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RADIATION CARCINOGENESIS

Progress Report IV

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DISCLAIMER

TABLE OF CONTENTS

U. S. ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION
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MEMBERS OF PROJECT

15 March 1976 through 15 May 1977

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ABSTRACT

The series of parabiont and irradiated rats has been completed, the lesions diagnosed and the data pertinent to tumors computerized and partly analyzed. The same series yielded 74 percent incidence of cataract in the irradiated partner following a whole-body dose of 1000 R with 0.2 percent in the shielded partner and also in controls. There was no abscopal effect. Other structures of the eye beside the lens, particularly the retina, showed extensive radiation damage.

Parabiosis increased the incidence rate of leukemia from one percent in control single rats to five percent. Irradiation of one partner decreased the rate to 2.5 percent. Similar effects were noted for solid lymphoid tumors.

A pilot study of prostatic cancer in irradiated parabiont rats demonstrated a tenfold increase in incidence.

Experimental protocols bearing on cocarcinogenesis have been initiated in mice and rats, using radiation, asbestos and chemical carcinogens, but no results have been as yet obtained.

We have obtained additional evidence suggesting the importance of prolactin as a cocarcinogen with radiation for induction of mammary tumors in the rat and are continuing our collaborative study of hormonal assays in the blood of parabiont rats.

Our study of preneoplastic and neoplastic lesions in the adrenal cortex of mice, now nearing completion, further emphasizes the importance of the hormonal milieu in carcinogenesis.

Two actively functional tumors, a pheochromocytoma and an insulinoma, transplantable in NEDH rats, continue to be useful in our own and other laboratories. The insulinoma produces both insulin and proinsulin.

NOTICE

STATEMENT OF TIME OR EFFORT OF THE PRINCIPAL INVESTIGATOR

During the current year of the project, the Principal Investigator, Shields Warren, M. D., Member at the Cancer Research Institute, has spent 20 percent of his time devoted to the research under this contract, but due to the restriction of funds caused by inflation has charged only 10 percent to the contract.

It is expected that during the coming year Dr. Warren will continue a similar arrangement.

INTRODUCTION

We are deeply indebted to Dr. William V. McDermott, Jr., Director of the Cancer Research Institute, for provision to us of the facilities of the Institute, especially the excellent Animal Farm without which we could not function. The animal facilities of the Harvard Medical School have continued to provide us with inbred pathogen-free rats.

Under a grant from the National Cancer Institute special study has been given to the effect of radiation on leukemogenesis in rats. Results thus far indicate no inducing effect and possibly a mild inhibitory one.

Dr. Gates has continued to devote a major portion of her time as a volunteer which has greatly facilitated our work. Dr. Clark E. Brown has continued to aid us as Consultant in Pathology, a portion of the time as a volunteer. We are deeply indebted to both.

We are grateful for assistance from the Biomedical Research Support Grant of the National Cancer Institute to the New England Deaconess Hospital for support of a pilot research project and for special assistance from the Institute's Laboratory of Histology.

While not directly related to our work under the contract, a study by Dr. John D. Boice, Jr. on the relationship of mammary cancer to radiation exposure through fluoroscopy in girlhood was completed under the supervision of Dr. Brian MacMahon at the Harvard School of Public Health. It provided useful epidemiologic information, and the data proved pertinent to policy decisions regarding mammography.

Dr. Warren resigned from the Space Program Advisory Council of the National Aeronautics and Space Administration.

He was asked by the National Council on Radiation Protection and Measurements to chair an ad hoc Committee to prepare a report on permissible levels of plutonium in drinking water.

He addressed the American Philosophical Society, discussing "Hiroshima and Nagasaki Thirty Years After." He served as chairperson at a session on "Carcinogenesis and Mutagenesis in Vivo" of the Radiation Research Society in 1977 and also spoke on "Leukemia and Lymphoma in Irradiated Parabiont Rats." Dr. Brown read a paper on "Breast Carcinoma in Parabiont Rats with Radiation, Unilateral Nephrectomy and Oophorectomy" to the American Association for Cancer Research in May, 1976, and gave a poster demonstration at the meeting in May, 1977.

In continuation of our efforts to familiarize pathologists in general and forensic pathologists in particular with the effects of ionizing radiation in man, the chapter prepared for a new textbook of forensic medicine, "Effects of Occupational and Environmental Exposures to Ionizing Radiation," in Forensic Medicine:A Study in Trauma and Environmental Hazards, is expected to be published shortly.

Radiation safety has been maintained with the aid of the Harvard University Environmental Health and Safety Services. In addition, Mr. Russell F. Cowing has served parttime as a Consultant in radiation safety and in the planning and dosimetry of radiation experiments.

MAIN RESEARCH ACCOMPLISHMENTS

1) Parabiont Irradiated Rats: Aspects of Carcinogenesis

The main series of parabiont and irradiated NEDH rats has been completed. All of the surviving rats lived out their lifespan in the course of the year, and all in the main series have been autopsied and examined histologically. The diagnoses of the lesions found and the data pertinent to the tumors have been computerized and partially analyzed. Complete tabulations have been prepared of both the benign and malignant tumors.

