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BIOLOGICAL STUDIES OF RADIATION EFFECTS

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RADIATION THERAPY AND BIOLOGY

IRRADIATION OF THE PITUITARY IN HUMANS

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The current investigation on the effects of irradiation on the human pituitary gland, using the beam from the 184-inch cyclotron, has been in progress since the Fall of 1954. The purpose of this study is to determine the possible beneficial effects on various neoplastic and metabolic diseases that are under endocrine control and can be mediated through the pituitary.

During the first year of the study, 30 patients were irradiated with the 340-Mev proton beam from the cyclotron. During the next two years studies of the patients continued but no further patients were irradiated because the cyclotron was torn down and rebuilt. One year ago the cyclotron was again placed in operation, and irradiation on human patients with various diseases was resumed. Because of energy changes a 900-Mev alpha-particle beam having tissue-destructive properties comparable to the proton beam was used in place of the proton beam.

Seventy-six patients have been irradiated, 64 of these because of metastatic breast cancer. Of the remaining twelve patients, three have diabetes mellitus with complications, and five have acromegaly; the other four have had respectively, chronic lymphatic leukemia, acute lymphatic leukemia, embryonal dysgerminoma, and malignant exophthalmos. Since our purpose is to determine the effects of this irradiation on the course of the particular disease and on certain physiological processes, a comprehensive clinical and laboratory study is carried out before irradiation and every 4 to 8 weeks thereafter. The comprehensive evaluation includes:

1. Complete physical examination
2. Appropriate x-ray examinations
3. Blood chemical tests of: electrolytes, renal function, liver function, thyroid function (PBI)
4. Twenty-four-hour urinary gonadotropins, ketosteroids, hydroxysteroids, estrogens, and calcium
5. Urinalysis, BSP, EKG
6. Biopsy and other diagnostic procedures, as needed
7. Blood volume, body volume, and in appropriate cases red cell life studies, erythropoietic studies, carbon-14 carbohydrate metabolic studies, and growth-hormone studies.

Of the 76 patients irradiated, 29 are living at present: the longest-surviving patients are living at 39 and 36 months respectively. Of the deceased patients, six of the seven who were terminal at the time of irradiation died during treatment, four died of other causes, and the remainder eventually died of their disease.

Of the 29 living patients 21 have metastatic breast cancer. In seven of these the period of follow-up has been too brief to determine the effects of therapy. We have observed subjective and objective improvement in seven of the remaining fourteen patients. In one there has been subjective improvement alone. In six we have so far noted either no improvement, or progression of their disease.

Laboratory and clinical data indicating the degree of completeness of hypophysectomy are being collected on all patients. The changes indicating successful hypophysectomy appear gradually and are by no means confined to those showing improvement. In 18 of the patients with breast carcinoma who are now deceased, there was objective evidence of temporary arrest or regression of their disease.

Early encouraging results are being observed in a group of eight patients with diabetes mellitus and acromegaly. All three diabetics treated had advanced eye complications. One also had advanced diabetic glomerulosclerosis with the nephrotic syndrome, uremia, and severe anemia. Following irradiation this patient's insulin needs dropped to zero and he lost a large quantity of edema fluid. The other two diabetics have experienced arrest or improvement of their diabetic retinitis and their insulin needs have decreased.

Five patients with acromegaly have been irradiated. One treated 6 months ago has shown a gradual reduction in insulin requirements and diphenyl biguanide, and his carbohydrate metabolism now appears to be normal. Another patient who is 1 month postirradiation has been able to eliminate insulin entirely although he was taking 80 units per day prior to irradiation. Two other patients show less striking evidence of improvement, while one shows no evidence of improvement.

In both groups of patients irradiated--those with the 340-Mev proton beam and those with the 900-Mev alpha beam--it is to be noted that the earlier cases in both groups received smaller radiation doses over longer periods of time than those irradiated later in the series. Also, more of the earlier breast cases had far advanced disease, some even near terminal. One can reasonably expect better results as patients are treated earlier in the course of their disease with the 900-Mev alpha-particle beam in the higher dose ranges. The early results of pituitary irradiation in the acromegalics and diabetics is encouraging. Pituitary irradiation will be continued in patients with breast carcinoma, acromegaly, diabetes mellitus, and other conditions that are under endocrine control through mediation of the pituitary. The results observed in the treated patients have been sufficiently encouraging to warrant continuation of the study so that a statistically significant number can be evaluated. The interrelated metabolic investigations yield data of importance in gaining an underlying knowledge of the disease processes involved.

