams in this study lie in the ability to produce lesions without operative procedures and in investigating the possibility that neurons and nerve fibers might be affected differentially. The well-known latency of radiation lesions and the time required for developing them appear to be a disadvantage.

Several authors have pointed out the connections between the hypothalamus and pituitary (see for example ref. 14) and the possibility of a feedback relationship in homeostatic control. In our experiments we postulate the existence of a feedback arrangement (one general form of which is shown on Figure 3), which may mediate the response of the body to various stimulating or deleterious effects. According to this model, the pituitary gland acts under control of neural and humoral agents from the hypothalamus. This latter is in turn under the influence of information received from the body tissues and endocrine target organs and is, in addition, in connection with the higher brain centers as well. Thus any imbalance in any part of the system may react on the other parts and bring about corrective or divergent changes in performance.

PITUITARY IRRADIATION

A reasonable body of data has been accumulated on the effects of deuterons on rat pituitary by Tobias, Van Dyke, Simpson, and Koneff over the past five years (13) (14). In this work a small beam of particles, triangular in cross section, 1 mm height 2 mm apex, was utilized, and groups of 22 day old male Long Evans rats were exposed to single doses, ranging from 945 rad to 40,000 rad. Many of the animals were studied for the rest of their life span to obtain information on the nature and duration of the effects on the efficiency of production of various pituitary hormones. The measurement of skeletal development and body mass indicated early that, in order to achieve a physiological state comparable to surgical hypophysectomy, massive doses (above 10,000 rad) were required and that in general, hypopituitarism appeared earlier and earlier as the dose increased. It is of interest to note, however, that when sufficient time was allowed, even the lowest dose of highly localized rays had profound effects on the animals. Even at low dose levels clear-cut differences were apparent in the ability of the pituitary to produce various hormones as evidenced by the size of the target organs, none of which had received appreciable doses of radiation.

The effect on body weight and tail length of some of the animals, as a function of dose, is shown in Figure 4. Regression of thyroids, adrenals, and gonads is indicated in Figure 5. It is apparent that dose-effect relationship for secondary suppression is different for each organ. Reduction of weight gain or tail growth to one-half normal takes about 6,000 rad, while a similar degree of effect on adrenals and thyroids is reached at 2000-3000 rad. The gonads take somewhat more, 3300 rad, for the same effect. One curious effect at 945 rad was the gain in weight of the animals in the post-irradiation period, during which this lowest dose group exhibited characteristic changes of obesity. We do not know at present whether this finding is entirely due to malfunction of the pituitary gland. Or, could it originate in surrounding injured structures? The well-known "obesity center" of the hypothalamus is far enough away to have received only a few roentgens.

Hypophyseal function is known to be related in some way to tumor formation. It was of interest, when high doses of pituitary irradiation were given, to find that at 24 months post irradiation the over-all incidence of tumors of the body as found at autopsy was about one-half the incidence in nonirradiated controls. On the other hand, at the lowest exposures (945 rad) the incidence of pituitary tumors showed a striking increase. Fifteen months post irradiation 100% of these animals had pituitary adenomas, with an average of 3.5 tumors per gland. The pituitary tumor incidence is shown on Figure 6. Among 70 animals that received over 3000 rad, not one had a pituitary tumor! The authors believe that this finding adds to the evidence pointing to endocrine factors in carcinogenesis. Apparently radiation carcinogenesis occurs following sublethal injury to the cells of a given tissue and is accelerated by feedback stimulation (Figure 3). If so, tumor growth may be initiated in response to need for more pituitary hormones. Furth (15) found that head irradiation induced pituitary tumor formation in mice. Pituitary tumors following radiation or chemical thyroidectomy are well known.

The above explanation for tumor induction fits in well with the findings of Bond, et al. (16) who found that mammary tumors in rats were induced by whole body irradiation and that the onset of such tumors is dependent on the function of the intact ovaries.

HYPOTHALAMIC RADIATION STUDIES

Since it seemed that chronic physiologic changes might be induced by pituitary irradiation, it became of interest to study proton and deuteron effects on brain and hypothalamus, in order to determine the radiosensitivity of these tissues and to find out if high energy particles can be useful tools in a study of feedback mechanisms of homeostatic control. During the past several years, many groups of rats have been exposed to deuteron beams ranging in diameter from 1.6 mm^2 to areas of 20 mm^2. Many of these suffered lethal effects. High doses resulted in shorter survival time than low doses. However, at constant dose, survival time decreased with increased irradiated volume. There is a correlation between integral dose and survival time, shown in Figure 7.

In an attempt to ascertain the effects of deuterons on the entire hypothalamus, an aperture was fabricated which would cover a major portion of the region. Parts of the mesencephalon, posterior to the hypothalamus, were also included; the shape of the aperture was designed to exclude the pituitary. Survival as a function of dose is shown in Figure 8. After receiving 9500 and 11,000 rad, the animals failed to gain weight and 10-15 days following irradiation exhibited marked rage. The animals were extremely difficult to handle, biting everything within reach. The rage continued until 2-3 days prior to death, at which time the animals assumed a "hunchbacked" motionless position and ceased to eat or drink. At autopsy all animals in these groups were consistently found to have gross petechial hemorrhages at the site of irradiation in the hypothalamus and anterior mesencephalon.

Next, two groups of 20 rats each were irradiated with a deuteron beam of 3.2 mm diameter. In one group the beam was directed to the anterior hypothalamus, in the other to the posterior hypothalamus. Each received the same dose -- 13,500 rad. These animals also exhibited rage and the characteristic hypothalamic radiation syndrome described above. In addition, convulsions, enophthalamus, ptosis, blindness, and bloody exudate from eyes and nose were exhibited. On autopsy many were found to have gastric ulcers and hemorrhages in the stomach or intestinal tract. Some of these findings are shown in Table I.

TABLE I

ACUTE FINDINGS IN HYPOTHALAMIC DEUTERON IRRADIATION

Location of lesion	Size of beam aperture, mm	Dose, Rad	Number of animals	Survival time days	No. with gastric ulcers	No. with hemorrhages in stomach or intestine	No. with hemorrhagic lesions at irradiated site	No. with bloody exudate from eyes or nose	Convulsions	Rage	Ptosis	Enophthalamus	Blindness
Anterior Dorsal Hypothalamus	3.2	13,500	20	18±5	5	7	8	3	5	6	0	2	1
Posterior Dorsal Hypothalamus	3.2	13,500	20	18±5	7	3	10	1	4	7	7	7	2

Following these initial experiments, the sagittal area of the hypothalamus of the rat was divided into 6 regions. By passing deuteron beams of varying cross sections through these, we hoped to reproduce various physiological effects attributed to surgically produced lesions as illustrated in Figure 9. We now wish to report briefly only on area IV, the median eminence, and area III in the posterior dorsal hypothalamus.

The animals which were irradiated in area IV, the region of the median eminence, frequently developed lesions which matched in appearance the contour of the irradiated area. In the center of the region, complete necrosis and liquefaction had occurred, and at the edge one could often observe microscopically a sharp region of demarcation between reasonably normal-appearing tissue and complete necrosis. An example is shown in Figure 10. A detailed time-dose study of the histological changes is in progress. Physiological changes in the animals are frequently observed even before evidence of complete necrosis. With time, the lesions may spread to other regions in the brain along channels of vascular supply or nerve trunk degeneration. The most immediate physiological changes observed in these animals were polyuria and polydipsia, increased food intake with transient hyperphagia, glycosuria, regression of the testes and thyroid metabolism abnormality. The urine output increased in some animals to twelve times normal in a period of fifty days. Regression of the testes occurred progressively with time, and in producing this result the hypothalamus seemed more sensitive than the directly irradiated pituitary.

Blanquet and Tobias (17) found that this group of animals, injured at the median eminence, exhibited a curious defect in thyroid metabolism: the iodine^{131} uptake of the thyroid remained normal, but the gland seemed to fail almost completely in its production of thyroxine, although labeled mono- and diiodotyrosine appeared in normal amounts. In this respect, the median eminence irradiated animals seemed to differ from hypophysectomized ones, which showed low amounts of each amino acid. The results of analysis are shown in Figure 11, where ion exchange analysis of the different iodinated compounds was used to obtain a quantitative measure of each present in the thyroid hydrolysate. This effect, which has been produced repeatedly, may eventually lead to the identification of more than one pituitary thyrotropic hormone and to the better understanding of the mechanism of hyperphagia.

