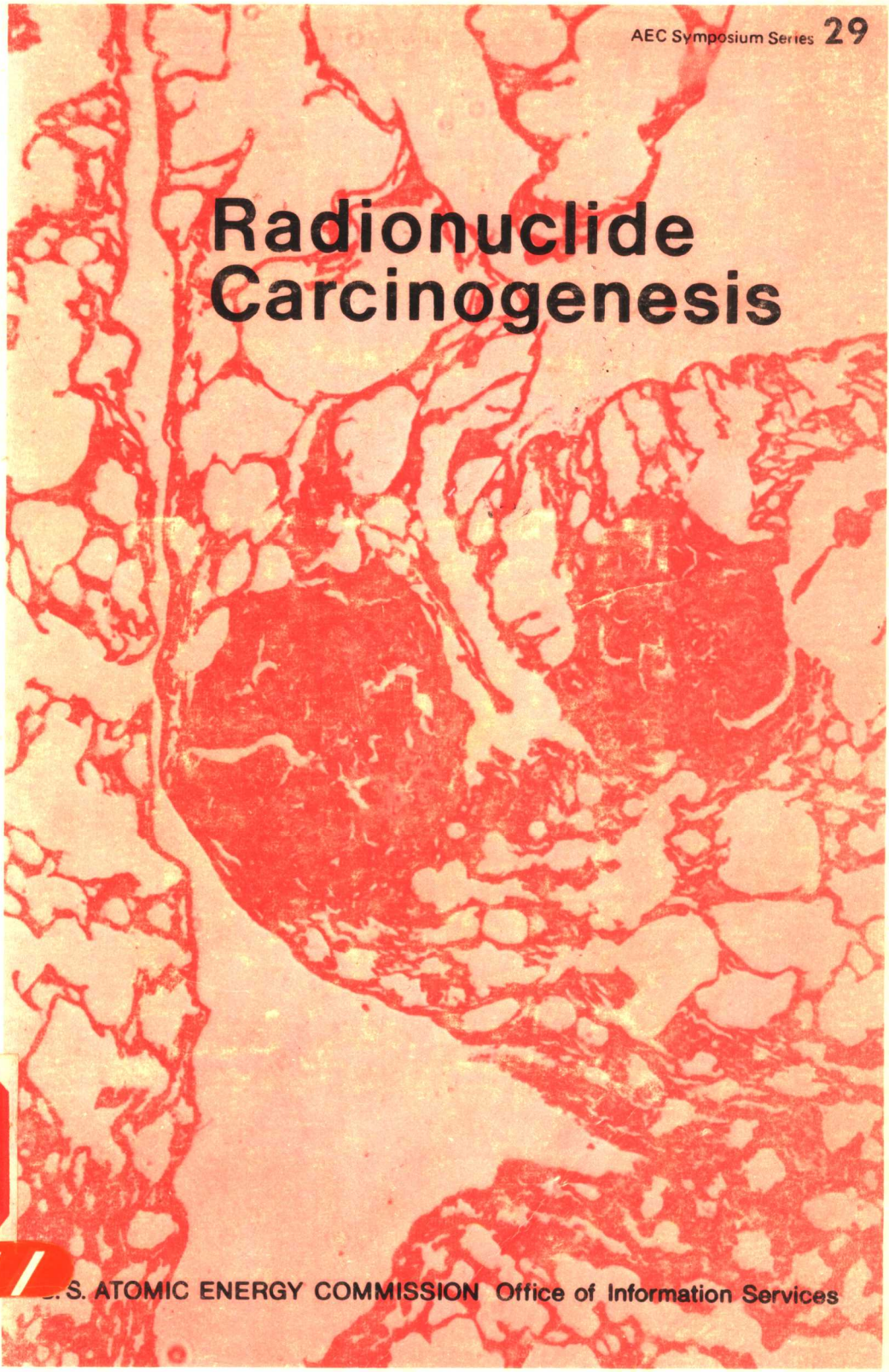
AEC Symposium Series 29

Radionuclide Carcinogenesis



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Radionuclide Carcinogenesis

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PREFACE

The broad objective of this symposium on radionuclide carcinogenesis was to update current knowledge of carcinogenesis from internally deposited radionuclides. An encouraging aspect of the symposium was the increasing emphasis being placed on the roles of hormones, viruses, nonradioactive cocarcinogens, and tumor-promoting agents acting together with radionuclides in the induction of tumors. From such studies will come an increasing appreciation of the mechanisms of cancer induction as well as a better understanding of potential hazards to man exposed as he is to the milieu of radioactive, biological, and chemical carcinogens characteristic of our sometimes polluted environs. Further encouragement was gained from the increasing emphasis on retrospective epidemiologic studies in human populations exposed accidentally, occupationally, or medically to alpha emitters and the attempts to relate observations in experimental animals to the human problem.

We are greatly appreciative of the efforts given by the authors, participants, and colleagues, which made this a worthwhile meeting. Special thanks goes to Judith A. Harrison, the symposium secretary, and to Glen Horstman, who was in charge of arrangements; and to W. F. Simpson, Technical Information Center, U. S. Atomic Energy Commission, Oak Ridge, Tenn., who edited the papers and coordinated publication of the proceedings.

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PATHOGENESIS OF RADIONUCLIDE-INDUCED TUMORS

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Before considering the pathogenesis of radionuclide-induced tumors, it is useful to consider the general aspects of the mechanisms of carcinogenesis, the contribution of radiation injury to these mechanisms, and the general principles of radiation carcinogenesis with respect to the question of threshold dose, dose–incidence relationships, influence of dose rate and radiation quality, and relevant dose. These considerations are followed by a general discussion of the carcinogenic pathogenesis of various radioisotopes.

