PETER OWEN LIMITED
50 Old Brompton Road
London SW7

Bound in Great Britain
Printed in the U.S.A.
MCMLX

Table of Contents

Radiation Biology and Cancer

Medical Applications of Radiation

RADIATION BIOLOGY AND CANCER

A Collection of Papers Presented at the Twelfth Annual Symposium on Fundamental Cancer Research, 1958

Introduction

R. Lee Clark, jr., m.d., m.sc., d.sc. (hon)
Director and Surgeon-in-Chief
The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas

The discovery of x-rays by Röntgen and radioactivity by Becquerel in the closing years of last century came at a time when cancer research was in its infancy. Radiation research and cancer research have had a curiously parallel development since that time. Each has acted as a stimulus and each has contributed to the other. Neither one nor the other is a new science. Many facts and theories have developed in each of these disciplines; however studied and learned, a great deal more must be known before we can hope to understand fully the twin mysteries of the biological effects of radiation and the origin of cancer. The interaction of these two fields upon one another has been extensive in the past sixty years. Today there is scarcely a phase of cancer research, etiology, diagnosis and treatment that does not involve radiation in one or more of its aspects.

In order to limit our discussion, which would otherwise be overwhelming, we have chosen the title for this Twelfth Annual Symposium on Fundamental Cancer Research as "Radiation Biology and Cancer." Few will deny the intimacy with which these two subjects are linked today, but in retrospect it is a matter of some wonder (and unfortunately of tragedy) that the damaging biological effects of radiation and particularly its carcinogenic action were so early recognized by radiation workers. They were, of course, without the benefits of modern radiation equipment and the conscious

need of protection from radiation. Their early ignorance led to the initial linking of these two fields of endeavor, radiation biology and cancer research. It was less than a year after the discovery of x-rays that the dermatological effects of radiation were first observed.

The first induction of malignant lesions was described only six years later, in 1902. By 1907, Porter and White had described the first eleven verified cases of x-irradiation induced cancers in man leading to fatal results. Many similar cases followed and although we have, by gradual realization of the dangers and corresponding control of radiation practices, reduced the number of these early radiation tragedies to small proportions, we are still aware of the fact that many fundamental questions remain unanswered. The less obvious hazards resulting from small chronic doses of radiation or from the ingestion of long-lived radioactive materials are still the object of much study. The dose levels at which hematological damage, leukemia induction, shortening of life span, genetic and other deleterious effects are likely to occur are still uncertain. These are important scientific and social problems that we all encounter in this era of radiation development and use. Many of them will be discussed in this symposium.

In addition, there are the fundamental aspects of the modification of the biological and biochemical structure of the cell by radiation, the fundamental processes by which radiation can produce effects leading to malignant change in the cell, which will also be discussed. We have tried, in arranging this symposium, to cover the different aspects of radiation biology and cancer, with special reference to those relating to cancer induction, in such a way that the presentations and discussions will provide a real contribution to knowledge in this field.

REFERENCES

Porter, C. A., and C. J. White: Multiple Carcinomata following Chronic X-Ray Dermatitis. *Ann. Surg.*, 46:649–671, 1907.

BERTNER FOUNDATION LECTURE

Radiation Neoplasia and Endocrine Systems

JACOB FURTH, M.D.

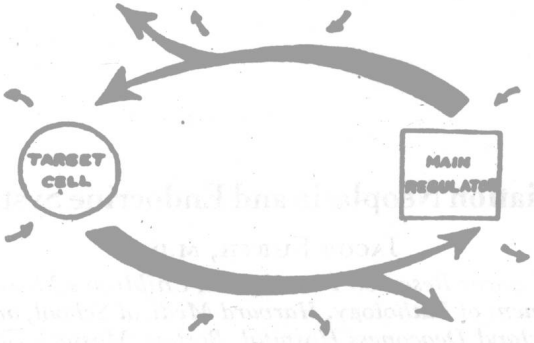
Children's Cancer Research Foundation, Children's Medical Center, Department of Pathology, Harvard Medical School, and New England Deaconess Hospital, Boston, Massachusetts