Irradiation of area III, in the posterior hypothalamus, led to a retarded development of bone growth as well as to decreased rate of body weight gain, as shown in Figure 12. At the same time, adrenals, thyroid, and gonads were developing at nearly normal rate. The first explanation might be that the hypothalamic "appetite center" is disturbed. However, the "appetite center" was not in the radiation field. Thus there is a possibility that the lesion had to do with control of growth and production of growth hormone by the pituitary gland. Thorell, working with us, studied the pathology of the pituitary gland and found that the pituitary acidophilic cells of the irradiated group were almost entirely depleted of their granules and these cells would not show the staining reaction so characteristic of acidophiles. Thus it appears as though irradiation of the posterior hypothalamus would lead to impaired bone growth and less weight gain. More work is being done on this problem at the present. It is apparent that irradiation of several hypothalamic areas can influence growth rate, and some of these areas are so close to the pituitary itself that part of the effect might be caused by direct pituitary radiation.

INVESTIGATIVE THERAPY OF MAMMARY CANCER BY PITUITARY IRRADIATION

In 1954 we treated some dogs with metastatic mammary adenocarcinoma, giving them single doses of pituitary radiation. Of 15 animals so treated, objective remission was obtained in 5, as measured by the diameter of tumor. One of these animals, in which the disease seemed to be arrested, lived for three years, and at death none of her metastases appeared active.

PROTON AND HELIUM ION HYPOPHYSECTOMY IN MAMMARY CANCER

Human application of high energy protons was initiated in 1954 by irradiating the hypophyses of 26 patients who had advanced metastatic mammary carcinoma. The method was described at the Geneva conference in 1955 (18), and a more detailed report has recently been published (19).

Technique. The internal beam of the 184-inch cyclotron is at present deflected by the magnetic regeneration method, magnetically sorted and focused into an approximately parallel stream of particles, arriving at the medical exposure room about 50 feet from the cyclotron. The beam, which was precollimated to about 3/4 inch diameter, is then shaped by passing through a brass aperture which has been individually designed for each patient. The electrical center of the beam is accurately kept on a hypothetical axis running parallel to an optical bench. Alignment of the object to be irradiated with the beam is accomplished by the use of two diagnostic x-ray machines, mounted at right angles to each other. As a result, any part of an animal or human body may be exposed to any shaped area of the parallel beam. While the beam is on, the body may be rotated around the center of the irradiated area. A photograph of the apparatus is shown in Figure 13. The procedure has been greatly speeded up by use of x-ray television image amplifiers for alignment and for checking alignment during the rotation of the patients. In 1957 the Berkeley 184-inch cyclotron was rebuilt, and it now operates with 900 Mev He^4 ions as well as with 450 Mev deuterons and 700 Mev protons. The range of the helium ions in tissue is about 22 g/cm^2, while the deuterons penetrate about twice as far and the protons stop at 190 g/cm^2. The mean linear energy transfer of helium ions is about 15 Mev cm^2 g^{-1}, or quite similar to linear energy transfer of secondary electrons from a 250 kev x-ray machine.

In the first series, 26 patients with metastatic breast carcinoma received pituitary proton irradiation. These patients were carefully selected with respect to the presence of progressive metastatic lesions. In all these cases, generally accepted forms of surgical and radiological treatment had been administered previously and the responses of the patients to palliative procedures such as oophorectomy, adrenalectomy, and endocrine therapy were evaluated. Twenty-three of the patients had previous mastectomy, 19 oophorectomy, and 16 bilateral adrenalectomy. Two-thirds of all patients were in a rapidly failing stage of their disease at the onset of pituitary irradiation and could be classed as terminal.

Proton irradiation was given in fractionated doses three times a week. Since protons have never previously been used to irradiate a human being and we had no direct knowledge of the pituitary radiosensitivity, the initial patients were treated with conservatively low doses over a protracted time period. In order to obtain evidence of the degree of pituitary damage obtained, the patients were divided into three groups, receiving 13,000 to 20,000 rad, 20,000 to 26,000 rad, and 30,000 rad, respectively, "nominal" dose. These "nominal" doses were the amounts delivered to the geometrical center of head rotation, that is, the center of the pituitary gland. The beam, shaped to fit the sella turcica in each individual, entered the head laterally; body positioning and head rotation achieved a very rapid fall-off of the dose outside of the gland. A typical three dimensional isodose distribution plot as measured by Welch is given in Figure 14. The greater part of the optic chiasm, the median hypothalamus, and mesencephalon were intentionally avoided in irradiation. As the subsequent clinical, physiological, and pathological evidence indicate, the hypophysis is destroyed as time progresses after radiation exposure, with higher doses accelerating the process. Objective evidence of decreased pituitary function was given by various measures. Decrease in pituitary gonadotropins (Figure 15) and thyroid I^{131} uptake (Figure 16) seemed most significant. The radiation caused progressive cytological destruction in the hypophysis. Several weeks after receiving the 30,000 rad dose, one pituitary had regressed so profoundly that on autopsy less than an estimated 5% of the cells remained. The progressive development of the atrophy of the gland is illustrated by Figure 17. The sequence appears to consist of a latent period during which morphologic changes are mild. This is followed probably in several weeks by extensive but subtotal necrosis. The cells lose their staining ability, develop cytoplasmic and nuclear vacuoles, and develop fragmented and clumped pyknotic nuclei. Later, when the debris has been removed the gland atrophies and fibrous tissue predominates. Parenchymal cells, however, still can be identified. They are pyknotic and presumably nonfunctioning. They tend to be grouped at one or another margins of the gland.

In view of the generalized nature, advanced state and rate of progress of the metastatic mammary carcinoma at the time of treatment, one could not expect very dramatic prolongation of life of the patient. It is believed that 10 of the 26 patients had objective remissions for various durations of time. Of these, 7 occurred among 13 patients treated at the higher dose levels and 3 among 13 patients with doses of 20,000 rad or below. One patient is still in good remission 2-1/2 years after radiation. Objective remissions involved regression of intraabdominal carcinomatosis, bone lesions, primary breast tumors, and lung and skin lesions. No benefit was seen in patients with liver or brain metastases. The postirradiation period was remarkably free of adverse secondary effects. Symptoms of endocrine deficiencies could be corrected by administration of hormone replacements. Three patients developed diabetes insipidus, which was managed satisfactorily. Third, fourth, and sixth cranial nerve palsies have been observed at the highest doses given. However, these remained stationary or improved with time. One patient, treated at 30,000 rad, developed occasional uncinate fits which have been satisfactorily controlled by anticonvulsant therapy.

In October, 1957 investigative therapy of mammary carcinoma was again instituted, using 900 Mev alpha particles. We hope to irradiate a sufficient number of patients to gain some statistical idea of the value of this procedure. A few patients with pituitary adenomas and one with advanced diabetes mellitus were also exposed to pituitary alpha irradiation. It is expected that full evaluation of the patient program may consume several years. At the date of this writing (April 1, 1958) 30 patients in the new series have been irradiated.

In summary, objective evidence was obtained to show that the course of advanced metastatic mammary carcinoma can be temporarily altered in some patients by massive doses of high energy protons to the pituitary gland. These same doses cause progressive destruction of the pituitary and its function with a minimum of adverse side effects.