GENERAL ASPECTS OF CARCINOGENIC MECHANISMS

Most, if not all, types of cancer apparently result from multistage or multievent mechanisms, including cellular initiating events that confer neoplastic potential upon cells and promotional events that act to permit or to stimulate the potentiated cells to proliferate as neoplastic cells.

Carcinogenic mechanisms may include events occurring at any time from the prezygotic stage to the time of the beginning of malignant neoplastic proliferation.

The cellular initiating events are thought to be mutations or chromosomal aberrations caused by physical, chemical, or biological (e.g., viral) agents. They may involve:

1. Prezygotic (inherited) germinal-cell mutations or chromosomal aberrations persisting in the formation of the zygote and transmitted to many daughter cells of many kinds through the cell proliferation in subsequent development of the organism.

2. Postzygotic somatic-cell mutations or chromosomal aberrations acquired throughout life, with variable degrees of transmission to daughter cells,

depending upon the cells acquiring the aberrations and the time of this acquisition with respect to the development of the tissues and organs of which they are parts.

The promoting events are variable for cancers of different tissues or organs. They may be caused by physical, chemical, or biological agents or by pathologic or basic aging processes and may include:

1. Local tissue damage and disorganization, i.e., so-called "precancerous lesion" or "chronic inflammation" in sites of origin of tumors, consisting of parenchymal degeneration and hypoplasia, vascular and interstitial fibrosis, and continued abortive or disorganized attempts at regeneration by remaining parenchymal cells.
2. Normal or enhanced hormonal proliferative stimulation of neoplastically potentiated cells in tissues under special hormonal control, especially in endocrine glands and gonads.
3. Depressed immune competence, which may be especially important in viral carcinogenesis and possibly in carcinogenesis in general.

It is apparent that there are two general classes of mechanisms of carcinogenesis, depending upon whether or not the required promotional tissue changes are located largely in the same locale as the potentiated cells that will originate the cancer.

