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DOSSIER

DU COMBUSTIBLE NUCLÉAIRE AUX DÉCHETS : RECHERCHES ACTUELLES

FROM NUCLEAR FUELS TO WASTE: CURRENT RESEARCH

Pathogenic effects of low dose irradiation: dose–effect relationships

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Abstract There is no evidence of pathogenic effects in human groups exposed to less than 100 mSv at low dose-rate. The attributed effects are therefore the result of extrapolations from higher doses. The validity of such extrapolations is discussed from the point of view of epidemiology as well as cellular and molecular biology. The Chernobyl accident resulted in large excess of thyroid cancers in children; it also raised the point that some actual sanitary effects among distressed populations might be a direct consequence of low doses. Studies under the control of UN have not confirmed this point identifying no dose–effect relationship and "*severe socio-economic and psychological pressures… poverty, poor diet and living conditions, and lifestyle factors*" as the main cause for depressed health. Some hypothesis are considered for explaining the dose-dependence and high prevalence of non-cancer causes of death among human groups exposed to more than 300 mSv. ***To cite this article: R. Masse, C. R. Physique 3 (2002) 1049–1058.***

low doses / mutagenesis / cancer / pathogenic effects / radiation sensitivity / linear no threshold hypothesis (LNT) / adaptive response / bystander effects

Effets pathogènes d'un faible débit de dose : la relation « dose–effet »

Résumé On ne connaît pas d'effet pathogène induit chez l'homme par des faibles débits de dose jusqu'à 100 mSv par an. Les effets attribués aux faibles expositions sont le résultat d'extrapolations. La validité en est critiquée sur la base des observations épidémiologiques et des acquisitions récentes de la biologie cellulaire et moléculaire. L'accident de Tchernobyl a occasionné un excès important de cancers de la thyroïde chez les enfants ; il a conduit en outre à attribuer à l'exposition aux rayonnements ionisants des effets sanitaires réels dans des populations en détresse ; les enquêtes conduites révèlent cependant que ces phénomènes n'ont pas de relation avec l'intensité de l'exposition et sont imputables à la désorganisation sociale, aux carences et éventuellement à d'autres facteurs de l'environnement. Diverses hypothèses sont envisagées pour rendre compte de la prévalence augmentée de maladies non cancéreuses dans les groupes humains exposés à plus de 300 mSv. ***Pour citer cet article : R. Masse, C. R. Physique 3 (2002) 1049–1058.***

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1. Introduction

Everyone is exposed to radiation from natural and man made sources. Pathogenic effects resulting from overexposures to X rays and radium were observed a few years following their discoveries and, many centuries ago, a kind of lung cancer called 'Bergkrankheit' was described in Saxony a long time before it could be attributed to radon inhalation in silver mines. Due to increasing concern about health effects, the International Commission on Radiological Protection (ICRP) was established in 1928 from International Society of Radiology and, following the last World War, the UN convened the United Nation Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) which has updated radiation doses and effects on human health every year since 1956, with comprehensive reports being published every 4 or 5 years.

Up to recent years it has been considered that early (deterministic) acute effects resulted only from cell killing in different tissues as a direct consequence of the dose delivered to irradiated cells [1–3]. Cellular death in itself, as a consequence of non-repairable hits occurring at random in DNA, was considered a stochastic event, the probability of which increased faster than proportionally to the dose, because of the growing complexity of the interplay between the lesions initiated in multiple sites and the enzymatic repair of these lesions. A sound explanation for a threshold, limiting the occurrence of pathogenic effects, was provided when considering that tissue repair, which depends on self renewal by stem cells and cell recruitment, was overwhelmed above critical doses. This mechanism held true for some later effects such as lens opacification or mucositis, taking in consideration the progressive loss of stem cells due to ageing and to the continuous influx of toxicants in the milieu from endogenic and environmental sources.

All deterministic effects are only observed for doses higher than hundreds of mSv delivered at a high dose-rate, the most susceptible tissues being, embryo, male germ cells and subclasses of blood cells progenitors. More recently, however, it became evident that some of the early effects leading to cell death or cell dysfunction resulted from a more complicated pathway involving induced intracellular signalling [4] and cross talk of different cell systems mediated via cytokins and growth factors [5]. Therefore, the possibility emerged that some functional deterministic effects, pathogenic or not, could be induced by doses lower than hundreds of mSv in addition to carcinogenic and genetic stochastic effects which were supposed to occur at random, proportional to the dose. This has led UNSCEAR, for example, to introduce as a new outline 'Health effects of radiation' for a comprehensive discussion in its latter session in Vienna in 2001.

