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BIOLOGICAL STUDIES OF RADIATION EFFECTS

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RADIATION THERAPY AND BIOLOGY

WORK IN PROGRESS: SUMMARY OF SELECTED STUDIES

Irradiation of the Pituitary in Advance Cancer With High-Energy Particles from the 184-Inch Cyclotron

With a general irradiation technique described in previous reports 340-Mev protons and 190 Mev deuterons have been employed in localized irradiation of brain and pituitary gland. Recently an improved apparatus was placed in operation at the Berkeley 184-inch cyclotron, utilizing 900-Mev alpha particles; x-ray-television is used for alignment of patients. With these technical improvements it is now possible to deliver intense radiation doses to well-localized, deep-lying volumes of 1 cm^3 in the human body (about 1 mm^3 in the rat), leaving intervening tissues relatively undamaged.

To date 60 patients, 51 with far advanced mammary carcinoma, have received pituitary irradiation with either the proton or alpha-particle beam from the 184-inch cyclotron. This represents the first use of high-energy beams in human therapeutic investigation. The purpose was to learn if high-energy particles could effectively "hypophysectomy," and thus avoid the high morbidity and mortality from surgical procedures. The basic objective was to determine the control exerted by the pituitary on other endocrine organs whose hormones are believed to regulate the growth and spread of breast cancer. The promising results on the first series of 26 cases so treated made the continuation of this work essential. It is believed that 10 of the 26 patients first treated had objective remissions for from 3 to 30 months, manifested by regression of intraabdominal carcinomatosis, of bone lesions, of primary breast tumors, and of lung and skin metastases. Clinical laboratory evidence indicated decreased function of the pituitary and the target end organs following pituitary irradiation. This was corroborated by histological evidence of extensive pituitary destruction.

The shutdown of the cyclotron for 20 months for complete rebuilding, interrupted the studies of patients. The work was resumed in October 1957, using the alpha particle beam, and an additional 30 patients have recieved pituitary irradiation. Of this group all but two had advanced metastatic breast cancer. It is planned to irradiate a series of 100 patients, in order to make an adequate statistical evaluation of this procedure as a palliative form of treatment for advanced metastatic breast carcinoma. Information from collateral studies is expected to afford a greater knowledge of the factors involved in carcinoma of the breast, which may in turn afford other therapeutic approaches. At the same time animal studies are being conducted in which various areas of the hypothalamus, which has a neuroregulatory influence over metabolic activities, are being selectively irradiated. Because of the accuracy with which this can be done without injuring other tissues, it is expected that this procedure will provide further understanding of the hypothalamic control and regulation of body mechanisms. This information promises to have specific application in malignant and endocrine diseases, and in understanding the control of metabolic activities of the body such as weight gain, body temperature, body activity, and water balance. This work will be further reported as studies progress. (Cornelius A. Tobias and James L. Born)

Hypophyseal and Hypothalamic Irradiation in Animals

In conjunction with the human studies, investigations of chronic radiation effects on the hypophysis and hypothalamus of rats are being continued.

It is now ascertained that deuteron irradiation of the pituitary of rats with doses of 950 rad and higher has chronic definitive effects. At the lowest dose, there is relatively little effect on bone growth and target organ functions. In about a year, however, the animals become chronically obese, even though the hypothalamic "obesity center" received less than 50 rad. In this same period 95% of the rats develop multiple pituitary tumors of all anterior-cell types. At higher doses, at which the pituitary cells die as a result of irradiation, the injury is manifested in gradual regression of bone and body growth and of the functions of the target organ instead of in pituitary tumors and obesity. At 6,000 rad or higher, the over-all tumor incidence in the rats in a 2-year span decreases to about one-half.

Hypothalamic irradiation of young rats results in development of reproducible lesions at the site of irradiation. In the course of development of these lesions one or more of the homeostatically controlled body functions exhibits chronic abnormality. Irradiation in the region of the median eminence by 8,000 rad results in diabetes insipidus, glycosuria, partial gonadal regression, and thyroid malfunction. The same dose given in a small region of posterior hypothalamus, away from the appetite center, has an effect of slowing bone growth in the animals, apparently mediated through the anterior hypophysis. Irradiation of the entire hypothalamus with large doses results in a delayed lethal syndrome frequently accompanied by severe clinical symptoms. (Cornelius A. Tobias and Graeme Welch)

The Influence of Ion Density on Radiobiological Effects

The heavy-ion linear accelerator (Hilac) has provided a unique tool for radiobiological studies at this laboratory. The beams of accelerated nuclei of carbon, oxygen, and neon from the Hilac provide radiations that, together with the beams of protons and alpha particles from the Crocker 60-inch cyclotron, cover a wider range of linear energy transfer (LET) than have previously been available for radiation studies. These beams are now

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HEMATOLOGICAL EFFECTS OF LOW-LEVEL RADIATION DOSES IN MAN

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An increased incidence of binucleated lymphocytes in the peripheral blood of humans exposed chronically to levels of radiation averaging 200 mrem per week has been confirmed at this laboratory This phenomenon requires clarification, particularly with respect to (a) relationship of response to dose and (b) the time pattern of response after single and multiple exposures.