GENERAL ASPECTS OF RADIATION CARCINOGENESIS

Mechanisms of Radiation Carcinogenesis in General

It seems apparent that, for radiation carcinogenesis from a particular radiation exposure, there are four general classes of mechanisms, with, of course, the usual overlapping subclasses:

1. Radiation induces the cellular initiating events and also the promotional events directly in the localized region of origin of the cancer.
2. Radiation induces the cellular initiating events and induces the promotional events largely indirectly through changes caused in regions remote from the site of cancer origin.
3. Radiation induces the cellular initiating events, but the promoting events are caused largely by other means locally or remote from the site of cancer origin.
4. Radiation induces the promotional events remote from the site of cancer origin, but the cellular initiating events are caused by other means than the radiation exposure in question.

None of the many types of changes that radiation can cause in cells or tissues is unique for radiation; these changes can be caused by a variety of agents or conditions, including many of those known or suspected to be carcinogenic or

cocarcinogenic, i.e., promotional. Therefore, radiation-induced changes of carcinogenic significance may be additive or synergistic with the carcinogenic effects of other agents or conditions.

Radiation can cause all the changes required to induce a particular cancer in an individual, or it may contribute only some of the required change, presumably even as little as one single-hit event, the remainder of the required changes being contributed by causes other than the particular radiation dose in question. Relatively small doses can cause genic mutations and chromosomal aberrations in high incidence; larger doses are required to cause the chronic tissue or organ pathology and dysfunctions that have been implicated as carcinogenic promoting factors and to cause these changes considerably earlier than they would otherwise develop as a result of natural aging processes.

The carcinogenic effect of radiation exposure may be either to cause earlier appearance of a cancer (i.e., temporal advancement) in individuals who would have had the cancer eventually without the radiation exposure or to absolutely induce the cancer in individuals who would not have had the cancer otherwise. The difference between temporal advancement and absolute induction of cancer by radiation exposure involves all grades of contribution of radiation to the total mechanism of the cancer and cannot be fully appreciated statistically without thorough ascertainment of the differences in total lifetime incidence, as well as in age-adjusted incidences, between exposed and appropriate nonexposed control populations.

In addition to the period of time from the completion of a carcinogenic mechanism to the detectability of the growing cancer, there is a period of time between the delivery of the effective radiation dose to an individual and the completion of the consequent course of pathologic processes required to fulfill the carcinogenic mechanism. Although the latter is the true latent period, the latent period in practice often refers to the two periods combined. For many cancers there is a tendency for the average latent period after brief radiation exposure to increase as dose decreases. Obviously, the life expectancy of the individual at the time of the radiation exposure in relation to the required minimal latent period for a cancer is one of the determining factors in the dose required to ensure the development of that cancer within his lifetime.

General Aspects of Dose Threshold for Radiation Carcinogenesis

In the question of dose threshold for radiation carcinogenesis, the radiation dose required to temporally advance or absolutely induce a particular cancer in an individual (i.e., his individual threshold dose) depends upon the extent to which the rest of the carcinogenic mechanism will have been completed by causes other than the particular exposure in question, before, during, and after this exposure.

The term "threshold dose" for carcinogenesis has real meaning only in terms of the radiation dose required to cause the effect in an individual or, if a population is being considered, only in terms of the dose required for the most susceptible individual in that particular population.

There is a finite probability, however small, that exposure to the smallest quantity of ionizing radiation could cause a change in a cell, e.g., a point mutation, which could contribute a part of the complex mechanism of carcinogenesis. Whether or not this change would result in the temporal advancement or absolute induction of a cancer would depend upon whether or not it occurred in an individual in whom the balance of the mechanism will have been provided by other means.

On logical or theoretical ground, it may be erroneous to assume the existence of an absolute threshold dose for cancer of any kind in populations of unlimited size and heterogeneity with respect to genetics, environment, clinical history, age, sex, etc., even if the probability of completion of a carcinogenic mechanism by a single quantum of radiation in an individual is extremely small and even though one or another sample of the population were to show an observed ("practical") threshold dose of substantial size.

