Radiation Carcinogenesis: The Sequence of Events

Complex interplay of many factors and mechanisms makes a simple dose-response relationship untenable.

Leonard J. Cole and Peter C. Nowell

In attempting to extend the pioneer studies of Furth (*1*) and others on radiation carcinogenesis in mice, we have used a number of experimental approaches. Variation in total radiation dose, dose rate, dose fractionation, and quality of radiation (for example, neutrons as compared with x-rays) have all been investigated as well as the effect of proliferative stimuli applied to certain target organs before and after irradiation. It has become increasingly apparent that such relatively simple concepts as dose-response curves (*2*) or "initiation" by a carcinogenic agent and "promotion" by a noncarcinogenic stimulus (*3*), while useful, are not adequate to explain some of the observed results. We have therefore proposed a conceptual sequence of events in radiation carcinogenesis, attempting to incorporate many of the complex interactions which appear to operate at the subcellular, cellular, and whole-animal levels. In the present article, this outline is presented, and certain points are illustrated by results of our recent experimental studies. We recognize that many of the concepts offered are not original and that many of the assumptions are not universally accepted (see *4*). The chief purpose in presenting this scheme is to combine in a unified theoretical framework certain aspects of the problem of radiation carcinogenesis which appear not to have been generally recognized and to indicate areas which warrant further exploration.

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Cells with Specific Mutations

The first step in the proposed sequence leading to a radiation-induced tumor is the production of a specific genetic alteration (a somatic mutation) in one, or in a small number, of the irradiated cells. This alteration may be produced by direct action of the radiation on the genetic apparatus of the cell or by an indirect mechanism involving primary damage to extragenetic sites (*5*) or activation of a latent virus (*6*). For the purposes of this discussion, all that matters is the result that the genetic apparatus of the cell has been specifically (and presumably irreversibly) altered. The nature and effect of this mutation at the molecular level is, of course, unknown (see *7*). The primary metabolic alteration in tumor cells has not been defined; nor is it known whether the same mutation occurs in every tumor, or whether different alterations lead to different kinds of neoplasms. The latter view has been supported by the observation that a characteristic chromosome abnormality, the Philadelphia chromosome, is consistently associated with a particular human neoplasm, chronic granulocytic leukemia (*8*). However, consistent chromosome changes have not been observed in association with other mammalian tumors (*9*). It may well be that the Philadelphia chromosome represents the specific carcinogenic mutation for chronic granulocytic leukemia, but that the specific mutations for other types of tumors are subchromosomal in nature, that is, too small or subtle to be demonstrated by current techniques.

Although we have spoken in terms of a single primary mutation, we recognize that, in fact, two or more specific mutations, in sequence, may be involved (*10*). Furthermore, the first of these sequential mutations may be a prezygotic or inherited alteration. This would explain, for instance, the increased susceptibility of certain strains of mice to tumor induction by radiation or other carcinogens. Whether such an inherited mutation should be considered an essential predecessor of the carcinogenic somatic mutation, or whether it would only render the second event more likely, is not known; and it is possible that the presumed prezygotic mutation could be, in some instances, a tumor virus, "vertically" transmitted (*11*), that is, by mother-to-fetus transplacental passage of tumor virus either in a latent, lysogenic-like state or as complete virus.

Mutagenic Effect of Ionizing Radiation

Although it has long been evident that the genetic damage produced by ionizing radiation depends in general on the radiation dose received (*12*), more recent studies indicate that factors such as dose-rate and radiation quality (for example, linear energy transfer, LET) can also influence the frequency of mutations (*13*). Further support for this thesis comes from data on chromosome aberrations, if the occurrence of visible chromosome damage can be taken to indicate mutational events. Thus, at high dose rates (30 rad/min), or using high LET radiation (fission spectrum neutrons), we have observed an increased frequency of chromosome aberrations in mouse liver cells, as compared to that occurring after exposure at low dose rates (1.5 rad/hour) or with low LET x-irradiation (*14*). Curtis *et al.* (*15*) have reported similar results.

