The Dose-Response Relation in Radiation-induced Cancer*

A. C. UPTON

(Biology Division, Oak Ridge National Laboratory,† Oak Ridge, Tennessee)

SUMMARY

Although ionizing radiation can apparently induce neoplasms of virtually all types, the relation between tumor incidence and dose varies, depending on the type of neoplasm, constitution of the host, conditions of irradiation, and other variables. Owing to statistical limitations, however, the existing data fail to provide an unambiguous picture of the dose-response relation for any form of cancer. More adequate data are, therefore, needed not only for estimating the hazards to be expected from small doses of radiation but for analyzing the mechanism of carcinogenesis.

The relation between the absorbed dose of a carcinogenic agent and the probability of neoplasia is of scientific as well as practical interest. Insight into this relation at the cellular level would help to elucidate not only the mode of action of the carcinogen but the nature of the neoplastic transformation itself. It would also, of course, facilitate setting of permissible exposure levels for safeguarding human beings against overexposure to the carcinogen in question.

Because it has been observed that large doses of ionizing radiation may cause leukemia, bone tumors, and others form of cancer, there is growing concern over the carcinogenic hazard of increasing environmental radiation from man-made sources (64, 69, 81). Existing data, however, are not adequate to permit confident estimation of the risks of small increases in background radiation, which will be discussed in the following. This and other aspects of radiation carcinogenesis have been reviewed elsewhere (7–9, 13, 27, 28, 48, 52, 67, 77).

CHARACTERIZATION OF THE DOSE RESPONSE

Quantitative measurement of carcinogenesis.—The carcinogenic hazard of exposure to radiation may be gauged by several types of response (11).

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To fully explain the action of radiation, however, which is important in evaluating the significance of human and animal data, it is necessary to know the probability of neoplasia per cell in relation to the cellular dose of radiation. Determination of the latter relationship is complicated in vivo by many variables, e.g., variation among cells in radiosensitivity and in the effective dose of radiation, the influence of systemic factors on the response of the cell to carcinogenic stimuli, variable anticarcinogenic and cocarcinogenic effects of radiation at different dose levels through side effects or toxicity, and difficulty in distinguishing between multiple primary neoplasms and metastases. Because of these variables, the kinetics of carcinogenic reactions in vitro cannot be analyzed as readily as those of other types of cellular reactions in vitro. For this reason, and because induction of radiation cancer in vitro is not yet experimentally practical, existing dose-response data are limited almost exclusively to one or more of the following gross parameters: (a) crude or age-adjusted incidence of cancer (i.e., proportion of individuals in a given population developing neoplasms), (b) induction period or age-distribution of neoplasms, and (c) number of neoplasms per individual.

Radiologic factors.—The effectiveness of a given dose depends in part on the duration of irradiation and on whether the dose is absorbed in a single exposure or in successive exposures at various intervals. Documented in sections to follow, the carcinogenic effectiveness of ionizing radiation generally diminishes as the dose rate is reduced,
with several notable exceptions. As yet, however, since relatively little quantitative information about the influence of time-intensity factors is available, this question remains poorly resolved. Hence, it is not possible to extrapolate from the effects of radiation at relatively high dose rates to predict results of low-level exposures at dose rates approaching the natural background level.

The ion density, or linear energy transfer (LET), of the radiation may also influence its carcinogenic effectiveness, densely ionizing particles being generally more effective than sparsely ionizing electromagnetic waves (86). The relationship between effectiveness and LET is not simple, however, effectiveness apparently being maximal at intermediate levels of LET. Unfortunately, data are not available in a single instance to define accurately the influence of LET on the dose response over a wide range of LET and dose.

Host factors.—The effects of constitutional, or host, factors on the response also deserve mention. These include genetic background (species, strain, race), maternal age, age at time of exposure to the carcinogen, sex, hormonal status, metabolic activity, and other variables (84). Because of the profound influence of these factors, the dose response may vary profoundly within the same inbred population, not to mention variation from one population to another.

Environmental factors.—Although their effects are less well characterized than those of the aforementioned variables, factors such as diet, ambient temperature, oxygen tension, population density, epidemiologic agents (parasites, bacteria, viruses, immunity), and extraneous physical and chemical factors have been shown to affect the development (35) of Japanese atomic bomb survivors (Table 1), patients given radiotherapy for ankylosing spondylitis (Table 2), radiologists exposed occupationally to radiation (35), and children irradiated over the mediastinum in infancy for thymic enlargement or for other reasons (Table 3). Smaller numbers of cases have also been reported among patients treated with 32P for polycythemia vera (63) and with 121I for thyroid cancer (40). The number of cases in patients treated with 131I for hyperthyroidism does not exceed that to be expected from natural causes (89). Although various statistical limitations (44) seriously weaken any conclusion that may be drawn from the existing data concerning the precise relation between radiation dose and leukemia incidence, particularly at low-dose levels, the data have been subjected to many analyses, with varying interpretations.