A "practical threshold" ascribed to insufficient life-span is only another way to indicate for a particular sample of a population the paucity or absence of individuals of sufficiently low threshold for a particular cancer to accommodate the required induction time for a low radiation dose within their after-survival time. The "practical threshold" may differ between different samples of a population according to size of sample (as it affects statistics) and actual differences in distribution of individual thresholds (and ages) at the lower exposure levels.

General Aspects of Dose–Incidence Relationships in Radiation Carcinogenesis

It is the distribution of the individual radiation dose thresholds for a cancer in any particular population which determines the shape, as well as the intercept, of the dose–incidence curve.

An observed dose–incidence relationship, usually involving only parts or combined fragments of the total curve, may be fairly linear or nonlinear (i.e., curvilinear) concavely or convexly. Portions or combined fragments of an observed nonlinear curve may be fairly linear. Any of these types of observed curves may or may not suggest a practical threshold directly or by extrapolation, and none of them excludes the possibility of lack of absolute threshold in a larger or more heterogeneous population.

Data over a wide range of single doses of low LET (linear-energy-transfer) radiation or data from composites of several different experiments comprising a wide range of single doses, with ascertainment of absolute lifetime excess incidence of cancers, are often compatible with a general sigmoidal curve

(Fig. 1). That is, there is a zone of uncertainty at the lower dose levels where no concrete data exist, followed by a rising concave portion, followed by a more rapidly rising fairly linear portion, followed by a convex portion leading to a plateau and then a convex falling portion.

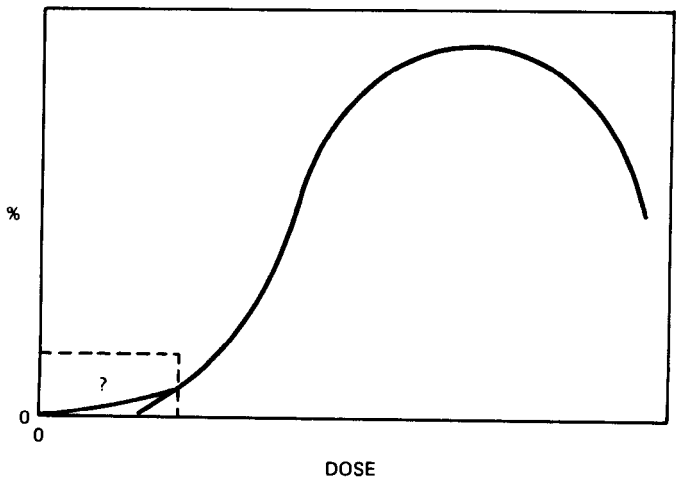

Fig. 1 General pattern of data for single doses of low LET radiation.

The decline in rate of increase in incidence at high-dose levels, first represented by the development of the plateau at peak incidence levels and then by a fall in the curve at still higher dose levels, has been attributed in experimental work to degrees of tissue destruction, cell killing and sterilization, which are excessive for cancer induction, and in some instances to shortening of life-span from other radiation effects.

For various types of cancers in various species or strains of experimental animals and for various qualities of radiation, the range of single doses involved in such a sigmoid dose–incidence curve may vary greatly, and the length and steepness of various parts of the curve may vary greatly, depending upon the distribution of individual thresholds for the after-survival involved. This distribution can skew the curve in various ways. For example, the tail of the curve in the lower dose regions may in some instances be long and low up to the point of substantial abrupt increase at a dose of substantial size, suggesting the possibility of a substantial "practical threshold" but not eliminating the possibility of no threshold.

However well this sigmoid type curve may represent the probability of the low LET radiation induction of a cancer in groups of experimental animals, which are usually relatively homogeneous (with respect to age at irradiation,

genetic background, environmental conditions and care, diet, treatments and procedures within experimental and control subgroups, etc.), the distribution of individual thresholds in a population that is highly heterogeneous in these respects, such as the human population, may often be greatly different, not to mention the great uncertainties concerning dose to relevant target tissues, dose rate, appropriateness of control populations, and incomplete follow-up and ascertainment of absolute excess incidence.