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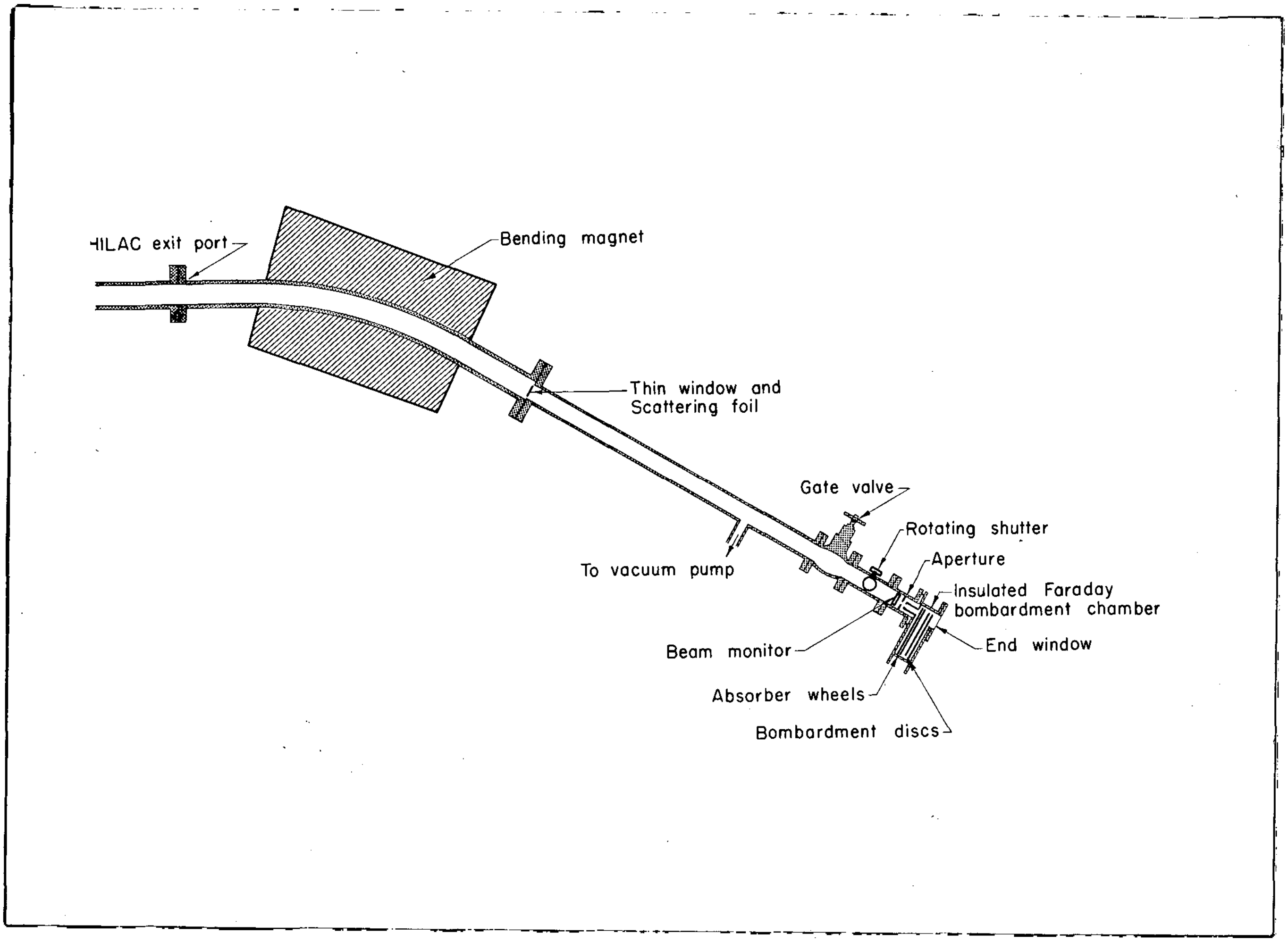

FIGURE 1

Schematic diagram of the apparatus used for the heavy ion irradiations. The beam is first magnetically analysed, then passed through a long evacuated tube before it impinges on the biological specimens. Dry molecules and phage are exposed within the vacuum chamber; wet specimens are exposed in air. The vacuum chamber is also used as a Faraday cage. Absorbers mounted in a disc are used to control the range of the particles.

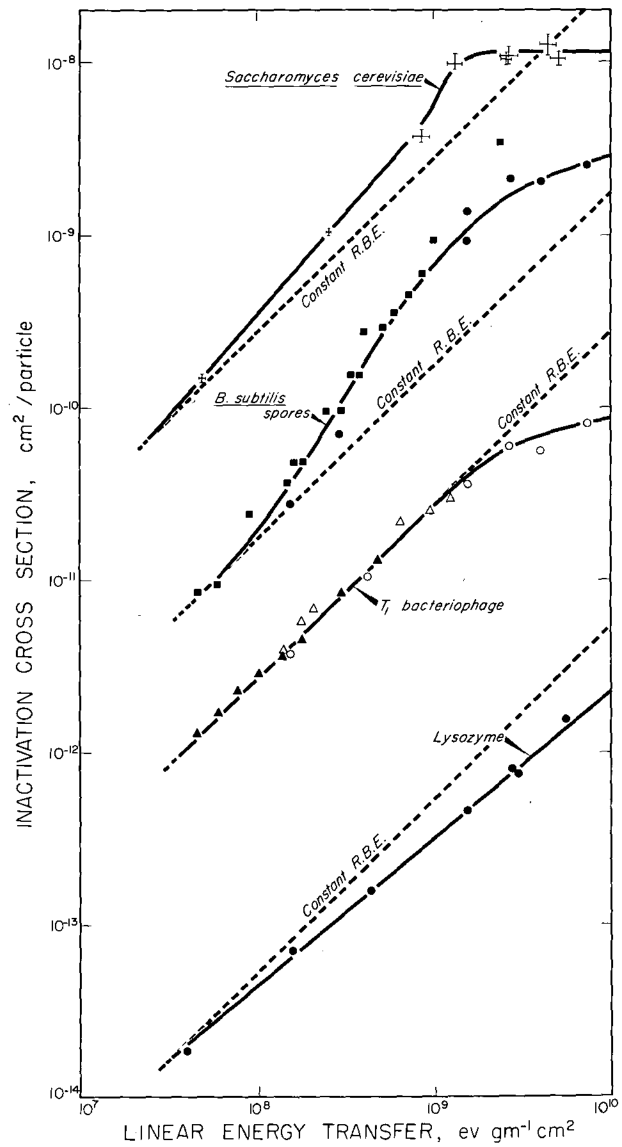

FIGURE 2

The measured cross section for inactivation of several biological materials as a function of the mean linear energy transfer of the irradiating particles. ╪ Data of Sayeg and Birge (6,7). ■ Data of Donnellan and Morowitz (20). ▲ Data of Forro and Fluke (10) at Brookhaven National Laboratory. △ Data of Fluke at Yale University cyclotron. ○● Data obtained in the present study at the University of California by Fluke and Brustad (8,9).

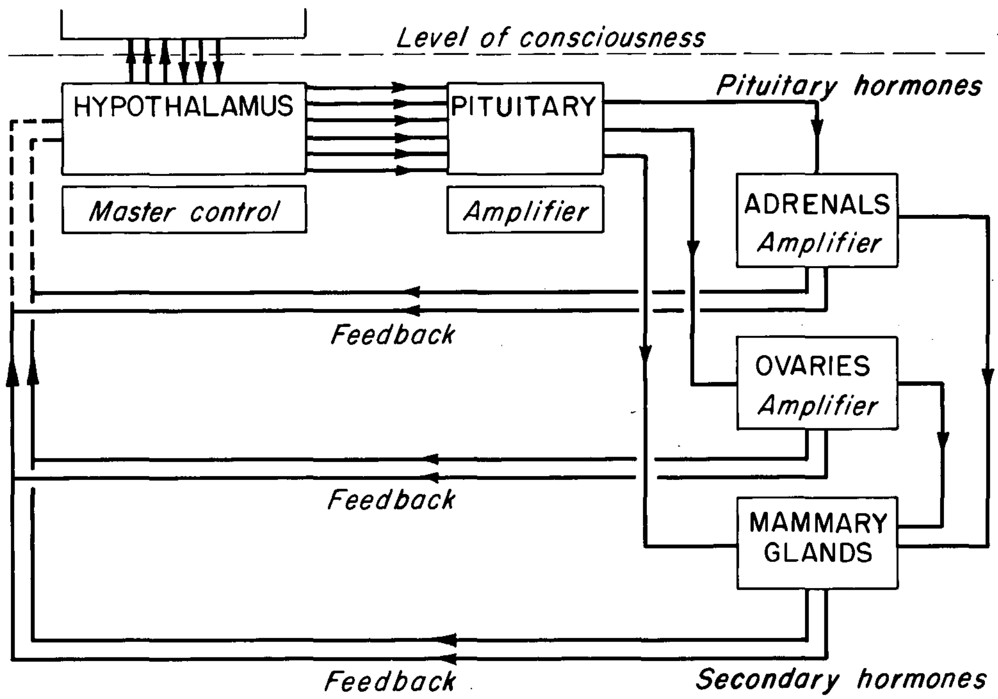

FIGURE 3

Pituitary hormones are assumed to be controlled by neural and humoral mechanisms from the hypothalamus. The endocrine "target" organs give rise to hormonal secretions under the influence of the pituitary hormones. The levels of metabolic activity in some, as yet unknown, way feed back to the hypothalamus. This latter has also neural connections with upper centers in the brain.