In addition to these considerations, data on the *survival* of human kidney cells irradiated in vitro with high LET α-radiation suggest a "single-event, no-recovery" type of action, in contrast to a "multi-hit" mechanism for such cells exposed to low LET x-irradiation (*16*). This difference between the modes of action of high and low LET radiation may reflect more severe intracellular injury by the former, and may well be relevant to our earlier observations of the greater carcinogenic potency of fast neutrons, as compared with x-rays, for induction of

gastrointestinal tumors (*17*) and hepatomas (*18*) in mice. However, the extent to which cell killing by different kinds of radiation (as measured by curves for cell survival in vitro) can be equated with carcinogenic alterations in the cell is not known.

Similarly, although the intracellular repair (see *19*) of cells irradiated in vitro, as measured by cell survival, is affected by such factors as dose rate or LET, it is not known to what extent such repair phenomena may operate with respect to the presumed carcinogenic mutations.

Stage of the Cell Cycle

An additional variable which may affect radiation mutagenesis is the stage in the mitotic cycle at which the cells are irradiated. There is considerable evidence that the cell-killing effects of radiation vary considerably with the cell cycle (*19*), although at which stage the cell is most sensitive is still a matter of debate; but whether the frequency or degree of carcinogenic mutation is influenced by the stage of the mitotic cycle at the time of irradiation remains to be elucidated.

We have attempted to obtain information on this point by investigating the frequency of radiation-induced hepatic and renal neoplasms in mice in which mitotic activity was induced in the target organs by a proliferative stimulus (administration of CCl_4, or unilateral nephrectomy) applied at various times prior to irradiation. Mice subjected to unilateral nephrectomy, followed by whole-body exposure to 690 rad of x-rays 3 hours or 48 hours later, showed a high incidence of kidney adenoma 12 or 18 months after irradiation. In contrast, no kidney tumors appeared in the control groups irradiated only, or nephrectomized only (*20*). A significant increase in the incidence of kidney tumors was also observed in mice unilaterally nephrectomized 1 day before exposure to 320 rad of fission-spectrum neutrons (*21*). Similarly, when mice received a single subcutaneous injection of CCl_4 1 day before exposure to fast neutrons (280 to 328 rad), almost all of these mice (92 percent) developed hepatomas (*21*). Additional experiments have now been carried out on sublethally x-irradiated LAF_1 mice receiving a single injection of CCl_4 before irradiation. The experimental results are summarized in Table 1. It is evident that administration of CCl_4 1 to 10 days prior to x-irradiation resulted in an increase in the number of hepatomas, though not to the same marked extent as was seen previously after exposure to fast neutrons.

In neither of these studies, unfortunately, are the results susceptible to an unambiguous interpretation. In the first case, there is the question of nonspecific tumor promotion, due to a continuing, increased cell turnover in the remaining kidney. In the second case, there is the possibility that the CCl_4 used to initiate the cell cycle in the liver is itself mutagenic. We have observed a definite increase in frequency of chromosome aberrations in liver cells of nonirradiated mice which had received a single injection of CCl_4, as compared with controls in which mitosis was initiated by partial hepatectomy (*14*). Thus, although the data suggest that mitotic activity in liver and kidney cells renders them more susceptible to the production of carcinogenic mutations by ionizing radiation, more definitive experiments are needed.

Cell Killing and Sterilizing

Once the specific mutation or mutations have been produced in the irradiated cell, it is also necessary that the cell survive with its proliferative capacity intact if it is ultimately to produce a tumor. A highly mutagenic agent such as ionizing radiation could kill or sterilize a cell so that it is effectively removed from the population at risk. We have invoked such an explanation for the apparently paradoxical observation of high frequency of hepatomas in mice, following their exposure to γ-radiation at low dose rates (*22*). In this experiment, x-rays given at a high dose rate (30 rad/min) produced more chromosome aberrations in liver cells, but fewer hepatomas, than did low-dose-rate γ-radiation (1.5 rad/hour), which evoked markedly fewer chromosome aberrations. We assume that many of the cells with visible chromosome aberrations were unable to complete mitosis, so that the actual number of mutated cells available for tumor production was smaller in the mice treated at the high dose rate than in the low-dose-rate group.

