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Chapter V

Somatic Effects - Cancer

II. Introductory Material

A. Mechanisms of Radiation Carcinogenesis
B. Concepts of Somatic Effects

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II. INTRODUCTORY MATERIAL

A. MECHANISMS OF RADIATION CARCINOGENESIS

The evidence available suggests that cancer induced by chemical or physical carcinogens, such as ionizing radiation, involves a multistage process comprising the evolution of a succession of molecular and cellular perturbations expressed at cell and tissue levels. At the earliest stage of the process, the initiation phase, events may occur within a single cell cell or a small group of cells, which must then transform into a neoplastic element. Regulatory control mechanisms could preclude the promotion of transformed cells into malignant clonogenic tumor cells. Such a model could probably apply to the low dose range of carcinogens, at which effects on individual cells might be expected to predominate and at which cellular events would be independent of more gross cell population effects, such as as cell-killing, tissue disorganization, and progressive breakdown of normal normal homeostatic mechanisms.

The experimental radiobiologic findings *in vitro* and *in vivo* are difficult to analyze with any simple cell model. Nevertheless, mechanisms of radiation carcinogenesis can be defined, in part, on the basis of consistent experimental evidence provided by cancer biology, to involve a number of complex interactions: the induced neoplasm arises through multistage evolution; the stages involve complex interactions between physiocochemical changes caused by radiation and regulatory factors in the host; these regulatory factors (e.g., genetic, hormonal, immunologic, and physiologic) operate at various levels of biologic organization in the host to control cell growth, division, and differentiation and to maintain cellular and tissue homeostasis;

and deterioration of some or all of these regulatory control mechanisms leads to the promotion of tumor formation.

Any cell model must be considered a gross over-simplification. However, that the process is primarily a cellular one not requiring gross destruction of cells or tissue disorganization due to radiation is suggested by the fact that, in some animals, detectable effects on the rate of tumor development and progression occur at a dose of less than 1 rad of fast neutrons. The experimental data from in vitro cell transformation studies imply that the probability of tumor development is strongly influenced by radiation-induced events that cause alterations in individual cells by affecting them singly or in very small numbers.

Analysis of mammalian cellular radiobiologic experimental data on the initiation and transformation of tumor formation has centered on radiation effects on single cells and concerned primarily the induction of chromosomal aberrations, point mutation, virus activation, and inadequate or incomplete repair mechanisms. Dose-response data for radiation carcinogenesis, even at the lowest doses, suggest that evidence is lacking to postulate the existence of a threshold dose for tumor induction. Most data, at least insofar as low-LET x rays and gamma rays are concerned, suggest that the cumulative incidence of tumors might follow the general function:

$$I = (C+aD+bD^2)\, e^{-pD-qD^2}, \qquad \text{(ref.1)}$$

where I is the incidence of tumors in the irradiated-cell population, C is the control incidence, D the dose of radiation, and a, b, p, and q are constants. Such a dose-incidence model appears to hold for radiation-induced mouse and rat tumors and may very well apply, in general, to the situation in man. In

the case of x rays and gamma rays, the dose-incidence curves frequently rise with increasing dose and dose rate to some maximum, at which a plateau is reached, then turn downward, presumably because of excessive damage at high doses and dose rates - primarily excessive cell-killing. Accordingly, the mathematical function contains a linear induction term (aD) and a quadratic induction term (bD^2). The constants a, b, p, and q determine the slope of the dose-incidence curve at low doses and the shape of the curve at higher doses; these values are not known with precision and may vary with individual experimental circumstances. At lower doses and dose rates, the linear induction term would predominate; the quadratic term would profoundly influence the slope of the curve at higher doses and dose rates. On the basis of available experimental evidence, the radiation dose at which the linear and quadratic induction terms would contribute equally to tumor induction is not likely to be less than about 50-100 rads of low-LET radiation.