When any part of this system changes its level of function, the rest of the system tends to modify its activity to return the system to normal ("Homeostasis").

Carcinogenic activity is expected from this system when a part of it has subnormal activity due to sublethal injury to its cells. Pituitary tumorigenesis following 945 rad dose is assumed to occur on the basis of feedback stimulation of the subnormally active, sublethally damaged hypophyseal tissue.

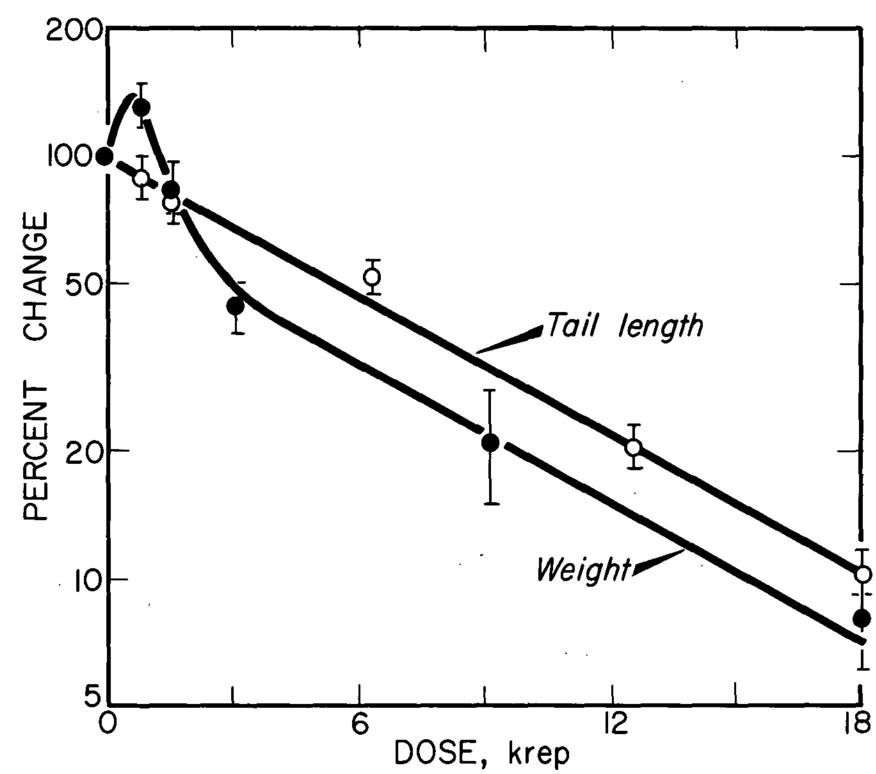

FIGURE 4

Relative increase in tail length and of body mass as function of deuteron dose to the pituitary gland, measured 18 months following exposure.

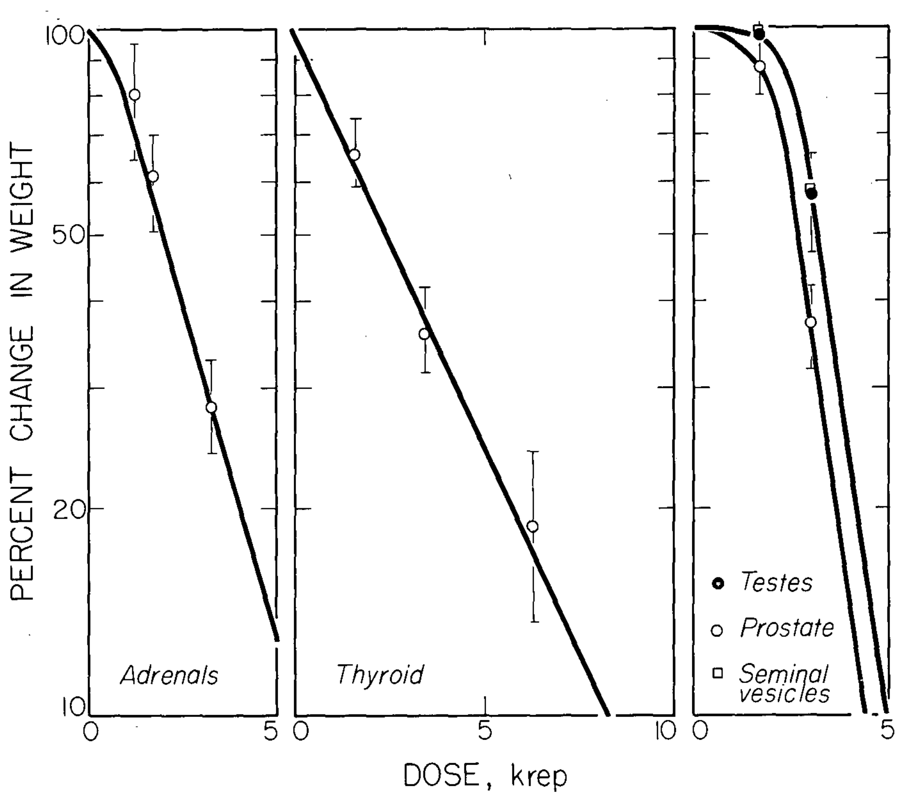

FIGURE 5

Relative decrease in endocrine organ weights 18 months after various doses of pituitary deuteron irradiation.

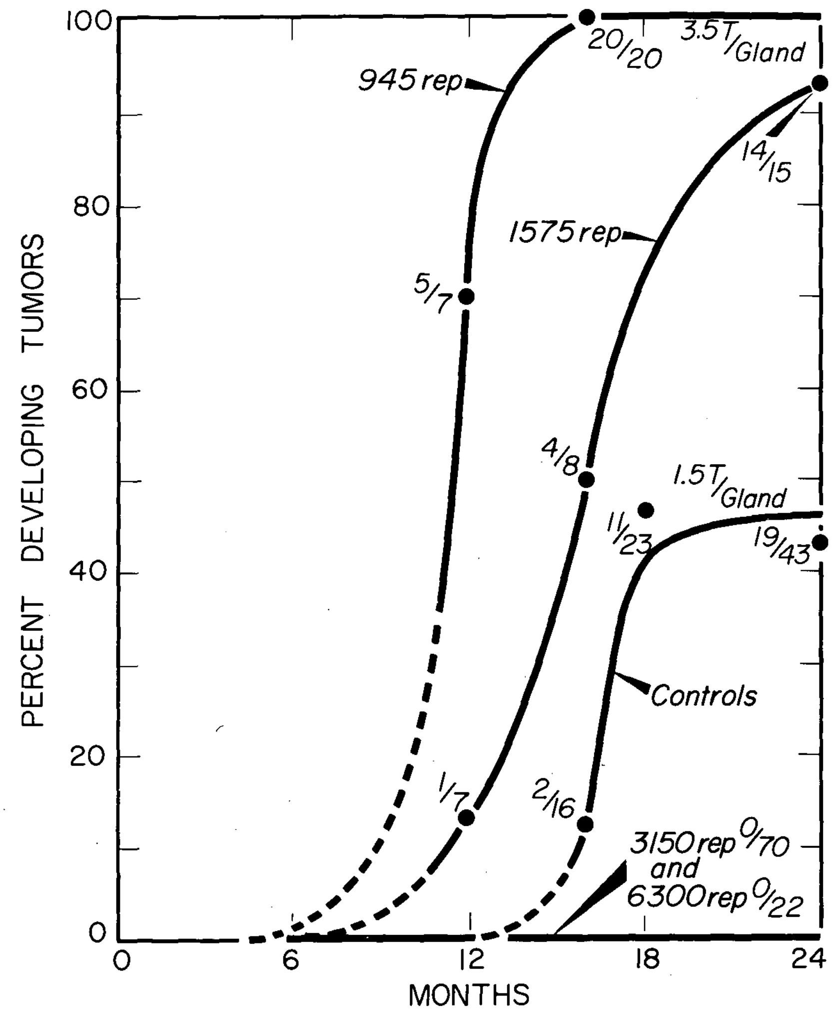

FIGURE 6

Development of pituitary tumors in normal rats and in rats that received various doses of pituitary deuteron irradiation at 28 days of age. The lowest dose, 945 rad, caused pituitary tumors in practically all animals, which appeared earlier than tumors in the controls. At high doses pituitary tumors were essentially absent.