Alternatively, as discussed with the section on cancer at low doses below, intracellular signalling results also in adaptive responses, through the induction of radical detoxification and DNA repair mechanisms [4] which may result in over-protective effects.

2. What are low doses?

According to UNSCEAR 1993 [2] "low doses and low dose-rates are doses below which it would be appropriate to apply reduction factors (dose and dose rate reduction factors: DDREF)... when assessing risks from information obtained at high doses and dose-rates." Epidemiological or experimental sources for quantification of DDREF are extremely limited and do not provide real information on a limit of dose or dose-rate below which no further reduction of effect should be expected. Therefore low dose definition is mainly based upon the target theory which postulates that initial events, susceptible to error prone repair, may result from single hits in DNA and that single hit mechanism leads to linearity of dose response when modelling pathogenic effects in the low dose range. Whether the target volume is the size of a gene or that of a cross-talking unit made of multiple cells, and depending onto the time necessary for the individual cell to restore to the initial naive state, the range of low doses may vary by several orders of magnitude [3]. It was therefore found more practicable to refer to low doses as exposure levels which were not associated with pathogenic effects: these include natural levels of 100 mSv per year and below [6], as encountered in the town of Ramsar in Iran, and 100 mSv and below in a single exposure at high dose rate for Hiroshima and Nagasaki survivors [3]. Having this approach on low dose definition, however, results in a circular

argument when dealing with the pathogenic effects of low doses; this means obviously that the low-dose issue is entirely governed by projection models of risk and understanding of cell and tissue damage involved in these pathogenic effects.

3. Genetic damage in the progeny of exposed parents

Up to now there is no unequivocal evidence of transmissible genetic damage, including childhood cancer, in Hiroshima and Nagasaki survivors and in patients medically exposed [7]. It is therefore unlikely that transmissible genetic damage be observed in populations exposed to much lower doses. Indeed, a genetic survey in high level natural radiation areas did not show congenital malformations [8] or chromosomal aberrations in the newborn [9], and there is no evidence of reproductive toxicity among parents occupationally exposed [10]. Recent observations, however, among Chernobyl liquidators progeny have shown that mutations could be genetically transmitted in their offspring. These mutations affected mini-satellites markers [11] or DNA fragments observed in multi-site fingerprinting [12]; there is no known pathogenic consequence of these mutations. The phenomenon seemed to be transient [13] and it was not observed in Hiroshima offspring [14]. Assessment of genetic damage in man is therefore only based upon extrapolation of animal data from the 1950s, which were most probably overestimated by up to a factor of 5 [15].

4. Cancer

Unlike transmissible genetic diseases, increase in cancer incidence has been observed in the groups having received more than 200 mSv in adults and 100 mSv in children [2,3]: the survivors of Hiroshima and Nagasaki, irradiated patients, nuclear workers, residents of the former USSR contaminated by nuclear wastes, infants exposed to iodine fall-out of Chenobyl accident in Belarus, Ukraine and western parts of Russia. No cancer excess was observed for doses lower than 100 mSv or 100 mGy to the thyroid in infants; a doubt remains nevertheless in the case of irradiation by X-ray in utero from 10 mSv, since the epidemiological data are contradictory [16].

Although there exists data [17] establishing that high natural exposure is associated in adults to an increased rate of chromosome aberrations, no global increase of cancer risk was detected in regions exposed to high level of natural radiation [18,19]; in many instances, indeed, the rates of cancer have appeared to be decreased [20]. Lung cancer associated with exposure to radon might be an exception, although different sets of data are difficult to reconcile: meta-analysis of case-control studies resulted in positive trend of lung cancer incidence, growing slowly with increasing exposure, while large scale geographic correlations provide recurrent evidence of negative trends after correction for confounding factors [3]. It must be remembered that the doses delivered by radon to the bronchial cells lay in the higher part of the scale for low doses [21], averaging in France an equivalent dose of 10 mSv per year with a few per cent of indoor exposures higher than 100 mSv per year for those houses where radon concentration in air reaches 1000 $\mathrm{Bq/m^3}$.