B. Concepts of Somatic Effects

Types of Effects

The relevant cytologic and cytogenetic effects of low-dose ionizing radiation, which give rise to somatic changes in exposed human and animal populations, are those which are ultimately manifested in recognizable lesions indistinguishable from those which appear spontaneously or are due to other kinds of toxic agents. These are primarily the induction of genetic mutations in the cell, chromosomal aberrations, cell-killing, teratogenesis, and carcinogenesis.[1,2,3] Each of these, alone or in combination, gives rise to delayed somatic effects that may fall into three classes - those in some way related to frequency of occurrence, varying with radiation dose, but not in severity with dose, and for which a threshold level may not exist; those in some way related directly to dose of radiation, both in severity and in frequency of occurrence, and for which a threshold level of dose may exist; and a combination of the two. The first class of effects are sometimes referred to as stochastic and, biophysically are considered to result from events in individual cells or small groups of cells (without cell lethality), thus permitting survival of mutated cells, which then continue to proliferate and divide.[4] Stochastic effects may be regarded as a function of radiation dose, without a threshold. Such effects would include the induction of genetic changes in somatic cells, chromosomal injuries, including the induction of genetic changes in somatic cells; chromosomal injuries, including aneuploidy; teratogenic effects; and carcinogenic effects.

Some effects are nonstochastic - that involve injury to cell populations and tissues, usually associated with extensive cell-killing and tissue disorganization, varying in severity and in frequency with dose, having a

threshold.[4] Thus, depending on the number of cells in the population damaged, the tissue response and disturbance of physiologic function may be manifested as cataractogenesis (induction of opacities in the lens of the eye), impairment of fertility and fecundity (decreased gametogenesis and gonadal cell damage), decreased hematopoietic activity (including impaired cellular immune response), and injury to blood vessels, connective tissues, and skin. It should be remembered that both stochastic and nonstochastic processes can occur in exposed subjects, and stochastic effects can be hereditary, i.e., can occur in future generations of the exposed populations. The most important somatic effect considered to arise from low-level exposure, and for which there may be no threshold, is the delayed radiation induction of neoplasms.

Dose-Response Relationships in Radiation Carcinogenesis

The International Commission on Radiation Protection,[5,6] the United Nations Scientific Committee on the Effects of Atomic Radiation,[7] and the NAS BEIR Committee[1] have attached great importance to the hypothesis of a linear dose-response no-threshold relationship for radiation carcinogenesis. However, it must be recognized that this has been done primarily for purposes of radiation protection; for some tissues and animals, radiation cancer may very well be governed by other nonlinear, multicomponent forms of dose-response relationships.[3,8-16] The linear dose-response relationship depends on three main quantities - the total number of cells in the population at risk, the total energy absorbed in the cells at risk, and the mean radiation dose. The interrelationship of these three essential determinants provides the notions of probability and of expectation of induction of radiation cancer.[9] The probability may best be defined as the fraction of cells that undergo neoplastic transformation, whereas the expectation is the probability

multiplied by the actual number of transformed cells yielding tumors. Any formulation of dose-response relationship for radiation carcinogenesis must regard each of the various physical characteristics (e.g., dose, dose rate, RBE and LET, dose distribution, and tissue geometry) and biologic characteristics (e.g., cellular sensitivity, genetic and immunologic factors, age, and sex) as factors that modify the basic dose-response relationship.

The most convenient formulation of the radiation dose-response relationship is a linear response without a threshold.[1,9] Mayneord and Clarke[9] have presented this in the form

$$\phi(p_c D) = p_c D.$$

The biologic response (ϕ) or effect - e.g., the number of tumors appearing in a homogeneous cell population or tissue - is expressed as a probability function of the cellular or tissue sensitivity (p_c) and of the radiation dose distributed in the tissue (D), i.e., the total energy absorbed in the tissue as a whole. At the cellular level, the response $\phi(p_c D)$ would represent the probability of a relevant biologic transformation in the cell, and p_c, the cellular radiosensitivity.