The major increase in all irradiated populations analyzed to date is in the acute and chronic

### TABLE 1

**LEUKEMIA IN HIROSHIMA ATOM BOMB SURVIVORS, 1950–1957***

<table>
<thead>
<tr>
<th>Distance from hypocenter (M)</th>
<th>Dose (rad)†</th>
<th>Cases of leukemia</th>
<th>No. persons exposed</th>
<th>Incidence per 10^6 per year</th>
<th>Estimated standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>700–899</td>
<td>2620</td>
<td>3</td>
<td>210</td>
<td>1790</td>
<td>1020</td>
</tr>
<tr>
<td>900–1099</td>
<td>1060</td>
<td>6</td>
<td>789</td>
<td>950</td>
<td>390</td>
</tr>
<tr>
<td>1100–1299</td>
<td>430</td>
<td>6</td>
<td>2100</td>
<td>355</td>
<td>145</td>
</tr>
<tr>
<td>1300–1499</td>
<td>177</td>
<td>2</td>
<td>3274</td>
<td>250</td>
<td>90</td>
</tr>
<tr>
<td>1500–1699</td>
<td>77</td>
<td>2</td>
<td>3615</td>
<td>293</td>
<td>50</td>
</tr>
<tr>
<td>1700–1899</td>
<td>34</td>
<td>0</td>
<td>3512</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1900–1999</td>
<td>19</td>
<td>0</td>
<td>1305</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2000–2499</td>
<td>&lt;0.1††</td>
<td>0</td>
<td>342,279</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>2500–4999</td>
<td>&lt;0.01††</td>
<td>0</td>
<td>342,279</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>5000–9999</td>
<td>&lt;0.01††</td>
<td>1</td>
<td>342,279</td>
<td>29</td>
<td>9</td>
</tr>
</tbody>
</table>

*From Heyssel et al., 1960.
† Estimated air dose (neutron plus gamma) at center of distance interval, in a typical Japanese-type frame house (sample limited to persons in such housing to minimize variations in dose from differences in shielding) unless otherwise specified.
††Dose unrestricted as regards shielding.

not available in a single instance to define accurately the influence of LET on the dose response over a wide range of LET and dose.

HUMAN DATA

**Leukemia.**—Of the neoplasms induced by radiation in human beings, leukemia is the best characterized in terms of dose response. The early literature on leukemia induction in man has been reviewed elsewhere (27).

Quantitative information about the relation between leukemia incidence and radiation dose is available primarily from epidemiological studies...
myelogenous types of leukemia. Assessment of the increase, however, has not always taken into account age-specific variations in the spontaneous incidence of different hematologic types of leukemia nor the possible variation of the induction period with hematologic type and with radiation dose (75). Another shortcoming in the data is the uncertainty associated with retrospective estimation of the radiation dose (19, 21, 35). Moreover, since radiation is not distributed uniformly throughout the bone marrow or other parts of the body, particularly in those exposed to partial-body radiation, the choice of dose appropriate for analysis of the leukemia data (i.e., mean integral dose to whole body, mean integral dose to marrow, maximal dose to marrow, etc.) varies, depending on the mechanism of leukemogenesis postulated (18).

The interpretation by Lewis (55) that the relation between leukemia incidence and dose is linear has been criticized by Burch (13), who suggested that the leukemia incidence varies more nearly with the square of the dose (Chart 1). Brues (9, 10) and Mole (68), on the other hand, have pointed out that the data are also compatible with other interpretations (Chart 2). Unfortunately, none of the alternative dose-response functions can be conclusively verified or refuted at present. Seemingly at variance with any of them, however, is the evidence suggesting that prenatal exposure to an x-ray dose of the order of 1 rad may nearly double the risk of leukemia subsequently in childhood (80). Although such data have not been consistently confirmed and are difficult to interpret for a variety of other reasons (20, 35), they suggest that susceptibility to leukemia induction may be relatively greater in the fetus than later in life.