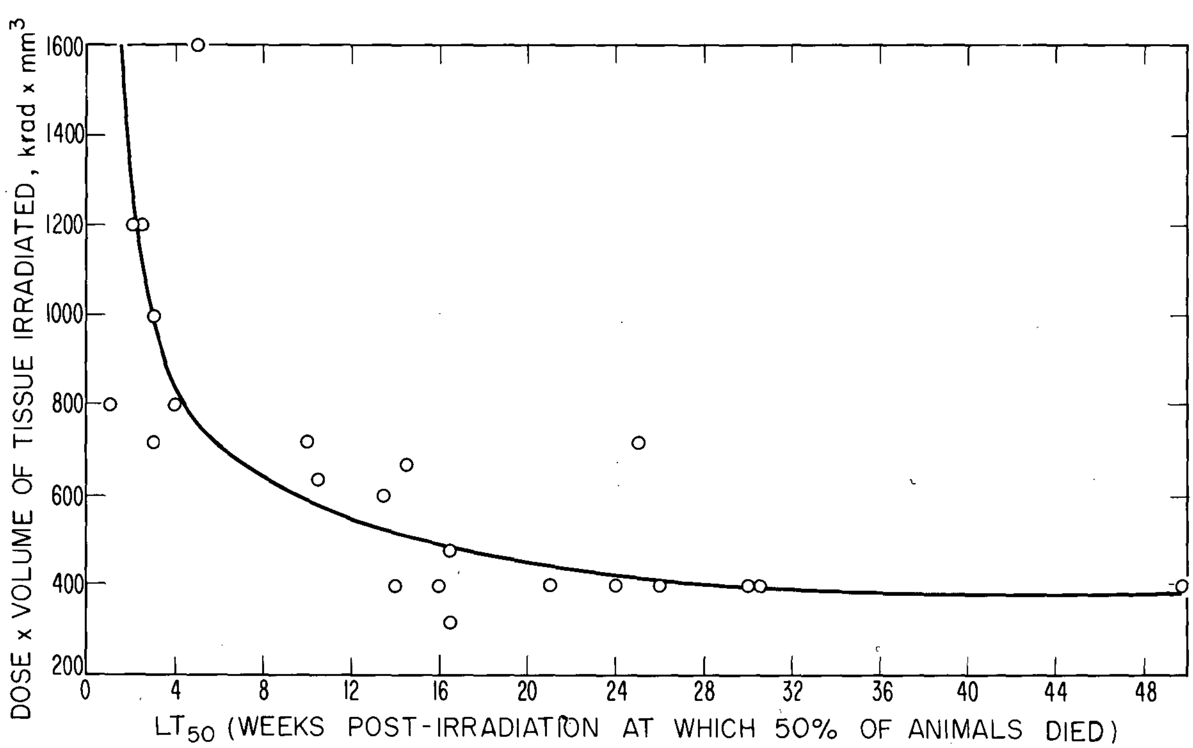

FIGURE 7

Survival of rats receiving various doses of deuteron irradiation to various areas of the brain. There is an apparent correlation between survival and volume of tissue irradiated as well as dose delivered.

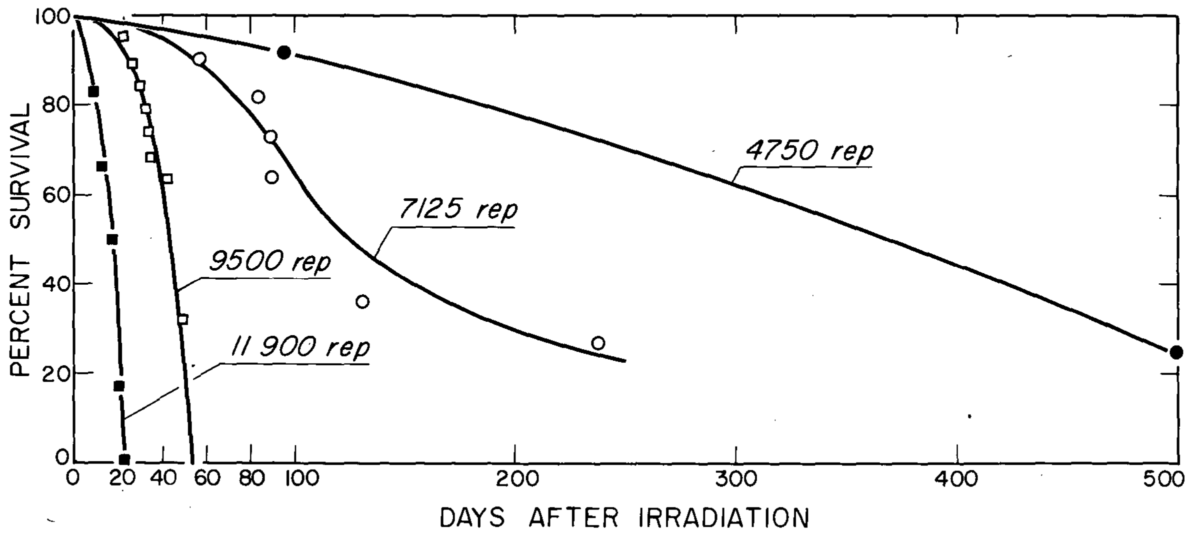

FIGURE 8

Survival of groups of rats receiving various doses of deuteron irradiation to the entire hypothalamus.