There can be numerous theoretical forms of nonlinear dose-response relationships for carcinogenesis in mammalian radiobiology.[3,8-15] The simplest is a response curve rising with the power of D at low doses, i.e.,

$$\phi(p_c D) = (p_c D)^h, \qquad (2)$$

where h is usually some small number, not necessarily an integer.[9] Cell survival and cell death are frequently studied dose-response functions. For low-LET radiation, the exponential form is commonly observed; this may be modified to the more complex form,

$$\phi_c(p\ D) = 1-(1-e^{-\lambda D\ h}), \qquad (3)$$

where h and λ are constants. Baum[15] has analyzed the dose-effect relations for tumors and cancers induced by low-LET radiation in drosophilae, mice, rats, and man and has demonstrated that an increase in incidence can often be represented by a simple power function of dose. At low doses, he represented the model to a first approximation by the multitarget, single-hit equation,

$$I = (1-e^{-D/D_o})^n, \qquad (4)$$

where I is the fraction of the population showing cancer incidence, D is the dose in rads, D_o is the mean dose per effect in a target, and n is the target number. In this regard, n may represent the number of specific mutational events that must occur for neoplastic transformation to ensue, e.g., the number of specific genes that must be mutated, specific molecular bonds that must be broken, or cells in a tissue that must be affected. This places the Mayneord-Clarke equation in the more conventional form. Account may be taken of heterogeneity of subdivisions of the population, with respect to their radiation response. For example, depending on the values of D_o and n, and with a dose exponent less than integer, the dose-response curve may be a slope gradually decreasing as a function of increasing dose, in contrast with

the usual linear function (where the dose exponent is 1.0), quadratic (dose exponent greater than 1.0), and threshold. The significance of such a composite curve is that the sensitive population yields a steep dose-response initially; that portion of the curve will be above the other curves at low doses and will thus predict even greater effects than the usual linear extrapolation from higher doses.[15]

Dose-response curves in the form of the linear-quadratic,--

$$\phi(p\ D) = a_c + a_0 D + a_1 D^2, \qquad (5)$$

a linear and dose-squared function--are often observed in experimental radiobiology, for both cytogenetic and somatic-cell effects.[3,9,10-14] Here, a_0 is the control frequency, and a_1 (or α) and a_2 (or β) are constants. Mayneord[9] and Clarke,[3] Upton,[1] Brown,[2] 13,14 and others[16] have provided examples of a number of experimental studies in mammals that demonstrate that the radiation response, as measured by the incidence of tumor induction (insofar as it is known), is sometimes linearly related to dose, and frequently it is not. Numerous examples from experimental animal data were reviewed in the 1977 UNSCEAR report.[16]

The dose-response relationship in experimental studies in animals is often a multicomponent one. In the case of radiation carcinogenesis, three distinct but interrelated components may sometimes be recognized: at low doses, around a few hundred rads, the tumor incidence initially increases linearly with dose (linear αD component); there is then an increase in dose to a maximum roughly according to some power law (frequently, a dose-squared βD^2 component); finally, at high doses 1,000-5,000 rads, the response curve "peaks," i.e., bends over and declines with increasing dose.[3,9,13,14,16]