Further attesting to the influence of age on the

| TABLE 2 |
| LEUKEMIA IN PATIENTS IRRADIATED FOR ANKYLOSING SPONDYLITIS* |

<table>
<thead>
<tr>
<th>Mean dose to spinal marrow (r)</th>
<th>No. men exposed</th>
<th>No. many-years at risk after irradiation</th>
<th>No. cases of leukemia†</th>
<th>Incidence per 10^6 per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2750 or more</td>
<td>45</td>
<td>151</td>
<td>1</td>
<td>6365</td>
</tr>
<tr>
<td>2500-2749</td>
<td>44</td>
<td>283</td>
<td>3</td>
<td>2318</td>
</tr>
<tr>
<td>2250-2499</td>
<td>118</td>
<td>509</td>
<td>4</td>
<td>928</td>
</tr>
<tr>
<td>2000-2249</td>
<td>172</td>
<td>939</td>
<td>2</td>
<td>551</td>
</tr>
<tr>
<td>1750-1999</td>
<td>305</td>
<td>1550</td>
<td>3</td>
<td>478</td>
</tr>
<tr>
<td>1500-1749</td>
<td>500</td>
<td>2437</td>
<td>3</td>
<td>733</td>
</tr>
<tr>
<td>1250-1499</td>
<td>938</td>
<td>5098</td>
<td>3</td>
<td>169</td>
</tr>
<tr>
<td>1000-1249</td>
<td>2324</td>
<td>10,632</td>
<td>3</td>
<td>699</td>
</tr>
<tr>
<td>750-999</td>
<td>2368</td>
<td>11,654</td>
<td>4</td>
<td>459</td>
</tr>
<tr>
<td>500-749</td>
<td>1912</td>
<td>10,120</td>
<td>6</td>
<td>242</td>
</tr>
<tr>
<td>250-499</td>
<td>1708</td>
<td>10,339</td>
<td>3</td>
<td>216</td>
</tr>
<tr>
<td>Under 250</td>
<td>1153</td>
<td>8184</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* From Court-Brown and Doll, 1957.
† Includes presumptive diagnoses.

| TABLE 3 |
| CANCER IN CHILDREN IRRADIATED OVER THE MEDIASTINUM IN INFANCY* |

<table>
<thead>
<tr>
<th>Study</th>
<th>No. children</th>
<th>Cancer of thyroid</th>
<th>Adenoma of thyroid</th>
<th>Leukemia</th>
<th>Other cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson et al. (1955)</td>
<td>1568/1933</td>
<td>11/0</td>
<td>5/0</td>
<td>7/0</td>
<td>3/0</td>
</tr>
<tr>
<td>Saenger et al. (1960)</td>
<td>1644/3777</td>
<td>11/0</td>
<td>7/0</td>
<td>1/3</td>
<td>6/1</td>
</tr>
<tr>
<td>Latourette and Hodges (1959)</td>
<td>867/0</td>
<td>1/0</td>
<td>0/0</td>
<td>2/1</td>
<td>0/0</td>
</tr>
<tr>
<td>Snegireff (1959)</td>
<td>148/168</td>
<td>2/0</td>
<td>5/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Conti et al. (1960)</td>
<td>1564/2923</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Total</td>
<td>3725/3795</td>
<td>25/0</td>
<td>17/0</td>
<td>10/3</td>
<td>10/0</td>
</tr>
</tbody>
</table>

* Modified from Saenger et al. (1960).
dose response are the higher proportion of acute leukemias in the Japanese atomic bomb survivors irradiated in childhood than in those irradiated in adult life (75) and the apparently greater increase in total incidence among children (37). The incidence appears to increase with age, however, among British spondylitic patients, from which it has been suggested that racial and environmental differences may also affect the dose response (18). That spondylitis itself probably predisposed to leukemia in the British cases (1) is a factor which may also have influenced the age-specific rate of the disease in this group.

Whether the induction period, as well as the incidence, of leukemia is related to the radiation dose is yet to be established, but the Japanese data suggest that it may vary inversely with the amount of radiation absorbed (37). The earliest Japanese cases were noted within ~8 years after exposure, and the incidence among those most heavily irradiated was maximal within 4–8 years. Among the spondylitis patients developing leukemia after a single exposure, the induction period was 4–5 years, exceeding 5 years in only one case (18). The peak incidence of chronic granulocytic leukemia occurred appreciably earlier than that of acute leukemia among the Hiroshima survivors exposed within 2,000 meters of the hypocenter (Chart 3); however, the relation between hematologic type and latency must be further evaluated for the influence of radiation dose and age at irradiation.

**Bone tumors.—** It is well established that external radiation or internally deposited radioelements can cause the formation of bone tumors (27). The most extensive dose-response data come from studies of persons who have ingested radium (Table 4). Estimation of the radiation dose in such persons is complicated, however, by the nonuniform distribution of radium within the skeleton and by variation among individuals in the rate of excretion of the element (58, 62). Thus, measurement of the amount of radium in the body at any one time does not provide a precise
hospital inmates). Despite these possible sources of error it is noteworthy, as observed by Marinelli (62), that the curve approximates the dose-response pattern obtained experimentally with inbred mice.