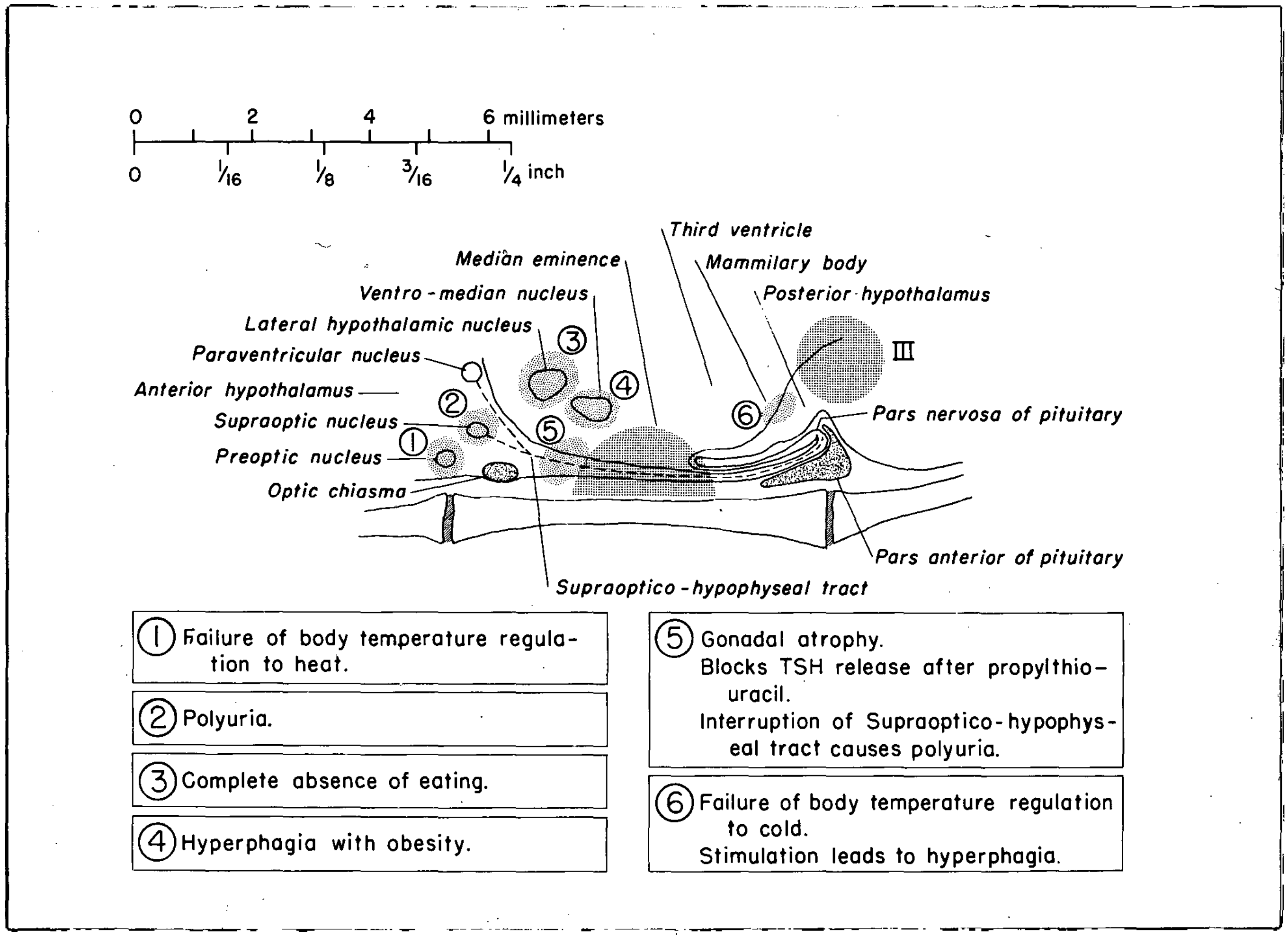

FIGURE 9

Lateral view of the rat hypothalamic region illustrating the effects of bilateral destruction of various structures. The location of two radiation-induced lesions is also shown.

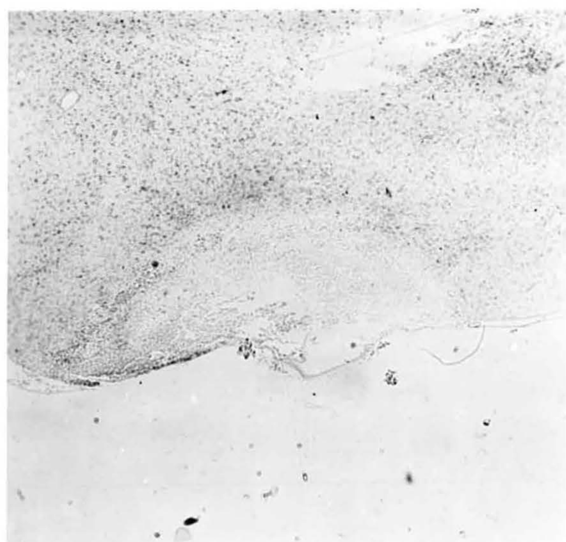

FIGURE 10

Transverse section of rat brain at level of and lateral to the median eminence showing demarcated destruction of nervous tissue 24 days after a dose of ~~20,000~~ 30,000 rad deuterons.

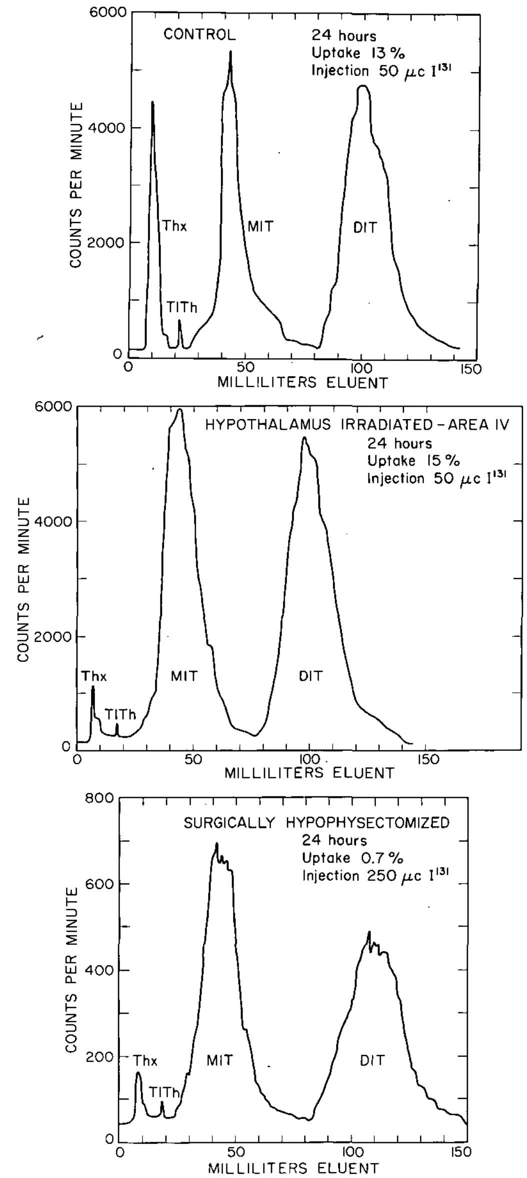

FIGURE 11

Diagrams obtained by ion exchange chromatography of rat thyroid hydrolysate from (a) Normal control, (b) Hypothalamic irradiated, and (c) Surgically hypophysectomized. Note the relatively low activity contained in the surgically hypophysectomized and the relatively small amount of thyroxin found in the hypothalamic irradiated animals.

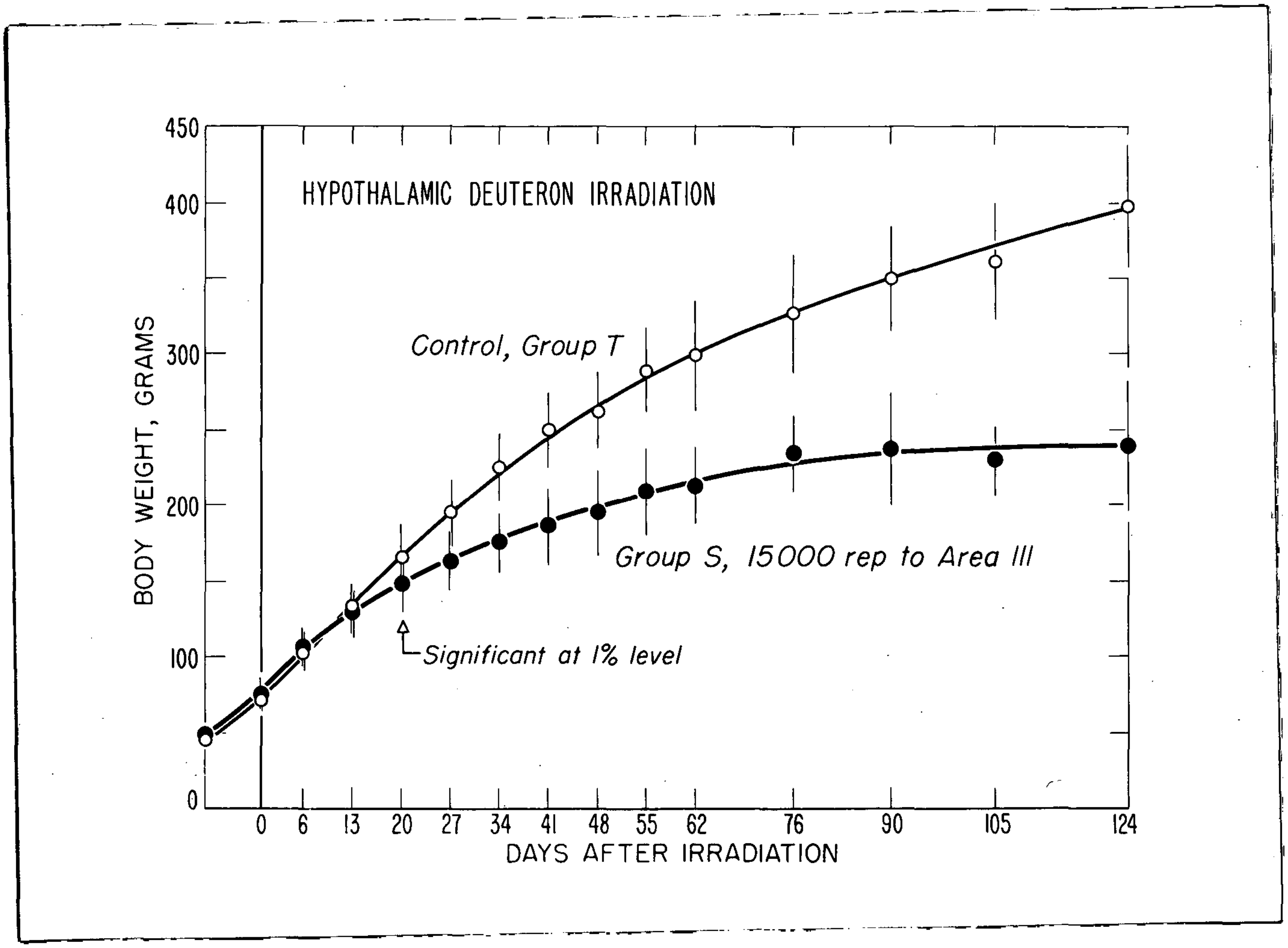

FIGURE 12

Retardation of growth in rats receiving deuteron irradiation to Area III of the hypothalamus. See Figure #9 for lesion location.