The so-called "therapeutic" effect of large single doses of radiation on certain tumors showing a high incidence in mice can be explained similarly. For example, in our studies, the frequency of lymphoid leukemia in LAF_1 mice exposed to a single high sublethal x-ray dose of 690 rad was reduced to 13 percent from a control (nonirradiated) value of 29 percent (*23*). Similarly, the frequency of occurrence of lung adenoma was reduced from a control level of 24 percent to 8 percent in mice which had received 800 rad of x-rays in a single exposure plus an injection of isogenic hemopoietic cells to permit survival (*17*). Presumably, under these circumstances cells bearing an inherited specific carcinogenic mutation (which could include cells specifically susceptible to tumor-virus infection or even cells carrying a latent virus) were eliminated by killing or sterilization from the population at risk, so that the number of cells which might give rise to leukemia and adenomas was reduced. Such a phenomenon has not been demonstrated in humans, of course, because it requires not only a large dose of radiation but also a much higher frequency of spontaneous neoplasms than occurs in human populations.

Table 1. Neoplastic and hyperplastic liver lesions in x-irradiated mice (500 rad) treated with carbon tetrachloride.

Treatment	No. of mice*	Age (mo)	Lesions (No.)	
			Hepatoma	Focal hyperplasia
CCl_4 1 day before 500 rad	19	19–22	3	3
CCl_4 2 days before 500 rad	22	20–22	5	2
CCl_4 3 days before 500 rad	19	19–22	2	1
CCl_4 10 days before 500 rad	10	20–23	3	0
Total	70		13	6
500 rad; CCl_4 30 days later	30	20–24	13	1
CCl_4 only	12	19–23	0	1
No treatment	28	21–23	2	0
500 rad only†	42	18–33	1	

* LAF_1 mice exposed at 3 months of age. † These data were reported previously (*21*).

Thus it is possible, at least theoretically, to explain how the mutagenic effect of ionizing radiation may not always closely parallel its tumorigenic action. Furthermore, such concepts may help to explain the lack of precise correlation between radiation-induced chromosome aberrations, as examples of "visible" mutations, and subsequent tumor development. Here, not only may cells bearing aberrations fail to survive or proliferate, but also, the aberrations observed may not represent the actual carcinogenic mutations. Hence it is not surprising that cells, and even clones, with chromosome aberrations may survive in the marrow of irradiated mice and humans for years without tumors developing (*24*).

In our present state of knowledge, it seems best simply to state that an agent which increases mutations may, in general, be expected also to increase tumor incidence, but that no precise quantitative dose-response relationships at the whole-animal level can, as yet, be drawn.

Development of a Tumor

Just as the production of the specifically mutated cell may involve several variables and require several steps, so also may the development of a visible tumor from the initial neopolastic cell. First, the genetically altered cell must enter mitosis. In some organs, such as bone marrow, bowel epithelium, and skin, where mitotic activity is normally great, this would be expected to occur as a natural event, although certain nonspecific agents (injury, infection, certain hormones) by increasing mitotic activity (that is, shortening the G_1 period) could cause a mutated cell to enter mitosis earlier than would otherwise be expected. Certain viruses (*25*) might be carcinogenic through such a mechanism rather than by the production of mutated cells; and radiation itself, by its destructive action on marrow and gut, with subsequent regeneration, could have a similarly nonspecific effect on cell proliferation.

In other organs, in which mitosis is a rare event and the vast majority of the cells remain dormant (that is, in the so-called G_0 stage) for long periods, certain organ-specific agents may play an extremely important role in bringing the mutated cells into mitosis and thus permitting a tumor to develop. For example, CCl_4 and subtotal hepatectomy for liver cells, unilateral nephrectomy for the kidney, and phytohemagglutinin or specific antigens with respect to lymphocytes, all represent means by which dormant cells (which may survive for prolonged periods—months and years—without dividing) can be brought into mitosis and tumor development begun.