Under these circumstances it is not suprising that the fragmentary epidemiologic data on correlation of radiation exposure (usually substantial doses) with excess incidence of one or another kind of cancer are compatible with linear relationships, though not necessarily excluding other relationships in the same or in lower dose ranges. Furthermore, the analysis of epidemiologic data often involves the selection of single values to characterize radiation exposure of collective subgroups as the significant dose parameter under conditions of nonuniform exposure and exposure rate, with neglect of dose rate. These procedures tend to preimpose linearity on the relationship and already contribute a presumption of linearity, since the linear hypothesis is the only one that normally permits these procedures.

General Aspects of Dose Rate, Distribution, and Relevant Dose

Marked reduction of overall radiation dose rate from intense exposure down to low rates by protraction of exposure or by fractionation of exposure over extended periods of time permits less interaction among the total ionizing events and permits more recovery of cells and tissues from radiation injury, to a much greater extent in the case of low LET radiations than in the case of high LET radiations.

Substantial reduction of the overall dose rate for a dose that, as an intense exposure, is in excess of the optimal dose to cause maximal carcinogenic effect may increase the carcinogenic effect by reducing excessive waste of dose, excessive damage of tissue, or the life-shortening effect of the intense exposure. Substantial reduction of overall dose rate of a dose that, as an intense exposure, is optimal or below optimal for maximal carcinogenic effect may reduce the carcinogenic effect of the total dose.

Under circumstances of prolonged protraction or fractionation of radiation dose, there is considerable uncertainty as to the portion of the total accumulated dose required for the induction of the cancer and that which is superfluous or wasted. For each individual it takes a certain amount of time to accumulate the induction dose, i.e., the dose required to assure that a cancer will be temporally advanced and/or absolutely induced and appear within his remaining life-span. After this induction dose has been accumulated, it takes some time for the mechanisms of induction to be completed and for the tumor to grow and appear.

A particular induction dose takes a relatively long time to accumulate at a relatively low dose rate, and this longer time is taken at the expense of time available for the latent period even if the dose rate does not influence the required size of the induction dose. To the extent that reduced dose rate does reduce the carcinogenic effect, the required induction doses may be larger at the lower dose rates and take still more time to accumulate at still greater expense of available latent period.

Nonuniformity of microdistribution of dose within the tissue of interest and among individuals of a study group with respect to this tissue and the associated problems of dosimetry and expression of relevant target dose also cause considerable uncertainty as to the relevant induction dose. The existence of "hot spots" of radioactive isotopes in tissues, e.g., alpha-particle-emitting isotopes, is a particularly notable example. There is uncertainty as to whether the relevant induction dose for carcinogenesis in individuals is more closely related to doses in or closely around the "hot spots" or in more distant regions of more diffuse distribution of the isotope.

PATHOGENESIS OF RADIONUCLIDE-INDUCED TUMORS

The individual and essential effects of radiations from internally deposited radioactive isotopes on cells are qualitatively similar to those caused by radiations from external sources. In addition, sufficient amounts of certain isotopes may also exert chemical influences upon cells and tissues that are probably much less well known.

The distribution and the degree of radiation effects, including neoplastic effects, in the body from internal radioactive isotopes are conditioned by several factors, among which are:

1. Physical-chemical form.
2. Amount administered.
3. Route of administration.
4. Changing tissue distribution and rate of excretion.
5. Radioactive decay of isotope and its daughters; type and energy of radiation(s); LET; and RBE (relative biological effectiveness).
6. Radiosensitivity and neoplastic susceptibility of irradiated tissues.

Some radioactive isotopes (e.g., tritium or sodium), upon deposition in blood, become widely and diffusely deposited throughout the body tissues. When given in sufficient amounts, they produce a distribution and pattern of histopathologic effects similar to those produced by total-body irradiation from external sources. Those isotopes deposited in blood which become highly concentrated and localized in certain tissues (e.g., radium in bone or iodine in thyroid) irradiate primarily these and adjacent tissues. They also may affect indirectly certain physiologically dependent tissues at a distance from the site of

deposition or other tissues *en route* to sites of localization. Intermediate in this respect are radioactive isotopes that, upon deposition in blood, become relatively concentrated in several tissues, with graded lower concentrations in many other tissues (e.g., polonium or cerium).