Although there is no direct evidence for cancer induction by doses lower than 100 mSv in man, there are some relevant dose–effect relationships which may be used for the purpose of risk projection below the level where epidemiology failed to show an effect. Due to statistical uncertainties and to the high level of cancer rate in western countries, such projected values cannot be excluded as a residual risk at low doses from the statistical point of view. Indeed, Hiroshima and Nagasaki survivors (HN) follow-up since the beginning of the 1950s provides a remarkable and unique example for a comprehensive approach to this risk assessment [2,3]. Apparent linearity of the dose response from 0 to a few Sv provided an excellent basis for deriving a single value of the nominal risk for all fatal cancers, which was set at 5% per Sv for the general population and 4% per Sv for workers by regulatory bodies [22]. These values were weighted according to: demographic considerations; use of multiplicative projection models for assessing life span risk; and choice of a DDREF of 2 for extrapolating over the extremely high dose-rate in the Japanese cities

towards the low dose rates to be found in the environment and at working places. When used for radiological protection purposes, these values allowed us to set safe limits at the work place and to develop optimisation of practices according to ALARA (As Low As Reasonably Achievable) principle.

Unfortunately this improvement of regulatory policy has also led public opinion to the feeling that there was definitely scientific evidence of cancer induction by low doses. As a consequence, it has been more and more difficult for the experts to convince

(i) that no effects could be shown, in normal and in accidental instances, for doses added to natural exposure in the range of the mSv and lower, although it was self-evident for simple statistical reasons [3], and

(ii) that multiplying minute individual doses in the range of μSv and less by the billions of persons living on the earth (world wide collective doses) had no meaning in terms of risk assessment, as repeatedly said within UNSCEAR meetings.

In fact, despite that linearisation of risk versus exposure is a common extrapolation method for assessing long term effects of genotoxicants in general, methodological, epidemiological and biological arguments limit the validity of such approach in the case of exposure to irradiation at low doses.

4.1. Methodological effects

If extrapolation of data from 100 mSv and above can be justified for regulatory policy over one or two orders of magnitude lower, extrapolating over more than three is obviously speculative in the context of no detectable effects for doses one thousand times higher. Moreover, dose-rate experienced HN were more than 7 orders of magnitude higher than those found in the environment, a huge scale, which may not be taken in account by using a single DDREF of 2.

Linearity of the dose response for HN survivors results only from an acceptable fit of the data by a straight line from 0 to doses up to a few Sv and it does not exclude other mathematical fits, including polynomial and threshold limited dose responses. Indeed, including a threshold was found to improve the fit [23].

Taking all cancers together is somewhat arbitrary since the mechanisms of induction may differ strongly in function of the tumour type and it may well be that apparent linearity is only the result of large statistical fluctuations due to inconsistent mixing up.

Despite several dosimetric reassessments since 1965, neutron dose remains largely unknown, notably in the fraction of Hiroshima survivors exposed at low doses. Recent data suggest strongly that neutron dose was underestimated [24]. Taking in consideration that the efficiency of fission neutrons versus photons for experimental cancer induction lies in the range of 50 [25] would result in a major inflexion of the dose–response curve for photons in the low dose part of the curve [24].

4.2. Epidemiological effects

If some dose responses in specific organs from sources other than HN can be fitted linearly, and indeed it appears to be the case with breast cancer, and thyroid cancers in infants [3], others cannot, and there are no example of supralinear dose–responses. Infralinear dose–responses on the other hand were frequently observed and among these: dose–response for bone sarcomas induced by radium 226 rejected linearity [26]; doses–responses for lung cancer seemed strongly influenced by dose fractionation and by time elapsed since exposure [3]. Non linearity is also suggested from all cancer surveys in exposed workers: in the cohort studied by IARC, less solid tumours were observed than expected from controls and the trend for dose response suggested a negative slope [27] and very much so in the US shipyard subcohort [28], British radiologists, whose cohort is the historic reference for exposed workers before limits of dose were set in 1921, showed fewer tumours since 1954 than non-exposed physicians in the latter survey [29]. In addition, many experimental data point to non-linearity and to threshold limited responses for the induction of cancer in different tissues [30]. There are therefore so many exceptions to linearity that LNT cannot be taken as a validated scientific hypothesis for the prediction of cancer risk at low dose. According to the precautionary

principle LNT is, however, useful for risk management in the 1 to 100 mSv range of dose, providing regulatory policy with an easy way to sum up the doses from different origins.