Once the specifically mutated cell (or cells) enters mitosis, the neoplasm may be said to have begun its development. For this discussion, we arbitrarily define a neoplasm as a cell or population of cells which continues to proliferate even when the initial stimulus has been removed. Administration of CCl_4 or unilateral nephrectomy may be necessary to bring such cells into mitosis, but once in mitosis the cells will continue dividing independently of the stimulus. This does not exclude the possibility that these cells may respond *quantitatively* to the effect of hormones or other agents (including a repeated dose of the mitotic stimulant). However, these effects will not restore the cells to their normal, controlled state but will simply increase or decrease the rate of tumor growth. Thus there is no conflict between this definition of neoplasia and the concept of "dependent" tumors, as promulgated by Furth (*26*) and others. The dependent tumor is simply one whose growth rate is still influenced quantitatively by hormonal control. [In this connection it is worth noting that radiation damage to endocrine organs may alter hormone levels (*27*); thus the development of *radiation-induced* dependent tumors may be influenced not only by the direct action of the radiation on the target organ, but also indirectly through its effect on hormone activity. Such considerations may apply not only to such obviously dependent tumors as those of the ovary (*28*) but also to some nonendocrine neoplasms, such as hepatomas, which may also respond to hormonal influences (*29*).]

Our definition of neoplasia does not require that the cells at the primary stage of development be capable of local invasion or of metastasis. The conversion from "benign" to "malignant" can occur at a later time. All that this definition requires is an "escape from growth control" so that the cells do not return to a normal state when stimulation ceases; and this change may be reflected in an increased rate of mitosis, in the failure of cells to differentiate, or in some other selective advantage over adjacent normal cells.

Tumor Progression

The subsequent progression of the tumor from this rather narrowly defined first stage of neoplasia to definite malignancy and complete automony, we conceive to be a process of repeated selection of sequential mutants from the initial tumor-cell population. As additional mutations occur in the population, they confer yet further selective advantages on certain tumor cells, and a clonal or stemline type of *micro-evolution* of the cell population continues throughout the life of the tumor (see *30*). A number of mechanisms can be postulated by which these additional mutations may be produced, and in fact different mechanisms may operate in different neoplasms.

In some instances a second application of a mutagenic agent in later stages of tumor development is apparent. Widely spaced doses of radiation could act in this fashion. In other instances, it is not clear whether the agents employed are acting as mutagens or simply as nonspecific stimulants to cell proliferation. Evidence is rapidly accumulating that many chemicals and viruses can produce genetic damage (*31*), and it appears that many presumed nonspecific "promoting" and "co-carcinogenic" agents may, in fact, be acting through a mutagenic mechanism. Thus in our observations of increased incidence of hepatoma in mice treated with CCl_4 *after* irradiation (Table 1; *18*), it is not clear whether the "promoting" agent is acting as a mutagen or as a nonspecific stimulus to mitosis, or both.

In many instances of tumor development, however, no additional stimulation, either mutagenic or nonmutagenic, is apparent. In these cases it has been generally assumed that the increased mitotic activity apparent in most tumors would be sufficient in itself to account for an increase in spontaneous mutations with consequent tumor progression. However, this thesis does not account for the high degree of genetic variation which often occurs quite early in the development of a neoplasm. Therefore, it has recently been postulated (*32*) that in many tumors either the initial genetic event

or one of the early ones is the activation of a genetic locus comparable to the nondisjunction gene (*32*) that operates in *Drosophila*, in certain plants, and apparently in certain human families (*33*). The effect of this gene would be to make the mitotic apparatus of the cell permanently unstable, so that in every subsequent cell division there would be an increased probability of nondisjunction or other chromosome rearrangements. Activation of such a genetic locus obviously would increase the number of cells in the tumor population with chromosome alterations and thus increase the opportunities for continued selection of altered clones.