Insoluble, poorly absorbed compounds of radioactive isotopes, when deposited in extravascular locations in the body, tend to remain there and primarily irradiate tissues in the region of initial localization, as in the inhalation of intratracheal administration or intradermal injection of such compounds.

The carcinogenic effects of internally deposited radioisotopes are determined by the localization of the absorbed radiation energy and the relative susceptibility of the irradiated tissues for induction of neoplastic response. The widest assortment of tumors is caused by isotopes that are distributed relatively uniformly within the body. Radioisotopes that become highly concentrated in few tissues tend to enhance neoplastic development much more in those tissues and nearby tissues than in other tissues, depending considerably upon the tissue penetration of the radiations emitted.

Radioisotopes that concentrate highly in bone may cause not only bone tumors but also neoplasms of other nearby tissues irradiated, including blood-forming tissue (e.g., leukemia), epithelium lining sinuses surrounded by bone, and the pituitary. Radioisotopes that concentrate in liver as well as skeleton may cause a wider variety of cancers. For example, intravenous injection of ^{144}Ce can cause not only tumors of bone and liver but also tumors of stomach and endocrine glands, apparently as a consequence of irradiation of these organs by beta particles from the isotope deposits in the liver. A similar spectrum of induced tumors can develop after injection of ^{147}Pm or ^{91}Y. Liver tumors, in addition to bone tumors and carcinomas of paranasal sinuses, are caused by injection of ^{239}Pu, which concentrates in liver, on bone surfaces, and in osteoid tissue. Intravenous injection of the alpha emitter ^{210}Po with the formation of colloidal aggregates in the blood results in especially high concentrations in various soft-tissue organs with abundant reticuloendothelial cells (lymph nodes, spleen, liver, and bone marrow) and in kidney, the chief route of excretion. The result is the induction of tumors in a wide variety of tissues, especially in liver, kidneys, connective tissue, vasculature, adrenal glands, and testes.

Most of the radionuclide-induced neoplasms, excepting many of the endocrine-gland neoplasms, appear to be caused by mechanisms that are largely localized within the irradiated tissues.

For many of the tumors of endocrine tissue, part of the tumor-promoting factor is provided by the tissue degeneration and disorganization in the organ in which the tumor will arise, but the remaining and often larger part of the proliferation-promoting factor is the stimulus of hormones from other endocrine glands either in normal amounts or in enhanced amounts owing to the stimulus of the hypofunction of the organ of tumor origin associated with the tissue degeneration and disorganization in that organ.

For example, the radiation induction of mammary carcinomas or adenomas usually depends upon the presence of normally functioning ovaries, which may explain the difficulty of inducing mammary carcinomas in males, although fibrosarcomas may be induced. Apparently mammotropic hormone can also act as a promoting agent, as administration of mammotropic hormones to ovariectomized irradiated animals can reverse the inhibition of mammary-tumor development caused by ovariectomy.

Total-body irradiation of mice can shorten the onset of pituitary tumors to degrees proportional to the shortening of life-span, without markedly increasing absolute incidence. The tumors are predominantly adrenotropic and mammotropic in female mice, and ovariectomy before irradiation almost completely prevents pituitary-tumor development. Head–neck irradiation causes similar increase in pituitary tumors, as compared with total-body irradiation, but thyrotropic tumors are more frequent. Abdominal irradiation causes no increase. Thus radiation effects on various endocrine organs in addition to the pituitary may be involved as indirect components in a complex mechanism.