Commonly observed dose-incidence saturation effects in experimental studies have been documented in a number of radiation cancers.[9,15] The tendency for the dose-incidence curve to peak was demonstrated well by Upton and colleagues[17] in RF mice; the dose-incidence curve for induction of myeloid leukemia in the mouse passes through a maximum at a neutron dose of about 100-200 rads. Upton[3] regarded such evidence as partial possible explanation for the curvilinear dose-incidence response for leukemia in atomic-bomb survivors of Nagasaki, who were irradiated almost entirely with gamma rays, whereas the response was more nearly linear in survivors of Hiroshima, where irradiation had a neutron component. Mole[10,11] has reported different relationships of dose-incidence responses of hematologic types of leukemia in atomic-bomb survivors, suggesting that the data were not sufficient to define a dose-incidence fit, that the different types of leukemia may represent very different types of diseases that are diverse in their pathogenesis and in their dose-response relationships, and that the data were too fragmentary to draw firm conclusions. However, the clinical evidence from the Nagasaki data may not be usable for assessing the influence of dose and dose rate in carcinogenic effects of low-LET radiation in human populations.[12] Nevertheless, although the Nagasaki data could imply a curvilinear dose-incidence relationship for the induction of leukemia by gamma rays, there is no reason to exclude a linear relationship. The evidence in the case of solid tumors appears to be consistent with both linear and linear-quadratic functions.[2,3] The extensive data on thyroid tumors[1,3,7,13,14,16] and on the breast cancers[16] from a number of studies are more consistent with a linear dose-incidence relationship, rather than a curvilinear one.[1,3,7,13,14,16] However, the epidemiologic evidence thus far implies that the dose-response relationships for carcino-

genesis, at least insofar as low-LET radiation is concerned, vary considerably in form, depending on the type of neoplasm, the cell type and tissue at risk, numerous host factors (including age, sex, environment, immunologic status, hormones, and the temporal and spatial distribution of dose), and the component of high-LET radiation that may be present. Thus, the dose-incidence curve for osteosarcomas induced by alpha-emitters generally appears to be linear in patients, whereas it appears to be more of a sigmoid function in radium-226 patients.[1-3,13,14]

The cause of the saturation effect at higher doses is not understood, but it is presumed to involve killing or sterilization of some potentially cancer-forming cells that might otherwise undergo mutation and transformation. This however, is not completely borne out by transformation studies of mammalian cells irradiated in culture.[18] Whatever the explanation for the shape of the dose-incidence curve for radiation carcinogenesis, any conclusions at present must remain tentative. The evidence, however, from both extensive experimental animal studies and the large body of data accumulated in epidemiologic surveys suggests that three important mechanisms are interrelated.[3] First, the radiation dose-response curves for all mutagenic processes in the somatic cell have similar forms, whether the effect measured is the induction of mutations, chromosomal injuries, cell lethality, cell transformation in culture, teratogenesis, or carcinogenesis. Second, common features for low-LET radiation, in general, include an increase in slope with increase in dose and dose rate, and this increased yield continues to some point at which high dose rates pass through a maximum. Third, for high-LET radiation with more densely ionizing tracks, the dose-incidence curve tends to have a steeper slope (the

incidence increases more rapidly with increasing dose), to assume a greater degree of linearity, and to be less dependent on dose rate.

These observations are derived primarily from extensive radiobiologic data on cell sterilization and, in large measure, may be quantified in the form of a complex function that has linear and quadratic components:[3,11,12]

$$Y = (C + aD + bD^2)e^{-\alpha D - \beta D^2} \qquad (6)$$

for carcinogenic effects, Y is the frequency (or incidence) of tumors induced in the mammalian cell population at risk; C is the control frequency expected in the population; D is the radiation dose absorbed; and a, b, α, and β are functions that account for dose-linear and dose-square responses, cell survival, and relationships of dose, dose rate, and LET.[3]

The mathematical model expressed in Equation 6 postulates that cancer induction results from somatic mutations that increase both linearly with the dose (the αD linear component) and quadratically with the square of the dose (the βD^2 quadratic component and develops in mutated cells that survive radiation injury. The precise values for the α and β constants are not known for most mammalian tissues, particularly for human cells. The experimental data suggest, however, that, for low-LET radiation (acute, high dose-rate), the linear and quadratic components may contribute equally to somatic effects in mammalian cells at doses of about 50-100 rads; i.e., $\alpha = \beta$ at 50-100 rads.[3] If this is correct, then at low doses (less than about 50-100 rads) and low dose rates of low-LET radiation the effect of the linear component will be greater than that of the quadratic component; i.e., $\alpha > \beta$ at less than 50-100 rads. The reverse would be true at high doses (greater than about 50-100 rads) and high dose rates; i.e., $\alpha < \beta$ at over 50-