Whichever of these various mechanisms operates to produce additional genetic alterations in a given tumor, the net result is that most mammalian neoplasms examined to date, in their late stages, consist of one or a few clones of cells which are markedly altered genetically. Chromosome studies have indicated that nearly all malignant neoplasms consist of a single, or a very few, stemlines of cells with a particular chromosome aberration. Except for the Philadelphia chromosome, these aberrations usually vary from case to case, but where repeated studies have been done, there has been good evidence for progressive clonal selection within individual tumors (*34*).

Immunological factors may be important in this aspect of tumor development. Certainly, many tumor cells with genetic aberrations produced in the course of tumor progression are recognized by the host as antigenically foreign (see *35*) and eliminated. However, the question that remains unresolved is whether those stemlines which do come to predominate in the fully developed tumor—and which almost invariably show marked chromosome aberrations—are not antigenically sufficiently altered to evoke an adequate homograft response, or whether the immunological competence of the host is in some way impaired (*36*).

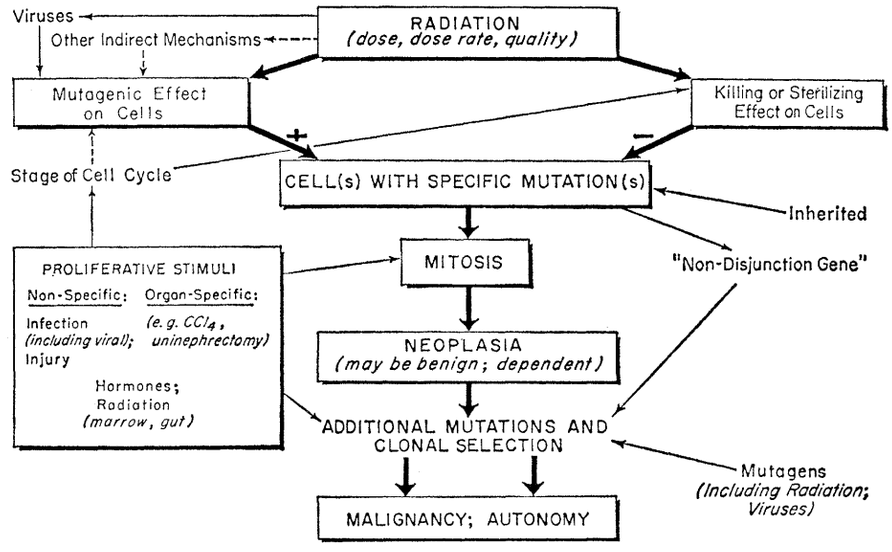

Fig. 1. Proposed sequence of events, and related factors, in radiation carcinogenesis.

Conclusions

These, then, represent our current concepts on the stages of carcinogenesis, specifically applicable to radiation-induced tumors and perhaps to carcinogenesis in general. In Fig. 1 we have attempted to summarize these ideas in schematic form. Note that somatic mutation is considered to be the "final common pathway" by which both radiation and viruses initiate neoplasia; in our view, chemical carcinogens probably act similarly. It is equally important to note, however, that *both* radiation and viruses can influence the eventual development of a visible tumor at several other stages. Each can induce additional mutations in an already neoplastic cell, and each can also act as a nonspecific proliferative stimulus affecting both initiation and progression of the tumor. In addition, radiation, through its damaging effect on the endocrines, can influence the development of dependent tumors by altering hormone levels.

When to all this is added the concept of the cell-killing effect of ionizing radiation, difficulties in the interpretation of results of experimental studies become apparent. For instance, we have recently observed no variation in the incidence of murine hepatomas after x-ray doses totalling 250 rad or 500 rad given in from 1 to 50 equal fractions, 7 days apart. At the same time, a leukemia incidence of 45 percent was observed in the mice (LAF_1 hybrids) receiving the most fractionated dose (5 rad × 50); this was a definite increase over the nonirradiated controls (22 percent) and over the other irradiated groups (17 to 30 percent). If the multiple small fractions permitted survival of a greater number of mutated cells, why was there not a similar increase in the number of hepatomas? Are hormonal alterations, which seem to influence hepatomas, of significance here, or was there a nonspecific stimulatory effect on the hematopoietic system by this radiation schedule which did not affect the liver?