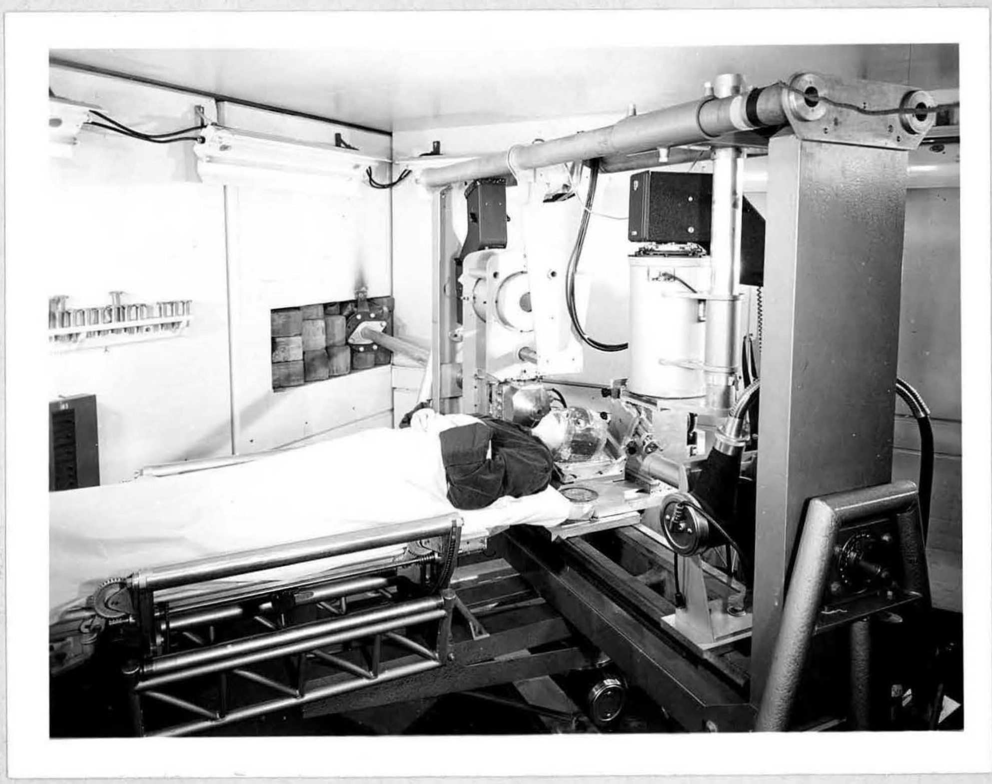

FIGURE 13

Patient being exposed to 900 Mev helium ions at the Berkeley 184" cyclotron. Note the plastic face mask for holding the head, which is continually in pendulum-rotatory motion. The beam enters on the right through the brass aperture.

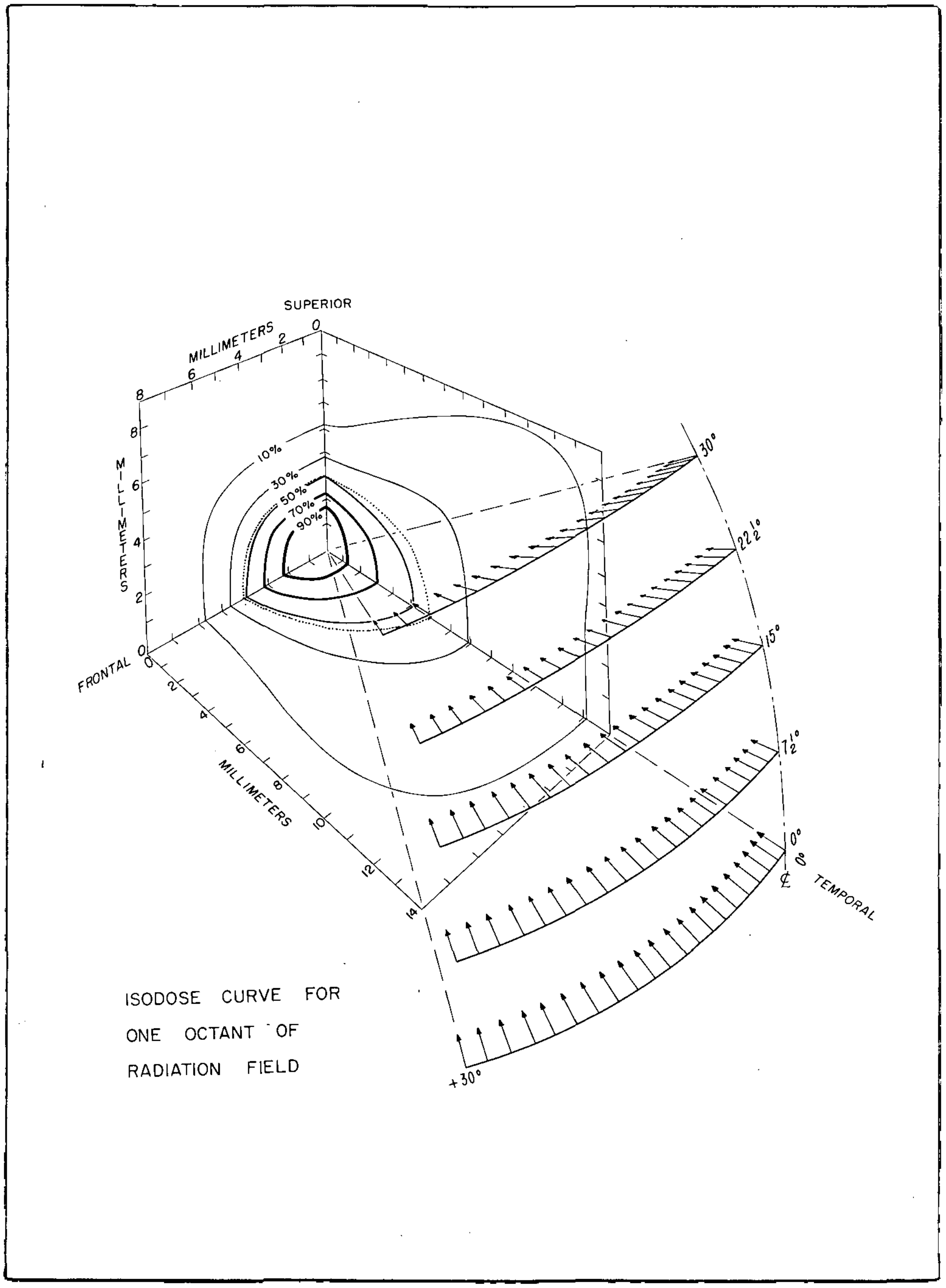

FIGURE 14

Isodose curves for pituitary proton irradiation in humans. The center of the coordinate system is at the anatomical center of the pituitary. Distances are indicated in mm.