Thirty years ago we began irradiating hundreds of mice as a means of producing leukemia. Success merely confirmed observations in man. Unexpectedly, a variety of tumors were found in the course of these and similar experiments performed later, and, remarkably, most of them were related to endocrine organs. The observation in man thus far, notably among the Japanese, similarly exposed to total body irradiation, raises doubts that radiation is as great a carcinogenic hazard in man as it is in the rodent. Only time will tell the magnitude of radiation hazard in man from the standpoint of neoplastic development. Extrapolations from animals to man are not warranted. A remarkable feature of carcinogenic responsiveness is its species and strain limitation. Let us tuck away in our mind possible events in man, make use of the animal dat in reducing exposure hazards, whenever possible, and turn no to the most fascinating aspects of experimental radiation carcin genesis: The insight it has given to the initiation and maintena of cancerous growth in general. We look upon research on the genesis and character of cancer as a likely major avenue to lead to the ultimate solution of the cancer problem.

When cancers appeared on the hands of pioneers exposed to x-rays or radioactive substances, it was natural to think of them as the consequence of some direct change in irradiated cells, endowing them with ability of unrestrained growth. The discovery that

radiations are mutagens and the induction of cancers by chemicals at sites of treatment, all fitted well the simple theory: Radiations cause cancer by virtue of their ability to cause somatic mutations. This we accepted and here we failed.

SCHEME OF FEED-BACK REGULATION



Pathogenesis of Neoplasia	Alteration Site	Alteration Character
1. Sustained deficiency of restraining force	Host	Somatic
2. Sustained excess of stimulating force	Host	Somatic
3. Altered responsiveness of target or regulator	Cell	Cytogenic

FIG. 1. Scheme of three basic mechanisms of tumor production.

When destruction of the thyroid led to the development of pituitary tumors, the exclusiveness of the mutagenic theory of radiation cancer collapsed. One exception followed another relating the origin of cancer and maintenance of neoplastic growth to disturbances in homeostatic equilibrium. The mutation theory, once so popular, is now relegated to a subordinate position (Brues, 1955) or negated altogether (Mole, 1957). Evidence will be presented pointing to the importance of both irreversible hereditary alterations in cells and indirect hormonal effects as the most powerful factors in the induction of neoplasms by radiation.

To begin with I shall redefine neoplasia. The evidence on which

it is built was gathered in the course of studies in endocrine neoplasia. It presupposes the correctness of two other theories on which it is built, that of the feed-back theory of cell regulation and the somatic mutation theory, and so it is more vulnerable than either.

Definition of Neoplasia and Basic Changes Inducing It

Neoplasia is a state of apparently unrestrained growth of cells, caused either by permanent alteration in the cell (mutation or abnormal differentiation) or by extracytogenic forces (feed-back derangement, virus).

In normal hosts the number of each cell is maintained at a definite level by a precise physiologic mechanism similar to a feed-back regulation. Neoplasia can arise 1) by sustained deficiency of the restraining factors; or 2) by sustained excess of the stimulating factor; or 3) by altered responsiveness of either the target organ or the regulators. In the first two the change is in the host; in the third it is in the cell. To exemplify each of these, radiation effects on three pituitary-target systems will now be considered.

EXAMPLES OF RADIATION-INDUCED TUMORS DUE BASICALLY TO

Deficiency in restraining force:	TtT
Excessive stimulation:	MtT
Altered responsiveness of cell:	MT, AtT
Combination of factors (2, 3):	OT

TtT=thyrotropic tumor; MtT=mammotropic tumor; MT=mammary tumor; AtT = adrenotropic tumor; OT = ovarian tumor.