Other neoplasms.—Although a wide variety of neoplasms besides leukemia and osteosarcoma have been observed to develop in irradiated tissues (27), none has occurred in large enough numbers to provide data useful for dose-response calculations, with the possible exception of carcinomas of the lung and skin.

The common occurrence of squamous-cell carcinoma of the skin among early radiologists is well known (39, 48), and, although safety precautions have all but eliminated it as an occupational disability, the hazard persists. Concerning the relation of this effect to dose, however, no statistically adequate data are available, but the risk of the neoplasm has been observed to vary with the severity of preceding radiodermatitis. Previous authors have estimated that the acute carcinogenic dose must exceed 1000 r, although the chronic dose may be less than 4 r per day (36).

The development of squamous-cell carcinoma of the lung in 44-75 per cent of pitchblende miners in Saxony and Bohemia is generally considered to be another historical example of radiation carcinogenesis (90). However, the significance of irradiation from inhaled radon (which is present in an average concentration of $3 \times 10^{-9}$ curie per liter of air in the mines) and from internally deposited radioelements absorbed from dust and water has been questioned because of the possible etiologic influence of other extrinsic and intrinsic factors (59, 90). Hence, although it has been estimated from measurements of the radioactivity in necropsied miners that 10,000 hours of exposure to the air of the mines was a minimal exposure time required for tumorigenesis (4), no confident definition of the dose-response relation is possible without more refined data.

Concerning neoplasms of other sites, a dose-dependent increase in the over-all rate of cancers other than leukemia is suggested by statistics for Hiroshima survivors (33), but the nature and significance of the increase remain to be disclosed.

TABLE 4
INCIDENCE OF BONE CANCER IN RELATION TO SKELETAL RADIATION DOSE*

<table>
<thead>
<tr>
<th>Skeletal dose†</th>
<th>No. persons</th>
<th>Incidence per $10^5$ per year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>10.8</td>
<td>30</td>
<td>1900</td>
</tr>
<tr>
<td>5.2</td>
<td>19</td>
<td>1836</td>
</tr>
<tr>
<td>3.0</td>
<td>196</td>
<td>493</td>
</tr>
<tr>
<td>0.06</td>
<td>10^4</td>
<td>6.20</td>
</tr>
<tr>
<td>2.2 $\times 10^{-3}$</td>
<td>10^6</td>
<td>1.77</td>
</tr>
<tr>
<td>1.0 $\times 10^{-3}$</td>
<td>4 $\times 10^6$</td>
<td>1.91</td>
</tr>
<tr>
<td>9 $\times 10^{-4}$</td>
<td>3.5 $\times 10^6$</td>
<td>1.97†</td>
</tr>
</tbody>
</table>

* From Marinelli (1938).
† Skeletal dose in units equivalent to 1 μc. of Ra226 + 0.3 μc. daughters permanently fixed in skeleton.
‡ Data for population of Chicago, 1940-1950 (incidence excludes cancer of jaw).

From the preliminary data it would appear that the dose-incidence correlation characteristic of leukemia is not unique for this neoplasm only.

Another neoplasm, the incidence of which may be highly correlated with exposure to radiation, is carcinoma of the thyroid in childhood. Too few cases have been recorded to provide quantitative dose-response data, but the incidence of this disease is significantly higher than normal in children irradiated over the mediastinum in infancy (Table 3). Although observed more frequently in children irradiated for thymic enlargement than in others, this difference may be attributable to the larger port size (and thus larger amounts of radiation) generally used in radiotherapy of children with enlarged thymuses (17), but its relation to other factors cannot be excluded.

ANIMAL DATA

Leukemia.—The induction of leukemia by radiation has been studied in mice of several strains. With few exceptions the data are restricted to but one or two dose levels and apply chiefly to lymphomas, since other forms of leukemia are less common in mice. Furthermore, in most stud-
ies no distinction was made between different hematologic types of the disease, and, because the various types of lymphomas and other leukemias differ in dose-response relationships, results of such studies are equivocal.

In mice of most strains, radiation-induced leukemia tends to arise in the thymus as lymphosarcoma within 1 year after irradiation. The relation between the incidence of this disease and the dose is complex and depends upon many radiological variables and host factors. When the radiation is administered in a single exposure early in life, a sigmoid dose-response curve is obtained, the slope and intercept of which vary with the strain and sex in question (Chart 5). When the radiation is administered in several successive exposures, the incidence varies not only with the total dose but with the number of exposures, dose per exposure, and interval between exposures (42). Under conditions of protracted intermittent irradiation, intermediate dose rates may be more leukemogenic than higher or lower rates (54, 60). Although the basis for these variations is unknown, they imply an interaction between radiation injury and reparative mechanisms; this is also suggested by the inhibition of leukemogenesis afforded through shielding of hemopoietic cells or implantation of such cells after irradiation (84).