4.3. Biological effects

Cancer masses result mainly from monoclonal growth of mutated cells. A simple mechanism has been therefore suggested considering that cancer could arise from a rare mutation in a critical gene induced by a single track of radiation in the DNA of a single cell. This is the rationale behind linear modelling which assumes in addition [31] that (i) the probability of a DNA lesion repair is constant whatever the dose and hence, the number of lesions provoked in the same cell or the surrounding cells; (ii) the probability for a damaged cell to evolve into a cancer is not influenced by the consequences of dose delivered into the tissue. Furthermore, it has also to be assumed that monoclonality is the result of an initial advantage conferred to the initiated cell and not the result of a selection of the most adapted clone.

The following points have however to be considered:

DNA is permanently repaired following interaction with endogenic radicals derived from oxidative metabolism (ROS). Compared to an average of 2 tracks per cell and per year due to 2 mSv of exposure to natural radiation this non-radiation origin contributes by 6 orders of magnitude more than radiation to DNA lesions when all types of lesions are concerned, and remains also much higher when more specific consequences of radiation such as Double Strand Breaks (DSB) only are considered [32].

Although there exists some biomarkers of radiation for early events: multiple damaged sites in DNA [3] and induction of dicentric chromosomal above a few tens of mGy [33], there is no evidence of signature in the latter stage of radioinduced cancers [3]. One can therefore consider that the same mechanisms involved in naturally occurring cancers are induced by radiation tracks and radicals created by water ionisation which contribute only to a minute fraction of all DNA damage by ROS. This damage may, however, be quantitatively significant for a limited period of time and, if so, it would be likely that the late effects of radiation depend on the concentration of the initial events, i.e. dose rate, which provides signal for a specific cell to proceed towards death, repair or mutation following initial damage.

Indeed, there are several arguments pointing at dose and dose-rate dependent mechanisms for cell survival, namely: adaptive response [4]; hypersensitivity at low dose which eliminates naive cells from the pool of potentially mutated cells [34]; and a bystander effect leading to delayed cell death through genetic instability [35]. The bystander effect was the only late detectable consequence of cell irradiation by gamma rays at doses lower than a few tens of mGy delivered at high dose-rate [35].

Induction of repair mechanisms at high dose-rate operates at doses higher than a few tens of mGy, leading to the well-known plateauing of cell survival curves up to the range of doses around 1 Gy [34]. When cells are primed by doses lower than 0.5 Gy, superabundant induction of repair mechanisms occurs, depending on protein synthesis, which allows the cells to improve their control of mutagenesis when challenged by a second exposition to 1.5 Gy a few hours later; this adaptive response [4,34] protects against endogenic or environmental toxicants as well [32]. Much more remains probably to be learned from the more than hundred new genes recently shown to participate in the response to radiation damage and other toxicants [36].

Bystander effect resulting from cell cross-talk using chemical signals is indeed a new concept whose meaning in terms of health effects is not well understood. It allows non irradiated cells to respond to the irradiation of their neighbour cells. This cell co-operation invalidates single hit modelling of further biological effects. It operates above critical dose levels in the range of a few tens of mGy (low LET) at high dose-rate and exhibits limited dose–response relationship between 0.01 and 0.5 Gy [35]. Although bystander effects mainly lead to cell killing by delayed cell death, recent data showed also that it could result in cell transformation at doses of 5–7 Gy [37]. Whether this pathway exists at lower doses and dose-rates remains uncertain but it has been suggested that bystander signals induced by radiation may combine with genotoxicants from environmental factors [38]. This may provide new insights into the detrimental

effects of low doses, above levels, however, which are needed to switch on bystander responses. Although these levels imply a few tens of mGy delivered in a short period of time with low LET [35], interaction with high LET is more complicated [39] since a few hits induced by a low fluence (50 mGy) of alpha rays in only 3% of cells plated in vitro led to detectable bystander effects in terms of point mutations [40].

5. Other effects at low dose

Some tissues are highly susceptible to radiation and indeed this is the case with embryos, the developing brain being the most at risk in humans [2]. There is however no evidence of damage below 0.2 Gy delivered at high dose-rate in between the 8^{th} to 15^{th} week of pregnancy, which is the most susceptible period. Some arguments point to delayed migration of neurones towards the cortex as a mechanism involved, rather than cell killing.