100 rads. For high-LET radiation, however, the linear component would appear to predominate consistently at all doses and dose rates.[13,14] The conclusions to be drawn from the above model, if valid, are that, provided the values for the ratio of to for most carcinogenic effects of low-LET radiation are in the range of 50-100 rads or greater, linear extrapolation from data on human populations after exposure to 100-200 rads at high dose rates will not be likely to overestimate the risks at low doses and low dose rates by a factor of more than about 2-3.[3,13,14] However, these observations, based on a mathematical model, must remain conjectural, because interpretation of experimental and human studies is complicated by numerous variables, particularly intracellular radiation effects.[3]

Summary

The functional forms fitted to sufficiently detailed dose-response data from many of the studies considered in this report are special cases of the general form

$$F(D) = \alpha_0 + (\alpha_1 D + \alpha_2 D^2) e^{(-\beta_1 D - \beta_2 D^2)}$$

where D represents radiation dose in rads, F(D) is the incidence of cancer at dose D, and the parameters $\alpha_0, \alpha_1, \alpha_2, \beta_1$ and β_2 are constrained to be non-negative. This functional form, which has been discussed in a slightly more general version elsewhere,[3] can be viewed basically as a linear function in which α_0, α_1, and β_1 are essentially the parameters relevant to risk at very low doses, with modifications that allow the fitted curve to express upward curvature at low doses (α_2) and downward curvature at high

doses (β_2). Because there is a tradeoff between the number of parameters fitted and the accuracy of the parameters estimate (assuming the model to be valid), parameters α_2, β_1 and β_2 are retained only if their inclusion significantly improves the fit of the model to the data.

To simplify the various functional forms, F may be denoted;

$$F_1(D) = \alpha_0 + \alpha_1 D, \tag{8}$$

$$F_2(D) = \alpha_0 + \alpha_1 D + \alpha_2 D^2 \tag{9}$$

$$F_3(D) = \alpha_0 + (\alpha_1 D)e^{(-\beta_1 D - \beta_2 D^2)} \tag{10}$$

$$F_4(D) = \alpha_0 + (\alpha_1 D + \alpha_2 D^2)e^{(-\beta_1 D - \beta_2 D^2)} \tag{11}$$

Thus, F_1 is the linear form; F_2, the quadratic form with upward curvature; F_3, the quadratic form with downward curvature; and F_4, the most general form, with upward curvature at low doses and downward curvature at high doses. The curve-fitting procedure is an iterative, weighted, least-squares procedure.[19] On any given iteration, the weight corresponding to the observed rate (simple or age-standardized) at dose D is assumed to be the number of person-years (PY) at that dose (usually the PY corresponding to a dose interval with average dose D), divided by the current value of the fitted function at dose D. That is, rate times PY is assumed to correspond to a Poisson variate with rate equal to PY times F(D).

The functional forms (Equations 8-11) are inconsistent with the possibility of a threshold radiation dose, below which there is no excess cancer risk. It has been argued on radiobiologic grounds that the concept of threshold dose is inconsistent with plausible carcinogenesis mechanisms at

the level of a single cell.[20] On statistical grounds, however, the existence or nonexistence of a threshold dose is practically impossible to ascertain, unless there is a marked increase in cancer risk for doses only slightly greater than the presumed threshold. That is because the sample size required to estimate or test an absolute cancer excess is approximately inversely proportional to the square of that excess. For example, if the excess is truly proportional to dose, and if 1,000 control persons are required to test the cancer excess adequately at 100 rads, then about 100,000 in each group are required at 10 rads, and about 10,000,000 in each group are required at 1 rad. It may be possible to assert that no threshold exists at any dose. Thus, it does not appear possible to speculate on the possible existence of a threshold dose for radiation-induced cancer in the absence of compelling epidemiologic evidence, in the form of a consistently observed sharp increase in risk.

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