Analysis of lymphoma induction is further complicated by the occurrence of an indirect induction of neoplasia in nonirradiated thymus cells when such cells are grafted into a previously irradiated recipient (3, 43, 53). These findings, coupled with evidence that filtrable leukemogenic agents may be recovered from some radiation-induced thymic lymphomas (30, 31, 56, 82), are inconsistent with the theory that the lymphomas must result from a direct mutagenic action of radiation on the thymus. Instead, the indirect leukemogenic action of radiation under these circumstances must depend on derangement of the internal environment of the host, possibly with changes favoring virus activation, virus-host cell interaction, selection survival and proliferation of altered host cells, or similar effects. The specific susceptibility of thymus cells to leukemogenesis is unexplained but varies with age and strain (84). Its relation to the high rate of cell turnover in the thymus, to the existence of local growth-stimulating factors such as the lymphocyteosis principle (65), or to unrelated organ-specific factors favoring the localized action of leukemogenic viruses remains to be elucidated.

Lymphomas arising outside the thymus, or at least without grossly detectable involvement of the thymus, may be increased or decreased in frequency by radiation, depending on the strain of mouse irradiated. In CBA mice the incidence of such growths is greatly increased by 500 r of x-rays (68), whereas in RF (88) or LAF 1 (86) mice the incidence is markedly decreased by comparable doses. Since, however, the nonthymic lymphomas include a variety of ill-defined proliferative diseases of reticular tissues that tend to occur late in life, changes in their over-all incidence need to be re-evaluated after more specific hematologic classification and after adjustment of their frequency for intercurrent mortality.

An increase in the incidence of granulocytic leukemia has been noted after irradiation in mice of several strains (86). In RF mice the incidence is increased many times by a single exposure to 150 r, the dose-response curve leveling off and declining between 800 and 450 r (Chart 6). The shape of the curve in the dose region below 150 r is not precisely known, but the available data are more consistent with a quadratic than with a linear function, the incidence varying nearly as the square of the dose (Chart 6). The influence of radiological and physiological variables on the dose response has been less thoroughly studied than in the case of the lymphomas, but a number of influences have been identified, including dose rate, volume of tissue irradiated, age at irradiation, sex, and other variables (82). Preliminary data also suggest that filtrable agents may be involved in the pathogenesis of this disease (82), as in the case of thymic lymphomas. Whatever its pathogenesis, granulocytic leukemia is more
readily induced in RF mice by small amounts of radiation and by partial-body irradiation than are thymic lymphomas (82).

Concerning the influence of dose on the duration of the induction period, available data indicate an inverse relationship for both lymphoma and granulocytic leukemia; that is, the higher the dose, the shorter the induction period (88). Moreover, the induction period for thymic lymphoma tends to decrease more rapidly with the dose than that for granulocytic leukemia or for other neoplasms (86).

**Bone tumors.**—The tumorigenic action of internally deposited isotopes on the skeleton has been studied extensively in laboratory animals, but the data are relatively fragmentary for species other than the mouse. In mice given injections of one of a variety of radioelements at 70 days of age, the probability of bone tumor varies with the injected dose of radioactivity (Chart 7). From these data it is also clear that cancerogenic potency varies not only with the amount of radioactivity in the body but also with the radioemitter, owing to differences among radioelements in uptake, localization within the skeleton, retention (biological half life), rate of decay, and emission (energy and type of radiation). None of the curves in Chart 7 suggests a linear relation between the probability of neoplasia and the dose of radioactivity injected. On the contrary, the curves appear sigmoid and highly variable in slope. Analysis of the tumor-dose relation is further complicated by the observation that a given total dose of isotope may vary in tumorigenic effectiveness depending on the dosage schedule (34, 26) and nutritional status of the animal (20).

Concerning the influence of radiation dose on the induction period of bone tumors, an inverse relationship has been indicated in some experiments (Chart 8), but the significance of this relationship has since been questioned (34).

**Mammary gland tumors.**—The induction of breast tumors by irradiation in rodents has been reported by many observers. One of the most notable dose-response studies on mammary tu-

![Chart 6](image)

**Chart 6.**—Incidence of myeloid leukemia in RF male mice exposed to whole-body x-radiation at 5-10 weeks of age (from Upton and Furth, 1954; Upton et al., 1954, 1958; and A. C. Upton and A. W. Kimball, unpublished data).