Register for birth defects and malformations operating in Belarus at the time of accident, made it possible to investigate the consequences of Chernobyl in contaminated areas [3]. A significant increase in polydactyly, limb reductions and multiple malformations was noted in the most contaminated regions (555 kBq/m^2 leading to less than 10 mSv in the first year) and other defects were also found increased in other parts of the country less contaminated; no changes of birth defects over time could be related to exposure to ionising radiation. The relationships with radiation were therefore questioned by UNSCEAR [3] which pointed out that "it was unlikely that the observed shifts in health status of children have been caused by radiation only." UNSCEAR addressed also the issue of pregnancy outcome in general and, although a significant decrease in birth rate occurred in many affected countries, no apparent relationship to ionising radiation was noticed.

UNSCEAR conclusions, following comprehensive peer reviews, identified thyroid cancer increase in infants as the only attributable pathogenic consequence of the accidental exposure to radiation, in terms of delayed health effects, in addition to the late effects in the group of 237 emergency workers heavily exposed [3]. These conclusions were challenged by OCHA, the Office for Co-ordination of Humanitary Affairs of UN [41]. Indeed, 15 years after the Chernobyl accident other types of health effects seemed to have emerged in Belarus and Ukraine including: primarily neuropsychiatric and cardiovascular diseases, deteriorating health and increasing invalidity among liquidators, and, among the general population, decreased birth rate, increased pregnancy complications, impaired health of new-borns and children. This had been examined by UNSCEAR which found no relationship with dose delivering and health status, despite many clinical investigations performed, especially haematological and immunological, among infants and liquidators [3]. An international meeting was therefore convened in Kiev, in June 2001 where "*Scientists and experts from the Republic of Belarus, Russian Federation, Ukraine, and other countries, as well as representatives of international organisations [the World Health Organisation (WHO), the United Nations Office for the Co-ordination of Humanitarian Affairs (OCHA), the International Atomic Energy Agency (IAEA), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the United Nations Chernobyl Programme in Ukraine, and the International Commission on Radiological Protection (ICRP)] participated in the work of the conference.*" The conclusion of the meeting stated that: "*A number of factors inherent to the Chernobyl accident, including worsening socio-economic conditions, continuing residence in contaminated territories, diminished food supply, vitamin deficiency, relocation, and psychological stress, may contribute to these effects.*"

Indeed, psychological stress and socio-economic conditions alone can result in deteriorating heath status [42], however, the possibility that direct health damage could be induced by low doses through deregulating cellular/molecular, paracrine and endocrine responses to radiation has been recently advocated [43]. This is mostly speculative but some aspects of poorly understood dose–effect relationships for pathogenic effects deserve some attention.

Non-cancer mortality, recently updated in HN survivors [44], was clearly dose related; circulatory diseases were the main cause of death and the dose–effect relationship excluded a threshold down to 0.3 Gy.

Some limited evidence of linearity for circulatory disease mortality was also provided in Canadian workers exposed to doses lower than 0.4 Sv, despite a strong healthy worker effect [45]. Causal relationship with low dose exposure remains extremely weak for such effects but a possible mechanism was postulated arguing that human atherosclerotic plaques were monoclonal [46]; this has led to the hypothesis that both cancer and atherosclerosis might follow a common pathway. The hypothesis is currently evaluated by UNSCEAR committee but bias for causes of death registering and strong confounding factors, such as alcohol consumption and smoking habits, have to be eliminated. No evidence of non-cancer mortality excess was provided in the British radiologists cohort [29].

So called 'radiation sensitivity', resulting from a radio induced neural pathway to diseases, mediated by cytokines, has been proposed as a specific pathogenic entity by analogy with chemical sensitivity syndromes [43]. It stemmed from recent observations in liquidators in whom

(i) a relationship between dose and vascular, mental and endocrine diseases was found in the range of 30 to 170 mGy [47] on the one hand, and
(ii) radioinduced cortico-limbic disorganisation of EEG which was noted in emergency workers who developed acute radiation sickness on the other hand [48].

This hypothesis remains speculative since there is

(i) no direct observation of such effects in patients exposed up to 6 Gy [43], and
(ii) no direct relationship between limbic deregulation and disease in the group of liquidators exposed to low doses.

In any case, from what is known from experimental data, such effects should require acute dose of tens of mSv at least and are not at concern for low dose-rate exposures [43].