A group of seven healthy individuals working at the Nevada Test Site during an operational period was chosen for study. In the course of his work each individual received a single total-body exposure of gamma radiation in a period of 15 to 30 minutes.

Hematological studies were conducted during a control period prior to exposure and for 11 days after exposure. On each subject five blood counts were taken daily at 2-hour intervals for a period of 3 days before exposure. The same procedure was followed on the day of exposure and 1, 2, 4, 6, 9, 10, and 11 days postexposure. Blood films made at the same time were treated with Wright's stain for binucleated lymphocyte counting. The slides were examined at .00 × magnification. To avoid possible bias, the slides had been independently coded with random numbers before they were examined. The total numbers of white blood cells and binucleated lymphocytes were recorded. On each slide 6,000 to 10,000 white blood cells were counted. Positional coordinates for each binucleated lymphocyte were recorded.

Preliminary results of this study are presented in Table I These represent binucleated lymphocyte counts for the control period of two pre-exposure days and for two selected postexposure periods. Data from the third pre-exposure day, the day of exposure, and the fourth and sixth post-exposure days are not available at this time. The first and second post-exposure days were considered together as Period I, and the ninth, tenth, and eleventh postexposure days together as Period II. Significant increases in binucleated lymphocytes were seen in the two subjects who received the highest doses: the subject who received 2.4 r showed an increase during the second postexposure period, and the subject who received 2.6 r showed an increase during the first postexposure period. This increase in binucleated lymphocytes was demonstrated at the 5% significance level by computation of the ratio of the means. Although a dose effect is suggested, since the persons receiving exposures of less than 2 r failed to show a significant response, the fact that each of these two individuals showed a response at only one of the postexposure times indicates that caution should be used in relating the binucleated-lymphocyte response to the radiation alone.

It is also of importance to note that the incidence of binucleated lymphocytes seen at control times in this group is rather higher than we have observed in previous experiments. It is possible that the erratic pattern of daily living of all seven subjects during the period of observation was responsible for the high incidence of binucleated lymphocytes seen during the control period; furthermore, otherwise detectable responses to the smaller radiation doses may have thus been obscured.

Although the results of this experiment are still incomplete, the apparent pattern is of great interest. Experiments are now being designed to further confirm these results and to explore the nature of this phenomenon. This information should be of value in furthering our understanding of the radiosensitivity of the lymphoid system, and may help in developing a biological method for observing small doses of radiation in the human.

Development of an automatic electronic counter to permit more rapid compilation of larger volumes of data on binucleated lymphocytes is being considered. It will probably be an essential tool in this work in the future.

Information of this kind should be of value in advancing our understanding of the radiosensitivity of the lymphoid system and may help in developing a biological indicator of small doses of radiation in man.

Table I

The incidence of binucleated lymphocytes (BnL) among leukocytes in the peripheral blood of seven normal persons before and after exposure to single doses of gamma radiation

Subject	Dose (r)	Number of leukocytes counted			Number of BnL seen			Calculated number of BnL per 50,000 leukocytes		
		Control Period	Period I[a]	Period II[b]	Control Period	Period I[a]	Period II[b]	Control Period	Period I[a]	Period II[b]
A-1	0.7	115,729	80,000	90,000	5	8	1	2.2	5.0	5.6
A-2	0.7	136,331	90,000	110,000	12	9	9	4.4	5.0	4.1
A-3	1.4	140,000	85,898	89,406	15	7	12	5.4	4.1	6.8
A-4	1.5	140,000	90,000	110,000	12	13	9	4.3	7.2	4.1
A-5	1.7	119,911	50,000	100,000	26	9	17	10.8	9.0	8.5
A-6	2.4	152,382	90,000	100,000	10	14	21	3.3	7.8	10.5
A-7	2.6	170,000	90,449	110,000	55	50	33	16.2	27.8	15.0

[a] First and second postexposure days were considered together as Period I.

[b] Ninth, tenth, and eleventh postexposure days were considered together as Period II.