Obviously, if one is to attempt to answer such questions, experiments in radiation carcinogenesis must be very carefully designed. If problems of "initiation" and "promotion" are to be investigated, one must consider whether the promoting agent is also mutagenic, and whether it induces mitosis in dormant cells or simply accelerates proliferation in a mitotically active population. Some attempt must be made to evaluate the indirect effects of the radiation-altered endocrine system on the tumors being induced. And, finally, the cell-killing effects of the particular radiation schedule and radiation quality cannot be ignored. If, in fact, radiation carcinogenesis depends on the survival of specifically mutated cells, then the number of tumors which develop will depend on the relative shapes of two dose-response curves for each experimental system employed —the curve for production of carcinogenic mutations, and the curve for cell killing or sterilization. To date, such curves have not been drawn, because, although data on cell killing are available (*19*) there is no accurate means of measuring carcinogenic mutations. Chromosome aberrations, as indicated, cannot be adequately interpreted without considerations of the concurrent cell survival, since many aberrant cells will not complete mitosis. A means of identifying and measuring carcinogenic

mutations is needed if the theoretical considerations offered here are to be confirmed, and this will require extension of present chromosome studies to the subchromosomal and perhaps to the molecular level. If such a measure were developed, it might be of considerable value in predicting for humans the carcinogenic potential of the low doses of radiation, small fractions, and varying dose rates to which many are exposed. Even then, however, the postmutational events discussed here in connection with experimental studies could well determine whether a tumor developed in a particular individual, and the possible effects of various environmental factors on these events would have to be evaluated.

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Fishing Treaties and Salmon of the North Pacific

Present treaties, economic in intent, cannot be made effective for conservation without more knowledge.

W. F. Thompson

The great expansion of world fisheries in recent years, particularly by Japan and Russia, has brought the ships of these nations to the fishing banks off our coast. They are exploiting whatever they can catch, of course, but we are particularly interested just now in their effect on our salmon. It seems a foregone conclusion that, unless restrained, they will affect all five species throughout their range as far south as California.

These salmon, then, must be conserved by treaty. There are already three treaties to restrain North Pacific high-seas fisheries. The oldest and most successful is the treaty between the United States and Canada for regulation of the halibut fishery. There is, at present, a treaty between Russia and Japan limiting their catch of salmon in the western Bering Sea, and one among the United States, Canada, and Japan regarding salmon fishery in the eastern Bering Sea and our coasts to the southward (see Fig. 1).

This last-mentioned treaty is not working to the satisfaction of the three signatories. If it is to be rewritten or if new treaties follow, we must know what we are doing. With what will these new treaties deal and how will they conserve the endangered species? Will the treaties be for conservation, or will they merely adjust economic interests? The history of the existing treaties throws light on these questions.

But first it must be understood what conservation means from the scientific standpoint. Perhaps the failure to understand the scientific facts leaves the battle to the short-sighted economics of competition for the catch.

The discussion can start with a point that may catch attention because it ties together space research, now in the limelight, and the basic biology of fish.

One of the first and greatest of the space-fiction writers was H. G. Wells, also a historian and biologist, who

The author, who died 7 November 1965, had been professor emeritus of fisheries at the University of Washington, Seattle, since 1958 and professor since 1930. From 1924 to 1937 he was director of the International Fisheries Commission, and from 1937 to 1943 he was head of the United States-Canada International Pacific Salmon Fisheries Commission. He founded the University of Washington Fisheries Research Institute and was its director from 1947 to 1958. He was also one of the incorporators and the first president of the American Institute of Fishery Research Biologists. This article was originally a talk given before the Seattle Power Squadron, 21 October 1965. Requests for reprints should be addressed to College of Fisheries, University of Washington, Seattle 98105, for the attention of Dean Richard Van Cleve.