6. Summary and conclusions

Low dose and low dose-rate exposures to ionising radiation, as those encountered under environmental conditions, do not result in detectable pathogenic effects. An exception has, however, to be made for radon exposure in some areas which may result, during a life time, in doses equivalents of a few Sv delivered by alpha rays to bronchial cells.

The pathogenic effects attributed to low doses are thus extrapolated from those evidenced above effective doses of 100 mSv or more delivered at high dose-rate. The validity of such extrapolation is limited by uncertainties whatever the effects considered: deterministic, genetic or carcinogen. These uncertainties rely mainly upon the mechanisms supposed to support linear dose–effects relationships.

Limited evidence of increased non-cancer mortality (especially cardiovascular) at low doses was provided among Hiroshima and Nagasaki survivors, together with impaired health status (psychiatric, cardiovascular, endocrine, infectious,...) in the populations affected by Chernobyl accident. These observations have raised the point that pathogenic effects could result from radiation-induced functional impairment of cell cross-talks (paracrine and endocrine). These mechanisms have not yet been identified and remain highly speculative for low dose-rate exposures. Most recent epidemiological surveys agree that stress, nutritive privation and psychosocial factors are main causal agents in Chernobyl affected regions, and that thyroid cancer in children is the only directly attributable pathogenic consequence of radioactive release.

Alternatively, recent data, however, have stressed the importance of intracellular and intercellular signalling in radio-induced mutagenesis, cell death and transmissible genetic instability, and indeed hundred of genes participate in the cellular response to radiation damage. New data suggest that bystander effects make up the main response to low doses and that adaptive response, switched on at up to a few hundred of mGy only, helps in scavenging radicals from different origins, providing eventually protection against endogenic toxicants.

Bystander effects and the adaptive response, whose relative contribution to death, repair and mutation depend on dose and dose-rate, are basic mechanisms which are not compatible with linear extrapolation of the risk of cancer at low doses.

Although there is no evidence of pathogenic effects transmitted in the progeny of irradiated parents, increased instability in highly mutable parts of the DNA was recently observed in infants born from Chernobyl liquidators. This observation has not been made in infants born in Hiroshima and Nagasaki and it will deserve further research to determine whether it is or not a transient bio-marker of radiation exposure.

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Discussion

Question de J. Lafuma

Aujourd'hui aux USA, on a analysé les caractères fonctionnels de la cellule cancéreuse qui la différencient des cellules normales :

1. Capacité à se donner à elle-même l'ordre de se multiplier, ordre qui ne vient que des autres cellules dans un tissu normal.
2. Capacité à « ignorer » les signaux d'arrêt de prolifération.
3. Capacité à ignorer les signaux d'autodestruction.
4. Capacité de développer un système vasculaire nouveau.
5. Capacité à l'invasion locale à la métastase.

Existe-t-il des publications expliquant comment on passe de la mutation initiale à la *vraie* cellule cancéreuse ?

Réponse de R. Masse

Il s'agit là d'une question très générale dont la réponse développée me paraît à elle seule justifier un numéro complet des CRAS !

La réponse la plus simple, à l'autre bout de la chaîne est simplement : oui ! on connaît en effet de multiples mutations rendant compte des différents comportements spécifiques de la cellule cancéreuse. C'est ce que Bernard Dutrillaux appelle « l'histoire naturelle des cancers », et cette histoire est différente pour chaque type de cancer.

En quoi est-ce que cette histoire peut être directement reliée à la mutation originelle radio induite est une question plus délicate. Il est évident qu'une seule mutation ne peut conduire directement au cancer. Néanmoins si elle touche des gènes impliqués – dans la réparation de l'ADN en particulier dans la réparation des mésappariements, – dans la réplication de l'ADN – et dans la ségrégation des chromosomes, elle peut conduire à une forme d'instabilité du génome qui ultérieurement permettra l'accumulation des mutations spécifiques au cancer en raison de l'avantage sélectif que confèrent ces mutations.

Par ailleurs, et c'est sur quoi K. Trott et moi même avons insisté, le phénomène d'instabilité génétique radio induit est une propriété acquise qui semble devoir être aussi interprétée comme la réponse au stress que constitue un niveau suffisant de lésions dans l'ADN car la taille de la cible pour cet effet est au moins aussi grande que le noyau cellulaire, en tout cas incompatible avec la taille d'un gène.