Interference with thyroid–pituitary hormonal relationships by radiation damage of the thyroid can result in the development of thyroid tumors as well as pituitary tumors. Sustained depression of thyroid hormone production elicits a persistent increase in production of thyroid-stimulating hormone by the pituitary, which stimulates compensatory hypertrophy and proliferation of thyroid follicular epithelium, with eventual formation of adenomas and, later, carcinomas of the thyroid. However, it appears that the induction of thyrotropic pituitary tumors in much greater incidence than thyroid tumors by irradiation of the thyroid gland seems to require marked destruction of the thyroid to greatly reduce its responsiveness to stimulation for proliferation, whereas the induction of a much higher incidence of thyroid tumors than of pituitary tumors by irradiation of thyroid requires a degree of thyroid damage sufficient to elicit a pituitary thyroid-stimulating-hormone response but not prevent proliferative response in the remaining thyroid epithelium.

Tumors of other endocrine glands and endocrine components of gonads appear to be induced also by complex mechanisms involving interglandular hormonal stimuli in the promoting processes, e.g., pituitary gonadotropins elicited by gonadal damage.

Radioiodine Induction of Pituitary, Thyroid, and Other Tumors

Iodine-131, which concentrates highly in the thyroid, can induce pituitary tumors in mice when the dose is large enough to cause virtually complete destruction of the thyroid gland, with marked atrophy, stenosing arteritis, and fibrosis. The deficiency of thyroid hormone production causes a sustained thyrotropic stimulation by the pituitary that leads to multifocal development of thyrotropic pituitary tumors that are dependent, i.e., responsive to correction of

the endocrine effect that promoted them. Near-total surgical thyroidectomy also can cause dependent thyrotropic pituitary tumors, suggesting that such neoplasms induced by ^{131}I might be induced solely by indirect mechanism, merely by depression of thyroid function. The autonomy of pituitary tumors induced by irradiation modes in which both pituitary and thyroid are irradiated suggests that irradiation of the cells of tumor origin causes irreversible cellular modifications that confer cancerous autonomy on the tumor cells.

Doses of ^{131}I that damage thyroid but spare some epithelium capable of proliferative response to thyroid-stimulating hormone cause thyroid carcinomas, preceded by patchy hyperplasia and formation of nodular adenomas. Antithyroid agents, such as thiouracil, iodine-deficient diet, or subtotal thyroidectomy, can elicit the thyrotropic pituitary response and can act synergistically with radioiodine radiation to cause thyroid tumors. Irradiation of one lobe of the thyroid causes adenomas in both lobes but carcinomas largely in the irradiated part.

The effectiveness of ^{131}I for induction of thyroid tumors is about one-tenth that of brief X- or gamma irradiation. The much lesser effectiveness of ^{131}I, as compared with mixtures of ^{132}I, ^{133}I, and ^{135}I and with external irradiation, may be due to its nonuniform distribution in follicular colloid and the relatively low energy of its beta particles, resulting in relatively nonuniform distribution of radiation dose and less uniform damage. The high energy of the beta particles from the other radioiodines and the more uniform radiation dose and damage from these radioiodines and external radiations, together with the higher rate of irradiation in these cases, may explain the differences in effectiveness as compared to ^{131}I.

The thyro-pituitary hormonal disorders caused by thyroid irradiation may result in more-widespread neuroendocrine disturbances and tumors of still other endocrine glands and physiologically related organs, such as tumors of the adrenal cortex, parathyroid, ovary, uterus, mammary gland, pancreas, testis, and prostate.

Astatine-211, an alpha-emitting homologue of iodine that concentrates in the thyroid gland, can also cause tumors of the thyroid, pituitary, adrenal cortex, and mammary gland.

Bone Tumors Induced by Radionuclides in Bone

Bone tumors have been induced experimentally by internal administration of many bone-seeking radioactive isotopes, including radioactive strontium, calcium, phosphorus, plutonium, radium, mesothorium, radiothorium, americium, neptunium, and cerium.

The bone tumors seem to be induced by a direct, localized mechanism involving localized tissue damage and disorganization as the promoting factor. The tissues that seem to be of prime importance in the neoplastic response are the osteogenic tissues at the surface of bone and in or near zones of