I^{131} Induced Pituitary Tumors (Example of Tumor Development from Deficiency of the Restraining Force)

Destruction of the thyroid by I^{131} in mice leads to the development of pituitary tumors (Gorbman, 1949). These tumors are thyrotropic (Furth et al., 1952). Radiation of the pituitary may not induce them but surgical removal of the thyroid will do so (Dent et al., 1955). Furthermore, blocking TH synthesis or mere iodine deficiency will induce pituitary tumors probably of the same type, in mice (Moore et al., 1953), and rats (Axelrad & Leblond, 1955). The induction of thyrotropic pituitary tumors by I^{131} is related not to the quantity of ionizing irradiation administered but to the completeness of thyroid destruction. It is possible to reduce the quantity of I^{131} necessary for destruction of the thyroid to one tenth by keeping the host on iodine deficient diet for several weeks before I^{131} is given. Administration of TH will prevent tumor induction and retard tumor growth.

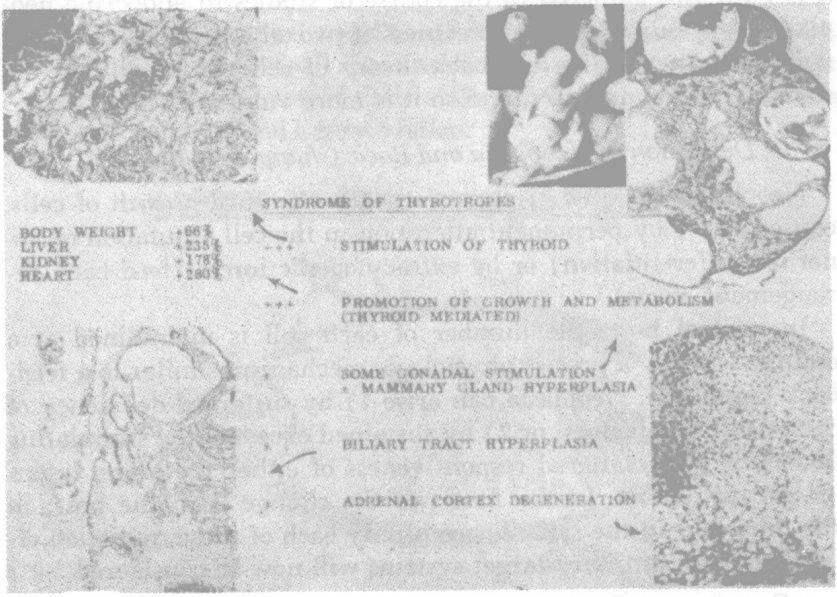


FIG. 2. The syndrome of grafted thyrotropic pituitary tumors.

These thyrotropic tumors are a unique tool to study the stages of transformation from a normal to highly malignant cell. It is the only type of tumor we know which is of the completely dependent type, not only in the original host but also in the first generation grafts. Some strains remained fully dependent during several years of successive generations. Increase in degree of autonomy appeared to occur step-wise, but, with rare exceptions, some hormone responsiveness of autonomous tumors was evident even after many years of successive animal passages.

Presently, V. H. Reynolds (personal communication) is studying the oxidative metabolism of these tumors and found that with change from dependency to autonomy there is a marked reduction in oxygen uptake (from about Q_{O_2} 9 to 5.5) and increase in lactic acid production both aerobically (from about $Q_A^{O_2}$ 1.6 to 4.3) and anerobically (from about $Q_A^{N_2}$ 3.3 to 10.5).

The thyrotropic levels at various stages of tumor formation were studied by several investigators (Burnett et al., Bates et al., and others). The greatest concentration is in the primary tumors which, by unit weight of tissue, exceeds that of the normal pitu-

itary. With increasing autonomy there is a decrease in hormone concentration. The syndrome exhibited by functional thyrotropes in mice is illustrated in Figure 2, the pathogenesis of some changes initiated by thyrotropes is shown in Figure 3.