![Chart 7](image)

**Chart 7.**—Incidence of osteosarcoma in mice in relation to dose of radionuclide injected (from Finkel, 1956).

![Chart 8](image)

**Chart 8.**—Daily probability of bone tumor development ($P_t$) in mice as a function of time after beginning of monthly injections of Sr$^{90}$. The figures beside the curves indicate dosages of Sr$^{90}$ in $\mu$g/gm (from Brues, 1949).

morigenesis is that of Bond et al. (5), who observed an essentially linear relation between the percentage of rats developing breast tumors and the radiation dose over the range 25–400 r. Interpretation of these results is hampered, however, by several factors. First, the analysis was made when the animals were only 11 months old, after which age the incidence of spontaneous breast tumors in the controls increased progressively with time, thus greatly changing the slope, if not the shape,
of the dose-response curve; the data, moreover, are not representative of the final tumor incidence even at high-dose levels. Second, the dose-response curve was based on the pooled frequencies of breast neoplasms of all histologic types, some of which showed greater changes in incidence than others. Consequently, if radiation affected the probability of different types of tumors in different ways, the relation between the over-all incidence of assorted tumors and the dose may have been fortuitous. In LAF1 mice exposed to γ-rays, for example, the incidence of mammary sarcomas decreased with dose, whereas the incidence of carcinomas showed the opposite relationship (86).

The relation between breast tumor incidence and dose is further complicated by the influence of hormonal activity and other extraneous variables. Thus, ovarian function enhances the development of radiation-induced mammary tumors in mice (34, 61) and rats (21) as it affects spontaneous mammary tumors in these species (7). The dose-dependent reduction in the incidence of mammary cancer in C3H mice (71) and of mammary sarcomas in LAF1 mice (86) may therefore conceivably represent the effects of radiation on the endocrine system rather than any direct "prophylactic" effect on the breast itself, although the latter mechanism cannot be excluded. Attempts to implicate the mammary tumor agent, or milk factor, in the pathogenesis of radiation-induced breast tumors have been unsuccessful to date (60), but such attempts have been inadequate by modern standards.

Ovarian tumors.—The well known tumorigenic action of radiation on the ovary of the mouse is dependent on abnormal gonadotrophic stimulation of interstitial cells in the ovary incident to bilateral sterilization (14). Owing to the high radiosensitivity of germ cells in the mouse ovary, a significant increase in the incidence of ovarian tumors may be produced by a dose as low as 32 r, and doses above this level are consistently tumorigenic (85). Although 16 r has been observed not to increase detectably the incidence of ovarian tumors (85), the data are not adequate to indicate the existence of a threshold at this level. The shape of the dose-response curve in the region below 100 r remains to be defined; it is clear, however, that the incidence of ovarian tumors tends to decrease at very high dose levels (Chart 9). The tumorigenic effectiveness of radiation for the ovary also decreases with decreasing dose rate (Chart 9) and is dependent on the age of the mice at the time of irradiation, mice being relatively less susceptible shortly before birth than later in life (87).

The high susceptibility of the female mouse to sterilization and ovarian tumor induction has not been noted in other species. Whether similar but less marked carcinogenic effects on the ovary occur in other animals remains to be disclosed.

Lung tumors.—As yet only fragmentary data are available concerning the relation between lung tumor incidence and radiation dose, although bronchogenic and alveolar carcinomas have been reported in mice and rats subjected to intensive irradiation of the lung by locally deposited or implanted radioisotopes. The dosages involved are, however, difficult to evaluate because of inhomogeneities in geometry, although they appear high (Table 5). With known, lesser amounts of external penetrating radiation, the tumorigenic response of the lung is variable (86).

Skin tumors.—The development of cutaneous carcinomas and sarcomas at the margins of radiation burns has been noted repeatedly in animals. Although the incidence and type of tumors vary with the species and site exposed and with the dosage schedule, the depth of tissue irradiated is also a determining factor. Existing data, reviewed elsewhere (29), are not adequate to indicate the shape of the dose-response curve but suggest that relatively large amounts of radiation are required to cause a high incidence of skin cancers, except possibly under conditions in which promoting agents (76) or chemical carcinogens (15) are applied concomitantly.