This parabiosed and irradiated series of rats has also given us information on radiation-induced cataract. Seventy-four percent of the irradiated partners receiving 1000 R whole-body irradiation developed cataract as contrasted with an incidence of 0.2 percent in the shielded partner. The incidence in control parabiont pairs was also 0.2 percent. Presence of the shielded partner gave no protection to the eyes of the irradiated partner and conversely, there was no abscopal effect of the radiation on the eyes of the shielded partner. The earliest time at which cataract was noted was 106 days postradiation (206 days of age). The peak rate of occurrence of cataract as determined by examination with the naked eye was between 300 and 400 days postradiation. Not only did cataracts develop, but there was also cystic degeneration and partial disorganization of the retina. In addition, the choroid iris and ciliary body showed increase in the connective tissue with hyaline thickening of the collagen and loss of many cells. Throughout blood vessels showed hyaline thickening of their walls and abnormal endothelial cells. This

study emphasized that development of cataract is not the only deleterious effect of radiation of the eye but that serious damage may be done to other structures as well.

While most of our work on leukemia and lymphoma was supported by the National Cancer Institute, some work was done producing further evidence that a dose of 1000 R to parabiont rats was ineffective in increasing the incidence of leukemia above that in control parabiont pairs and indeed may have had a slightly inhibitory effect.

A collaborative investigation was done with Drs. Herzfeld and Greengard of the Growth Laboratory of the Institute on tissue enzyme studies in parabiont rats inoculated with transplantable tumors. Both lymphoma and fibrosarcoma were transplanted subcutaneously into single rats and into one partner of the parabiotic pair. This study suggested that humoral factors may be responsible for mediating the effects of the neoplasm on the general tissues of the host. The plasma thymidine kinase activities were followed. In single hosts the control values were exceeded by more than 100 times, but in the parabiont hosts the increase was only about tenfold in either the tumor-bearing or the tumor-free animal.

A study of cancer of the prostate was carried out in irradiated parabiont rats. A low but significant incidence of 2.2 percent appeared in the irradiated male partners, as compared to 0.17 percent in the shielded partners. The incidence rate in the combined single and parabiont controls was also 0.17 percent. Radiation apparently can induce a more than tenfold increase in incidence of prostatic cancer. The cancers are predominantly adenocarcinomas and show the same tendency to perineural invasion that is such a striking feature of prostatic cancer in man.

In collaboration with the Joslin Diabetes Foundation and the Medical School of the University of Massachusetts, we have studied further the transplantable insulinoma that arose in a parabiont pair of our NEDH rats occurring in the radiated partner of a pair of male rats. This provides well-granulated beta cells with high insulin content. Not only insulin but proinsulin is produced. Over 90 percent takes of the tumor were obtained in males, 69 percent in females. The tumor is apparently free of A cells.

Experimental procedures in two special groups of parabiotic and irradiated rats were completed, but as some of the rats still survive, conclusions cannot yet be drawn.

The first is a series of parabiont rats in which the right-hand partner was given a 1000 R dose of whole-body radiation, and a varying number of days later the previously shielded partner was also given 1000 R. The anastomotic region between the two partners due to overlapping fields received 2000 R. This doubled dose appears to induce an increased incidence rate of fibrosarcomas and myosarcomas in the anastomotic line.

The second special group consists of parabiont pairs, one shielded and one treated with 1000 R of whole-body radiation in the standard manner, but instead of permitting the parabiosis to continue the animals were separated at intervals of a few days postradiation. Through this early separation we hope to determine in which partner the commonly shared tumors in the regular series, leukemia, lymphoma, and anastomotic tumors, first arose and the approximate time after parabiosis and irradiation the cellular changes occurred that led to their development.

2) Cocarcinogenesis

In the experiments combining irradiation and administration of asbestos (another physical carcinogen), the protocoled experiments have been carried out almost entirely, and we are awaiting results. The asbestos, suspended in saline solution, was administered to rats and mice intratracheally, intrapleurally and intraperitoneally. In another series Rhodesian chrysotile asbestos and Canadian chrysotile asbestos was administered combined with methylcholanthrene in sesame oil. The same routes of injection were used. A few tumors have already appeared in this latter series.

3) Leukemogenesis

As in the previous year the bulk of our work in this area was supported by the National Cancer Institute. In our experience induction of leukemia in rats by radiation is far more difficult than in mice. In mice lymphoid leukemia is most common, whereas in rats monocytoid and myeloid leukemias are the more prevalent types. In mice the thymus is very frequently involved in the leukemic process. Thymic involvement is rare in the rat, however. Irradiation of one of the parabiont partners does not increase and may even inhibit the induction of the disease.

4) Solid Tumors

The planned study of multiple malignant tumors has been postponed owing to lack of funds. The study of radiation-induced preneoplastic and neoplastic changes in the adrenal cortex of mice has entailed a comprehensive review of adrenal radiation tumorigenesis and the endocrine factors involved. Consideration of the little understood relations of

parallel tumorigenesis in the cortex and medulla, the interplay of hormonal changes incident to radiation of the pituitary and ovary and their neoplasms serve to bring out more clearly the specific action of radiation.

5) Transplantable Tumors

The actively functioning pheochromocytoma which produces hypertension in rats and the insulinoma have been of interest to a number of laboratories. We have provided both NEDH breeder rats and transplants of the tumor to laboratories here and abroad.

The cancers originating in man that have been transplantable to the hamster cheek pouch and have survived heavy doses of radiation are being stored in the frozen tissue bank.

PUBLICATIONS SUPPORTED BY

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