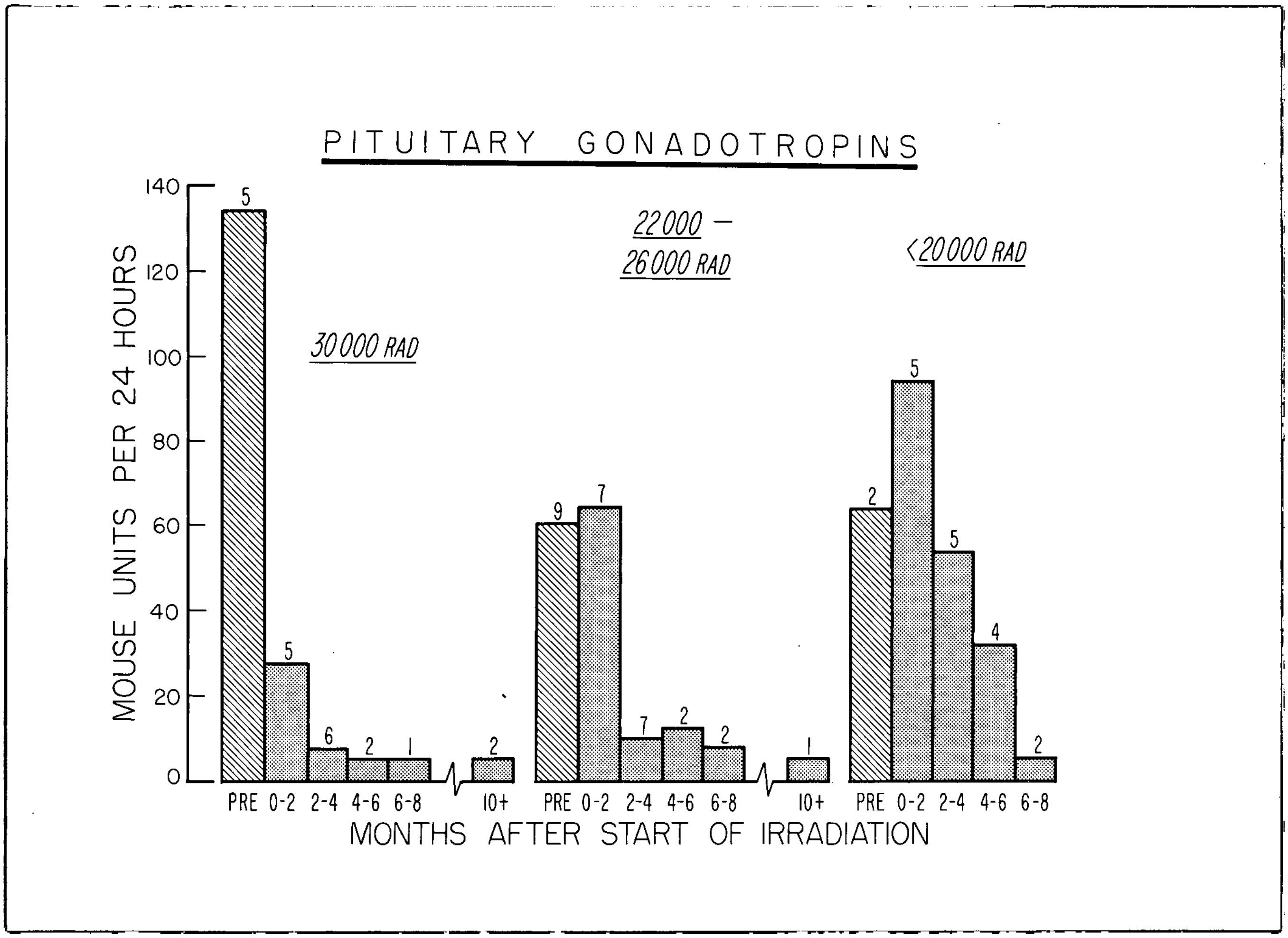

FIGURE 15

Urinary FSH measurements in patients exposed to various doses of hypophyseal proton irradiation.

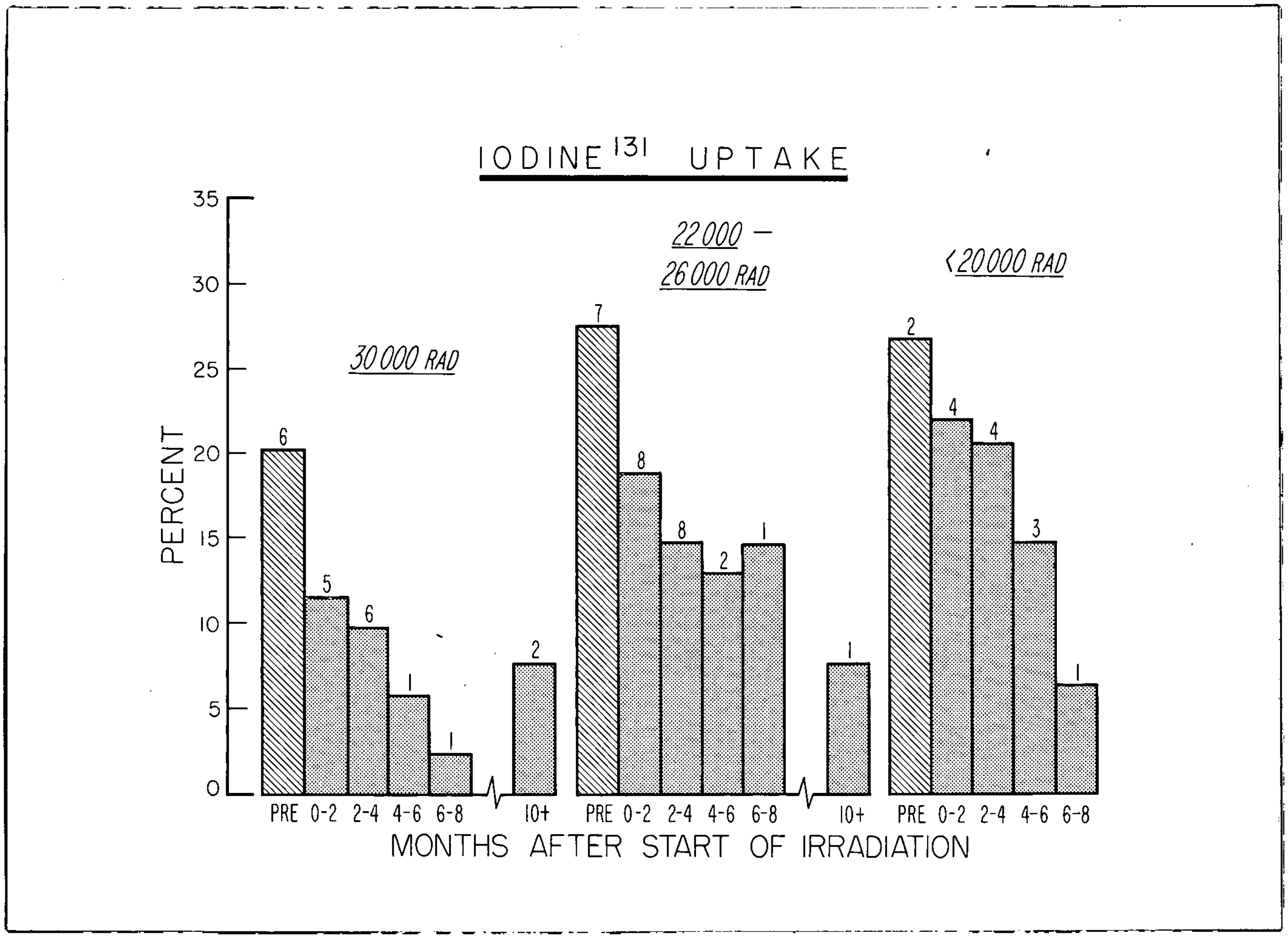

FIGURE 16

24 Hour I^{131} uptake in patients exposed to various doses of hypophyseal proton irradiation.

FIGURES 17a, 17b, and 17c

a. Nonirradiated human anterior hypophysis, hematoxylin eosin stain.

b. Human anterior hypophysis 2 weeks following 20,000 rad dose to the pituitary stained as 17a. Acute radiation necrosis is setting in. Notice nuclear and cytoplasmic vacuoles and fragments, and loss of selective staining ability.

c. Human anterior hypophysis 14 weeks following 30,000 rad dose to the pituitary stained as 17a. Dead cells fragment and completely disintegrate. Cellular debris is gradually eliminated. Note the appearance of a few viable cells with pyknotic nuclei.

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