Other tumors.—Limited dose-response data are available for a variety of additional neoplasms in experimental animals. From the few results summarized in Chart 10, it is evident that the relation between tumor incidence and dose is highly variable. The same results, however, sug-
gest that the relation between dose and induction period (or age-specific death rate) may be relatively constant; i.e., the mean age at death of mice dying with the tumors shown in Chart 10 was decreased to a similar extent for almost all types of tumors at any one dose level, whether the tumors were increased or decreased in frequency and whether they occurred early or late in life among controls. It remains to be disclosed whether this pattern is characteristic of radiation cancers in general or whether it is peculiar to growths induced by whole-body radiation, to certain types of tumors only, or to certain species and strains of animals.

One apparent exception to the above pattern is the effect of radiation on the development of neoplasms having a high spontaneous incidence; i.e., sublethal irradiation has been observed not to hasten the onset or increase the frequency of lymphomas in mice of certain high-lymphoma strains (32, 46, 73) nor of hepatomas in mice of the hepatoma-prone CBA strain (16). Nevertheless, the variability of dose-response patterns for different neoplasms within the dose range 100–1000 r (Chart 10) may conceivably reflect merely differences in the range of the effective tumor-inducing dose for different growths rather than absolute differences in inducibility. Whereas in most experiments to date irradiation has not been observed to shorten the latency of leukemia in AKR mice, a pronounced acceleration was noted after a dose of 500 r administered at birth (50).

The tendency for the carcinogenic dose-response curve to eventually reach a saturation point and decline at high levels appears to be a consistent phenomenon (Charts 6, 7, 9, 10) with many types of neoplasms. It is particularly conspicuous in the induction of thyroid tumors by I$^{131}$ in rats (Chart 11), owing presumably to the extent of thyroid destruction at the higher dose levels.

![Chart 10](chart10.png)

**Chart 10.**—Incidence of various neoplasms in relation to age at death in (C57L x A/He)F$_1$ mice exposed to whole-body γ-rays when 6–12 weeks old (from Upton et al., 1960).

### TABLE 5

**Malignant Tumors after Pulmonary Deposition of Radioactive Particles***

<table>
<thead>
<tr>
<th>Material and radiation*</th>
<th>Tumor</th>
<th>Animals affected</th>
<th>Radiation dose (rad)</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Po$^{210}$ (alpha)</td>
<td>Squamous-cell carcinoma</td>
<td>2/15 rats</td>
<td>2,500</td>
<td>Scott (1957)</td>
</tr>
<tr>
<td>Pa$^{239}$O$_2$ (alpha)</td>
<td>Epidermoid carcinoma</td>
<td>2/16 rats</td>
<td>12,000– 20,000</td>
<td>Lisco (1959)</td>
</tr>
<tr>
<td>Ba$^{137}$ (beta)</td>
<td>Squamous-cell carcinoma</td>
<td>5/26 rats</td>
<td>200,000–900,000 at 100 μ from source</td>
<td>Cember and Watson (1958)</td>
</tr>
<tr>
<td>Cr$^{51}$ (beta)</td>
<td>Bronchogenic carcinoma</td>
<td>2/23 rats</td>
<td>30,000– 70,000</td>
<td>Kuschner et al. (1957)</td>
</tr>
<tr>
<td>Co$^{60}$ (gamma)</td>
<td>Lymphosarcoma and carcinoma</td>
<td>1/27 rats</td>
<td>2,400</td>
<td>Cember and Watson (1958)</td>
</tr>
<tr>
<td>Ce$^{141}$P$_2$ (gamma)</td>
<td>Squamous-cell carcinoma</td>
<td>1/37 rats</td>
<td>5,100</td>
<td>Cember (1957)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/23 rats</td>
<td>10,700</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7/36 rats</td>
<td>21,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/15 rats</td>
<td>250,000–400,000</td>
<td></td>
</tr>
<tr>
<td>Co$^{60}$ (gamma)</td>
<td>Epidermoid carcinoma</td>
<td>1/17 mice</td>
<td>12,000–400,000</td>
<td>Warren and Gates (1959)</td>
</tr>
<tr>
<td>Pa$^{239}$O$_2$ (alpha)</td>
<td>Squamous-cell carcinoma</td>
<td>1/41 mice</td>
<td>200,000–400,000</td>
<td>Wager (1955)</td>
</tr>
<tr>
<td>Rb$^{86}$O$_2$ (beta)</td>
<td>Bronchiolar</td>
<td>1/11 mice</td>
<td>4,000</td>
<td>Temple et al. (1959)</td>
</tr>
<tr>
<td>Rb$^{86}$O$_2$ (beta)</td>
<td>Lymphosarcoma</td>
<td>1/10 mice</td>
<td>300</td>
<td>Temple et al. (1959)</td>
</tr>
<tr>
<td></td>
<td>Alveolar-cell carcinoma</td>
<td>1/11 mice</td>
<td>4,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-differentiated tumor</td>
<td>1/33 mice</td>
<td>9,000</td>
<td></td>
</tr>
</tbody>
</table>