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the postirradiation period there follow occasional shocks, resembling epilepsy, which may lead to the death of the animal. If irradiation is turned on continuously until the animal dies then the over-all amplitude of the brain waves are found to continuously decrease until its vanishing at or near the time of death. Somewhat similar electroencephalographic changes already have been previously reported by Russian workers and by some workers in the United States. Our efforts are directed to better understanding of the mechanism of development of these effects and also toward finding regions in the brain that may be responsible for the frequency and amplitude distributions of brain waves.

BIOLOGICAL EFFECTS OF HEAVY-ION BOMBARDMENT

Donald Fluke

The completion in 1957 of a new linear accelerator for ions of carbon, nitrogen, oxygen, and neon has made possible a study of radiobiological effects at higher values of ion density than are encountered with alpha rays. The work is of interest in considering effects of fission fragments and of heavy cosmic-ray primaries outside the earth's atmosphere, as well as in more theoretical aspects of radiobiology. Following assembly of apparatus suitable for use with the new machine and for coping with the unusual problems of dosimetry involved, a study has been made of direct-action effects in bacterial spores, in a bacteriophage, and in several enzymes. The greater efficiency of slow alpha rays in rendering bacterial spores incapable of producing microcolonies has been followed by decreasing efficiency at still higher ion density values, much as in earlier work with vegetative yeast cells. The heavy-ion studies of effects on infectivity and host-killing properties of bacteriophage have emphasized the remarkably constant response of this organism to all "ordinary" values of ion density, but at highest ion densities a saturation effect is seen. The effect of delta rays on this system is clearly involved, and both spores and phage show behavior at high ion density which can reasonably be represented as saturation of a cross section for the incident particles. That the enzyme work has not shown such saturation is probably associated with the fact that efficiency begins to decline at lower ion density. The decline continues smoothly throughout the region studied, and a reasonable delta-ray correction gives no assurance that a target concept alone can represent the radiobiological processes involved in the inactivation of the catalytic property. The apparatus has now been modified so that vegetative cell preparations can be studied, and it is expected that the work will next concentrate on high-ion-density effects in metabolically active cells.

HEMATOLOGICAL EFFECTS OF LOW DOSES OF RADIATION IN HUMANS

Howard Parker

The double-nucleated lymphocyte response to repeated low-level doses of ionizing radiation has previously been confirmed in this laboratory. During the past year studies have been carried out in an attempt to establish what size of single whole-body dose of ionizing radiation would give rise to this response. There is an indication that the response is detectable in two

humans who received the highest doses--of the order of 2 5 r gamma radiation

Repetition of such studies and further animal experiments will be necessary to establish the response at this dose level and to elucidate the dose-response relationship.

These studies are still in progress, and require the counting of literally tens of millions of white blood cells individually by eye, with the use of motor-driven-stage microscopes. Investigation of the feasibility of performing these cell counts automatically was recently carried out with the help of the Data-Reduction Electronics Group, UCRL. Automation in such a problem still presents very great difficulties (and hence is still prohibitively expensive). However, an automatic counter has a would be tremendously valuable in cell counting of many sorts if it could be made to discriminate elements of form and color as well as size.

Information on the binucleated lymphocyte response should be of value in furthering our understanding of the radiosensitivity of the lymphoid system, and may incidentally be of help in developing a biological method for observing small doses of radiation in the human.

WHOLE-BODY HUMAN COUNTER AND LOW-BACKGROUND COUNTING FACILITY

Howard Parker

Still in the early development stage is the human whole-body counter at Donner Laboratory.

In recent months the problem has been studied, similar facilities visited and experts consulted, the counting equipment ordered, and architectural plans for the facility begun.

The facility will consist of a well-shielded underground steel room containing a large NaI crystal 100-channel scintillation spectrometer, as well as associated low-background rooms for other biological studies.

The human counter will be prepared for diagnosis in radioactivity accident cases, either occupational or resulting from a disaster in any near-by community. It will also be used in research in natural and fallout activities in humans and animals, in assessment of body K^{40} activity (and hence "lean body weight"), and in the measurement of blood loss by total-body Fe^{59} activity in some Donner Clinic patients Many new uses for this facility are expected to be found. It will identify and quantitate gamma-emitting isotopes in amounts as small as 10^{-9} curie.

The counter will produce a great volume of potentially useful data, and hence plans are being made to use card-punch data storage and automatic computer methods wherever possible

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