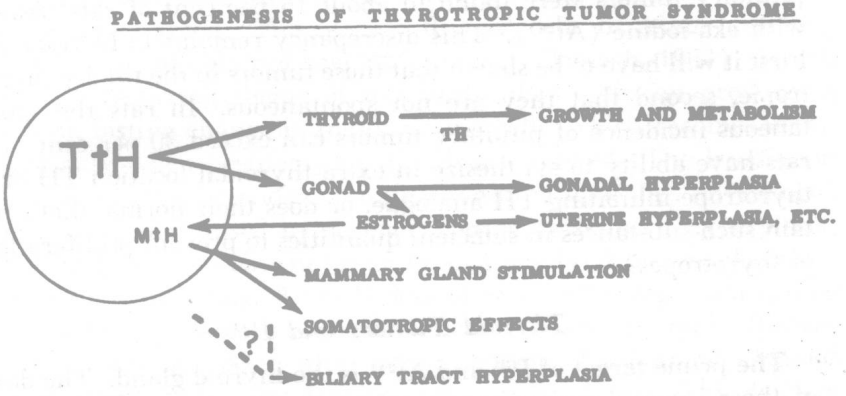


FIG. 3. Scheme of the pathogenesis of the thyrotropic syndrome.

There are remarkable exceptions from the usual pattern. V. H. Reynolds (personal communication) observed recently that one thyrotropic strain is highly hormonal responsive yet it is barely functional. Earlier, an autonomous strain was noted to be stimulated by TH instead of being restrained. Reverse responsiveness is well known in the field of chemotherapy.

In general, it is true that dependent tumor cells lack the morphologic features of cancerous cells while the autonomous tumor cells possess them. This correlation is, however, crude and not good enough for diagnosis. Are the fully dependent thyrotropes entirely normal cells? They are poor in aldehyde fuchsin reactive granules which are characteristic for normal beta cells from which they are derived (Halmi and Gude, 1954). We failed, but Purves and Griesbach (personal communication) succeeded in demonstrating such granules in dependent thyrotropes. Similarly, Marilyn Farquhar (personal communication) recognized the characteristic beta granules in the electron micrographs of the thyrotropes.

Normal thyrotropes do not function adequately in extra-sellar location, severed from their portal vessels, but dependent thyrotropic tumors do. (It remains to be seen whether they are stimulated at all by hypothalmic hormone.) From what is now known of feed-back regulation of thyrotropes (Brown-Grant, 1957) this may

not be a basic difference, indicative of a change in normal thyrotropes when they form dependent tumors.

Administration of I^{131} to rats on normal diet failed to induce pituitary tumors, as did rigid low iodine diet alone and antithyroidal drugs but in recent experiments of Durbin and Asling (1957) pituitary tumors were found in about 15 per cent of rats treated with eka-iodine (At^{211}). This discrepancy remains to be resolved. First it will have to be shown that these tumors in the rat are thyrotropic, second that they are not spontaneous. In rats the spontaneous incidence of pituitary tumors can exceed 30 per cent. Do rats have ability to synthesize in extra-thyroidal location TH or a thyrotrope-inhibiting TH analogue, or does their normal diet contain such substances in sufficient quantities to prevent proliferation of thyrotropes?

Thyroid Tumors and I^{131}

The prime target of I^{131} and At^{211} is the thyroid gland. The dose of these internal emitters required to destroy most of the thyroid requires thousands of r. Therapeutic irradiation in man for advanced cancer with 3.000 to 10.000 r caused only slight depression in gonadotropins and thyrotropins without distinct histologic changes. Best response was obtained for hypophyseal exophthalmus (Plunkett, 1957). The thyroids of tens of thousands of people and animals received I^{131} between a few to thousands of r (depending on the dose administered and functional state of the cell). Were tumor production a mere matter of mutation, thyroid tumors should be common in man and animals that had been treated with I^{131} or At^{211} but this did not occur. There are a few reported cases in man (Uhlmann. 1957; Duffy, 1957) and in animals but it is doubtful if I^{131} alone induced more than compensatory, adenomatoid nodules. The contrary view of Goldberg and Chaikoff is explained by more recent work of their team (Lindsay et al., (1957). In their colony of rats the incidence of thyroid tumors was high among both control and I^{131} treated rats but the neoplasms in the I^{131} treated rats were of different type and more malignant appearing, though non-metastasizing. It has been shown earlier by Doniach that I^{131} enhances the tumorigenic action of goiterogens and some such factor may be operating in Chaikoff's colony. In the experiment of Doniach (1957) a single exposure of 1,100 rads x-rays (equivalent to 30 μc I^{131} in potency) "initiated"