* From Bair, 1960.
INTERPRETATION OF DOSE-RESPONSE DATA

It is evident that adequate information is not available to indicate the quantitative relation between tumor incidence and radiation dose for any type of neoplasm in animals or man, particularly at dose levels approaching the natural background radioactivity of the environment, as has been emphasized previously (49). Furthermore, the data suggest that the dose-response curve may vary in slope and intercept, depending on the type of neoplasm in question, the constitution of the animal irradiated, the way in which the radiation is distributed in space and in time, and on various other influences. In no instance, recorded to date, has a linear relationship between neoplasia and radiation dose been adequately demonstrated. Consequently, attempts to estimate the carcinogenic hazards of exposure to small amounts of radiation, such as the average dose to the population from nuclear fallout, are necessarily speculative.

Nevertheless, despite the inadequacy of existing data, several generalizations appear warranted: First, all forms of ionizing radiation are carcinogenic. Second, tumors of virtually any histologic type may be induced by irradiation under appropriate conditions in susceptible subjects. Third, although the probability of neoplasia per unit dose of radiation varies with host factors, susceptibility to the carcinogenic action of radiation appears to be widely, if not universally, shared by different species of animals, including man. Fourth, the incidence of some types of neoplasms is greatly increased by relatively small amounts of radiation, and, in certain of these instances, the incidence and induction period are correlated with the dose, dose rate, volume of tissue irradiated, and linear energy transfer of the radiation. Fifth, indirect effects of radiation on the host are responsible for some types of neoplasms, indicating that radiation need not always be absorbed at the site of carcinogenesis to induce cancer.

From the practical standpoint, the establishment of permissible radiation exposure levels commensurate with public safety requires that the toxicity of small amounts of radiation be tentatively estimated, even by extrapolation from animal data when human statistics are lacking. In reckoning the carcinogenic hazards of fission products, for which it is to be hoped that human data never will materialize, the toxicity of an element relative to that of radium may be tentatively gauged from animal experimentation, if appropriate allowances are made for species differences in metabolism and dose distribution (25, 67). In making such extrapolations, however, questions arise for which there are yet no adequate answers (8, 12, 45); i.e., what is the significance of the induction period in carcinogenesis and its relation to accumulated dose of radiation and to the age and life span of the species? How can the dose response be adjusted to correct for intercurrent mortality from lethal effects other than cancer? To what extent do species differ in susceptibility to the carcinogenic effects of radiation? How may species differences in the geometry of irradiation affect the carcinogenic response?

From the theoretical standpoint, although it is disappointing that the existing dose-response data are not statistically more adequate, dose-response curves based on the incidence of cancer in populations of multicellular individuals cannot be interpreted in terms of cellular hit theory without serious reservations (91). The prevailing dose-response relationships favor the interpretation that cancer arises through multiple radiation-induced intracellular changes (66) such as mutations or chromosomal breaks (9, 13, 67) rather than through a single molecular alteration (5). Because, however, of statistical limitations, it is not yet feasible to define the kinetics of carcinogenesis or to prove the existence or absence of a threshold dose for carcinogenesis by extrapolation of the dose-response curve from regions of detectably significant dosage (41, 67).

More importantly, since cancer arises spontaneously through the presumably additive and cumulative effects of agents other than radiation and since the neoplastic transformation seems to be a multistage process, at least in certain instances the dose-response curve may vary, depending on
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the condition of the irradiated individual. Hence, for a heterogeneous population, the curve may represent not one but a combination of relationships which differ in their practical and theoretical implications. From the available data, no generalization can be made to account for the various dose-incidence relationships recorded. Furthermore, because of the side-effects resulting from large doses of radiation, existing data must be supplemented by information about smaller doses.

The problem of interpretation is complicated further by evidence that the induction of mutations by radiation and their subsequent expression may not follow simple one-hit kinetics but may depend on the dose rate and total dose (38) and by evidence that radiation may induce certain neoplasms through the activation of oncogenic viruses (30, 56, 82). Further evaluation of the carcinogenic action of radiation in terms of the somatic mutation or virus theories will, therefore, require not only more adequate dose-response data but considerably greater information about the effects of radiation on genes and viruses than is now available.

REFERENCES


64. Medical Research Council. The Hazards to Man of Nuclear and Allied Radiations. London: Her Majesty’s Stationery Office.
68. The Development of Leukemia in Irradiated Animals. Ibid., pp. 174-77.
The Dose-Response Relation in Radiation-induced Cancer

A. C. Upton


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